Does Respiratory Viral Testing in Adult Hospitalized Patients Impact Hospital Resource Utilization and Improve Patient Outcomes?

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Abstract

Respiratory viral testing in hospitalized patients is thought to improve quality of care by reducing the use of diagnostic tests, guiding infection control precautions, and rationalizing antimicrobial therapies. Few small published studies have tested these assumptions, and have demonstrated conflicting results.

We conducted a retrospective cohort study of 24,567 hospitalizations using administrative data to determine the associations between viral testing, patient outcomes, and process of care.

Viral testing was not associated with improved mortality or length of stay in hospital, and resulted in more resource utilization. The test result did not influence the duration of isolation precautions. This implies that health care providers may not use the results of testing in making management decisions, or in guiding the use of isolation precautions. This study provides the foundation for further scientific evaluation and reform of our current respiratory infection control policy.

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Introduction

1.1 Overview

This research thesis examines the use and impact of respiratory viral testing in adult patients hospitalized with respiratory symptoms. In this introduction I describe how viral diagnostic testing is theoretically thought to improve the quality of health care from a patient and public health perspective, and why it may not be meeting our current goals.

I will first explain the health impacts of respiratory viral infections, followed by an illustration of how nasopharyngeal viral swabs aim to improve quality of care. I will discuss the current policy and process for evaluating patients with respiratory symptoms and will describe current knowledge gaps in this area along with the proposed hypothesis and objectives for this research thesis.

1.2 Impact of Respiratory Infections

Respiratory infections are common, costly to the health system common, associated with significant morbidity and mortality, and have a strong public health impact due to infection transmission between patients.[2,3] Acute respiratory viral infections have garnered specific attention in this regard, as recent outbreaks of severe acute respiratory

syndrome (SARS) and pandemic influenza strains have demonstrated their impacts on patients, health resources, financial resources and public health safety.[2,4]

1.2.1 Epidemiology and Clinical Impact of Respiratory Infections

In a report published by the World Health Organization in June 2013, lower respiratory tract infections were the third leading cause of death worldwide, accounting for 3.2 million deaths in 2011.[5] In Canada, the Canadian Institute for Health Information (CIHI) cited respiratory infections as the leading cause of infection-related death, causing 8000 deaths, 1 million physician visits, and 60,000 hospitalizations annually.[2] Viral causes of respiratory infections are now recognized as an important etiology in up to one third of patients hospitalized for community acquired pneumonia.[6–8] These rates are likely underestimated due to insensitive viral diagnostic technologies used in previous studies.[7] Further, co-infection with viruses and bacteria occur in up to 15% of patients with respiratory infection, and are associated with increased disease severity as assessed by validated pneumonia risk indices including the CURBage score and the PSI risk class.[6,9,10] Respiratory Syncytical Virus (RSV), Rhinovirus, Influenza A and B, Human Metapneumovirus (HmPV) and Parainfluenza are the most common viruses isolated from adults with viral pneumonia.[7]

Considerable mortality has been associated with many respiratory viral infections including Influenza and RSV. The United States Centers for Disease control estimate a range of influenza associated deaths in the United States between 3000 and 48,000 annually, depending on the influenza season and circulating viral strain (CDC Seasonal Influenza webpage). In Canada, statistical models have estimated annual influenza re-

lated deaths between 3500 and 6000 people, according to a recent study by Schanzer and colleagues.[11] In 2003, Thompson and colleagues demonstrated an increase in influenza associated deaths between 1976 and 1999 that was largely attributed to an increase in deaths in patients over the age of 65 years.[12] Subsequently, in 2005, Falsey and colleagues performed a study evaluating Influenza and RSV infections in healthy and high risk adults.[13] They identified RSV infection in 10.6% of patients hospitalized for pneumonia with a death rate of 8%.[13] Twelve percent of those with RSV infection required admission to the intensive care unit.[13]

1.2.2 Economic Impact of Respiratory Viral Infections

The clinical impact of respiratory viral infections leads to an important economic and health system impact. An American study estimated the cost of treating hospitalized patients with pneumonia at 3.6 to 4.8 billion dollars annually.[14] In the last decade, research efforts have focused on targets to reduce the economic burden of respiratory infections. A Canadian study by Marrie and colleagues demonstrated that using a standardized pathway in assessing and treating patients with community acquired respiratory infection improved patient health related quality of life, and significantly reduced the number of patient hospital-bed days, which could translate to significant health care cost savings.[15] Several studies have also demonstrated significant costs associated with hospitalization for pneumonia.[16–18] In 2009, an American study by Raut and colleagues demonstrated that a half-day reduction in hospital length of stay (LOS) for patients with pneumonia could save between 500 and 900 million dollars annually.[16]

1.2.3 Respiratory Viral Infection Transmission

It is clear that respiratory viral infections have a significant personal health and economic impact. In addition to this, patients and public health officials are now aware of the dangerous consequences of viral infection transmission between patients and health care workers, and between virally infected and uninfected patients in hospital. Following the worldwide SARS virus outbreak in 2003, viral infection transmission between close contacts in hospitals garnered significant attention and identified global deficiencies in hospital respiratory infection control practices.[19,20] SARS was responsible for infections in 8096 people and 774 deaths in China, Vietnam, Singapor, Taiwan, and Canada.[21] SARS was caused by a novel corona virus which is thought to have been transmitted from small mammals to humans, occurring for the first time in the Guangdong province of China.[19,20,22] The infection spread quickly between close contacts of persons with SARS, suggesting that direct or indirect contact with large respiratory droplets (greater than 10 µm) was responsible for the transmission.[19,20,22] Further, 21% of infected cases were noted to occur in health care workers caring for patients with SARS, fuelling the understanding and importance of viral infection transmission in the health care setting.[21,23] During the SARS outbreak, the Ontario Ministry of Health mandated symptom screening questionnaires for all patients presenting to emergency rooms to ensure the identification of potential SARS cases.[24] In addition, a collection of hospital infection control practices including individual patient isolation, frequent hand washing, environmental decontamination, use of personal protective equipment by health care workers and hospital visitors (gowns, gloves, masks), and specialized quarantine wards were introduced in hopes to contain the outbreak.[20] The eventual control of the outbreak was attributed to use of these screening and isolation practices.[20,25–27] The individual, population, and economic

impact of this outbreak prompted government health bodies to mandate widespread symptom screening questionnaires and respiratory isolation practices for patients presenting to hospitals with febrile respiratory illnesses in future.[24] These practices were mandated in the non-outbreak setting as well.[24]

Given the impact of viral respiratory infections on patients, providers, health system resources, and public health safety, it is important to understand how our current hospital practices for testing and treating respiratory infections impact patient and financial outcomes.

1.3 Evaluation of Hospitalized Patients with Suspected Respiratory Infection at The Ottawa Hospital

The current hospital policy for evaluating and treating patients with febrile respiratory illnesses in the non-outbreak setting is guided by recommendations from the Infection Control Standards Task Force and the Public Health Agency of Canada.[24,28] These policies were developed by expert consensus based in part upon the observations of nosocomial infection transmission during the SARS outbreak.

When a patient presents to the emergency room, they are assessed by triage personnel with a screening questionnaire termed the Febrile Respiratory Illness (FRI) questionnaire (Appendix A.1). This symptom surveillance tool queries whether the patient is experiencing new or worse cough or shortness of breath, and fever (either subjective or documented temperature of 38 C). If both of these criteria are met, the FRI question-

naire instructs triage personnel to place a face mask on the patient and initiate use of droplet isolation precautions. Droplet isolation precautions are used for infections that are spread by large respiratory droplets, greater than 10 µm in size.[29] Droplet isolation precautions require all health care personnel and visitors to wear gloves and respiratory masks with a shield when in contact with the patient. Further, the patient should be placed in an isolation room if resources allow it.[30,31] If a private room is not available, the patient must be placed at least 3 feet away from other patients in the hospital room and the curtain around the patient should be closed with appropriate signage indicating droplet isolation precautions are in effect.[29,31] Other types of isolation precautions including airborne and contact precautions may also be applied at the time of admission if the patient is suspected of having a condition transmitted via small respiratory particles less than 5 µm in size (such as tuberculosis) or infectious diarrheal illnesses, such as Clostridium difficile.[30]

Once droplet precautions are applied, the patient is tested for viral infection using a nasopharyngeal swab (NP Swab) at the discretion of the treating physician or infection control practitioner. The NP swab is designed to obtain a cellular sample of nasal mucosa and is routinely processed by direct fluorescent antibody (DFA) testing and viral culture. Polymerase chain reaction (PCR) techniques are also used, but only for samples from patients admitted to intensive care and bone marrow transplant wards, or if the swab is taken during an outbreak or pandemic period with a novel virus.[32] Conventional DFA can yield a result within 24 hours, but has a 70% sensitivity (varies with different viruses) and 98% specificity, raising concerns about false negative results.[33] Reverse-transcriptase multi-plex PCR testing is highly sensitive, fast (turn-around time within hours), and can detect a panel of several respiratory viruses, however it is much more expensive and requires specialized resources.[33,34] It is currently not used routinely as the

primary testing modality for respiratory viruses in most Canadian hospitals.

Once a patient is under droplet precautions, isolation precautions can be removed if the NP swab yields a negative result. However, if the NP swab identifies a virus, the patient remains under isolation for a minimum of 5 days unless clinical symptoms dictate that isolation should continue longer.[29,35,36] Isolation for a five day period is recommended to account for the average viral shedding time in a non immunocompromised patient.[29,35,36] However, immunocompromised patients and children may shed the virus for much longer durations.[29,37,38]

Overall, this screening and isolation policy is designed to be conservative, such that potentially infectious and transmissible cases of infection are not missed. It also aims to determine the etiology of the infection promptly (with viral testing) to guide treatment and use resources efficiently.

1.4 The Intended Benefit of Viral Testing in Hospitalized Patients

1.4.1 Individual Patient Benefits of Viral Testing

Testing for viral illness in hospitals serves two main purposes: improvement of the individuals care, and safety of the hospitalized population.

Regarding the care of the individual, it is difficult to determine whether a patients infection is viral or bacterial in etiology since the presenting symptoms are typically non-specific (fever, cough, shortness of breath) and could also be associated with other disease conditions such as heart failure or pulmonary embolism. Studies have attempted

to determine and validate a clinical prediction rule for respiratory viral infections, specifically influenza, but have been unsuccessful.[39,40] Performing an NP swab in this patient population can help to clarify whether the patients infection is caused by a bacteria or virus. This distinction is important because it affects subsequent medical treatments and procedures. The intended goals and consequences of viral testing for the individual patient are described in Figure 1.1.

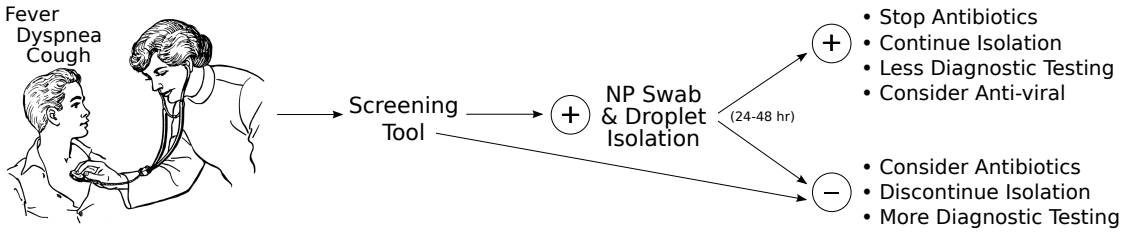


Figure 1.1: Process and downstream effect of viral testing in a patient presenting with infectious respiratory symptoms.

If an NP swab is performed and identifies a respiratory virus, antibiotic therapy may be discontinued, and additional testing to investigate other potential diagnoses may not be required. Additional testing might include laboratory tests (sputum and blood cultures), radiographic imaging (chest radiograph, computed tomography scans, doppler ultrasounds) and endoscopic procedures (bronchoscopy). Identification of a viral pathogen can aid in determining the patients prognosis, need for antiviral treatment, and may influence the decision to keep a patient hospitalized. For example, in a patient with underlying immunosuppression or chronic respiratory disease, viral infections such as RSV and influenza can have a fatal course, and the patient may require more advanced support in hospital (such as invasive or non-invasive ventilation). Further, if the NP swab does not identify a viral infection, isolation precautions can be safely removed. Removing isolation is in the best interest of the patient, as several studies have shown isolation precautions to be associated with more adverse clinical events, higher scores for patient

anxiety and depression, reduced patient satisfaction, and fewer visits by the clinical care team.[41,42]

Overall, the viral testing process aims to improve quality of care for the patient by increasing diagnostic certainty, avoiding unnecessary testing, determining prognosis, and avoiding unnecessary use of potentially harmful isolation precautions.

1.4.2 Public Health Benefits of Viral Testing

Viral testing in hospitalized patients is also beneficial from a public health perspective, mainly with respect to transmission of viral illness. The intended benefits of testing patients for viral infection from a public health perspective are described in Figure 1.2.

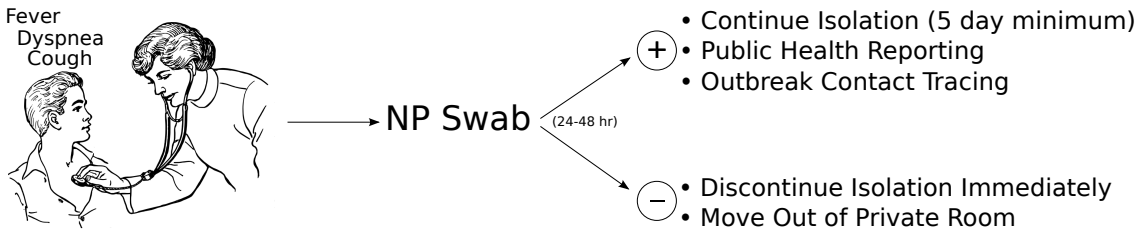


Figure 1.2: Intended benefits of testing hospitalized patients for respiratory viral illness, including re-allocation of hospital bed resources and appropriate discontinuation of isolation precautions.

If a virus is identified, isolation precautions should be continued for a minimum of 5 days (according to policy) until a patient is deemed non infectious by clinical symptoms or physician judgment. This practice is thought to prevent transmission of viral illnesses to other patients and health care workers, as demonstrated during the SARS outbreak.[20,25] If no virus is isolated, respiratory isolation precautions can be safely discontinued in a timely fashion. This would make efficient use of hospital resources including isolation equipment, additional nursing time required to care for a patient under isolation, and

private hospital rooms. Lastly, identifying patients with a viral infection can help public health administrators monitor viral infection prevalence, and detect the source of infectious outbreaks, especially in enclosed hospital units such as intensive care units and oncology wards.

Overall, viral testing aims to improve quality of care from a public health and cost perspective as it provides an objective method by which to discontinue isolation precautions in hospital, identify infectious outbreak sources, and provide important epidemiological information.

1.5 Consequences if NP Swabs Results are Ignored

If NP swabs are not used in the context described above, there are several potential consequences. First, the lack of diagnostic clarity without an NP swab would likely lead to unnecessary and inefficient use of other diagnostic tests (culture specimens, radiographic imaging, invasive procedures). Second, if NP swabs are not performed, there would be no current method to guide use of isolation precautions. This could lead to unnecessary use of isolation precautions (in patients who do not have infection), or increased nosocomial virus transmission in hospital (if patients with infection are not isolated). Excess use of isolation precautions could predispose patients to harm.[41,42] Lastly, if NP swabs were not performed or the swab results were not incorporated into subsequent care decisions, there would be an inevitable strain on hospital resources and escalation of hospital costs.

1.6 Literature Review: How Does Viral Testing Impact Patient and Public Health Outcomes?

While the intended benefits of testing hospitalized patients for respiratory viruses are well recognized, only few studies have evaluated the impact of testing on adult patients and hospital outcomes.

1.6.1 Impact of Viral Testing on Patient and Hospital Outcomes

Several studies have been done in the pediatric population to investigate the relationship between viral testing and resource utilization and outcomes, with mixed results. A controlled trial by Wishaupt and colleagues in 2011 looked at use of reverse transcriptase PCR for 17 respiratory viruses in addition to nasal washes in pediatric patients presenting to the emergency department with suspected acute respiratory tract infection.[43] Earlier knowledge of the viral test result did not lead to reduced hospital admissions, length of stay in hospital, or antibiotic use.[43] Similar results were obtained by Iyer and colleagues in 2006 when they investigated the effect of influenza testing on subsequent laboratory testing, chest radiography, antibiotic use, costs and lengths of stay in the emergency department and inpatient admission among children presenting to the emergency room.[44] The authors conducted a prospective quasi-randomized trial on 700 children presenting with fever during an influenza outbreak in 2003-2004 and found no difference in resource utilization or clinical outcomes when the rapid influenza test was used.[44] The only exception was less urinalysis and urinary cultures in children with a positive rapid influenza

test.[44]

In contrast to these findings, a 2009 study among 97 Turkish children (age 3 – 14 years) presenting to the emergency room with influenza-like illness showed a 30% reduction in antibiotic use when the clinician was given the result of the rapid respiratory viral test.[45] Similar results were obtained by Bonner and colleagues who studied 319 patients aged 2 months to 21 years in the emergency department.[46] They found that among patients with a positive influenza diagnosis, the cases where the clinician was aware of the early diagnosis had reductions in the number of blood cultures, urinalyses, chest radiographs, antibiotics prescribed and length of stay in the emergency department.[46] The studies showing a reduction in resource use have been limited by relatively small sample sizes.

Among adult hospitalized patients, three studies have evaluated impact of viral testing on antibiotic use, costs, and length of stay in hospital.[47–49] A randomized controlled trial of 107 patients by Oosterheert and colleagues studied the effect of RT-PCR viral tests in patients with lower respiratory tract infection on antibiotic use and diagnostic costs.[47] The authors found that RT-PCR testing for respiratory viruses did not lead to significant reductions in antibiotic use, length of stay in hospital, or the number and costs of additional diagnostic tests (cultures, blood gases, CT scans, bronchoscopies).[47] Subsequently, Hernes and colleagues conducted a prospective cohort study to determine if RT PCR for respiratory viruses impacted length of stay and antibiotic use in hospitalized elderly patients in Norway.[49] They found that a positive viral test did not lead to a reduction in antibiotic use in a majority of cases, or in length of hospital stay.[49] Finally, an earlier study by Barenfanger and colleagues demonstrated that DFA testing for respiratory virus compared to viral culture was associated with significant reductions in length of stay, reduced costs per patient, and reduction in antibiotic use.[48] Although

this study suggested that respiratory viral testing is associated with improved outcomes, it was retrospective and less methodologically sound compared to the studies by Oosterheert and Hernes.

In both the pediatric and adult literature, there have been conflicting findings as to whether respiratory viral testing improves patient outcomes and utilization of hospital resources.

1.6.2 Knowledge Gaps

Past experiences with the SARS outbreak and H1N1 pandemic have guided current screening, testing, and treatment policies for patients presenting to hospital with infectious respiratory symptoms over the last decade. It is assumed that the current hospital practices achieve the goals of timely diagnosis, improved patient clinical outcomes, and treatment and prevention of infection transmission. However, only few studies in adult patients partially address these assumptions, and have demonstrated conflicting results.

Recognizing the increasing burden on the health system, Canada is developing health system funding reforms to reward quality of care for individuals, cost effectiveness, and public health safety.[50] In order to meet these goals, a scientific evaluation of our current viral testing process and policy is vital to ensure safe and financially sustainable care in the future.

1.7 Study Hypothesis and Objectives

To address the knowledge gaps identified above, the overall objective of this thesis project is to understand how our current process for testing hospitalized adult patients for respiratory viral infection impacts individual outcomes (death, ICU admission, length of stay in hospital), use of hospital resources, and provision of isolation precautions to prevent infection transmission.

1. To describe the use of respiratory viral testing by NP swab and isolation practices in a tertiary care hospital
2. To determine the association between viral testing and use of hospital resources during hospital admission (laboratory tests, procedures, provision of isolation precautions, radiographic images, and antimicrobial prescriptions)
3. To determine the association between viral testing and important patient outcomes including in-hospital death, admission to the intensive care unit, and length of stay in hospital

Based upon clinical experience, we hypothesize that the current testing and isolation process for respiratory viral infections in hospitalized patients will not be associated with improvements in use of hospital resources, or individual patient outcomes. This study will not evaluate the impact of viral testing and isolation on infection transmission or the cost effectiveness of viral testing in the hospital environment.

Methods

2.1 Design and Setting

We conducted a large retrospective observational cohort analysis based at The Ottawa Hospital (TOH).

TOH is an adult academic hospital located in Ottawa, Ontario, Canada, with approximately 1100 inpatient beds. TOH is a tertiary care referral centre, providing care for 1.2 million patients in the Eastern Ontario region. It is comprised of 4 campuses which provide a combination of emergency, inpatient and outpatient care. The two main campuses which provide emergency and inpatient services are included in this study. The Ottawa Hospital Research Ethics Board approved the study protocol (Appendix A.2).

2.2 Population Inclusion Criteria

We included hospital admissions (also referred to as encounters) for adult patients (greater than 18 years) admitted from the Emergency Department (ED) with a presenting complaint of cough and/or fever and/or shortness of breath. Encounters were included if they were admitted after January 1^{st}, 2004 and discharged before December 31^{st}, 2012. Patients receiving treatment in the ED for respiratory complaints and not requiring immediate subsequent hospitalization were excluded. Patients transferred di-

Table 2.1: Description of secondary outcome variables.

Outcome Variable	**Description**
Antibiotic Prescriptions	At least one prescription of oral or intravenous antibiotics recorded during admission
Antiviral Prescriptions	At least one prescription of an antiviral recorded during admission (Oseltamivir or Zanamivir only)
Chest Radiographs & Computed Tomography	At least one chest radiograph or computed tomography scan performed during the admission to hospital
Blood Culture & Sputum Culture	At least one blood and sputum culture performed during the admission
Bronchoscopy	Bronchoscopy procedure performed during admission to hospital
Isolation Precautions	Isolation precautions applied during admission to hospital, including droplet, airborne, and general isolation precautions for infection control
Duration of Isolation Precautions	Number of days the patient remained under isolation precautions in hospital, based upon information entered in the patient registration system

rectly to TOH for admission from other institutions were also excluded. The individual hospital encounter was the unit of analysis.

2.3 Outcomes

The primary outcome in this study was inpatient mortality.

Secondary outcomes included admission to the intensive care unit (ICU) and length of stay in hospital. Other secondary outcomes along with their definitions are described in Table 2.1.

2.4 Data Sources: The Ottawa Hospital Data Warehouse

The OHDW is a relational database containing information from several of TOHs most important operational information systems.[51] These include the patient registration system, the clinical data repository (containing laboratory, pharmacy, radiology, and clinical notes), and the discharge abstract database.[51] Data from the operational systems are loaded into the OHDW on a daily basis. Extensive assessments of data quality were performed during the development of the DW and are executed routinely as new data are loaded. The OHDW encompasses TOH hospitalization data from 1996 to present.

The OHDW is divided into 4 main entities describing individual patient, encounter, service, and facility variables as they relate to a hospitalization. Within each entity is a series of connected tables. For example, the tables stored within the service entity contain radiology, pharmacy, report transcription, and laboratory data pertaining to a hospitalization. The organization and linkage of tables is demonstrated in Figure 2.1.

Each OHDW table contains unique patient or encounter numerical identifiers that enable users to link variables between tables to retrieve data associated with a patient encounter.

The main tables accessed for this study include the Patient, Encounter, Service, and Facilities tables. In several cases, we cross referenced variables obtained from the OHDW with information stored in TOHs electronic medical record to ensure accuracy and completeness of the data.

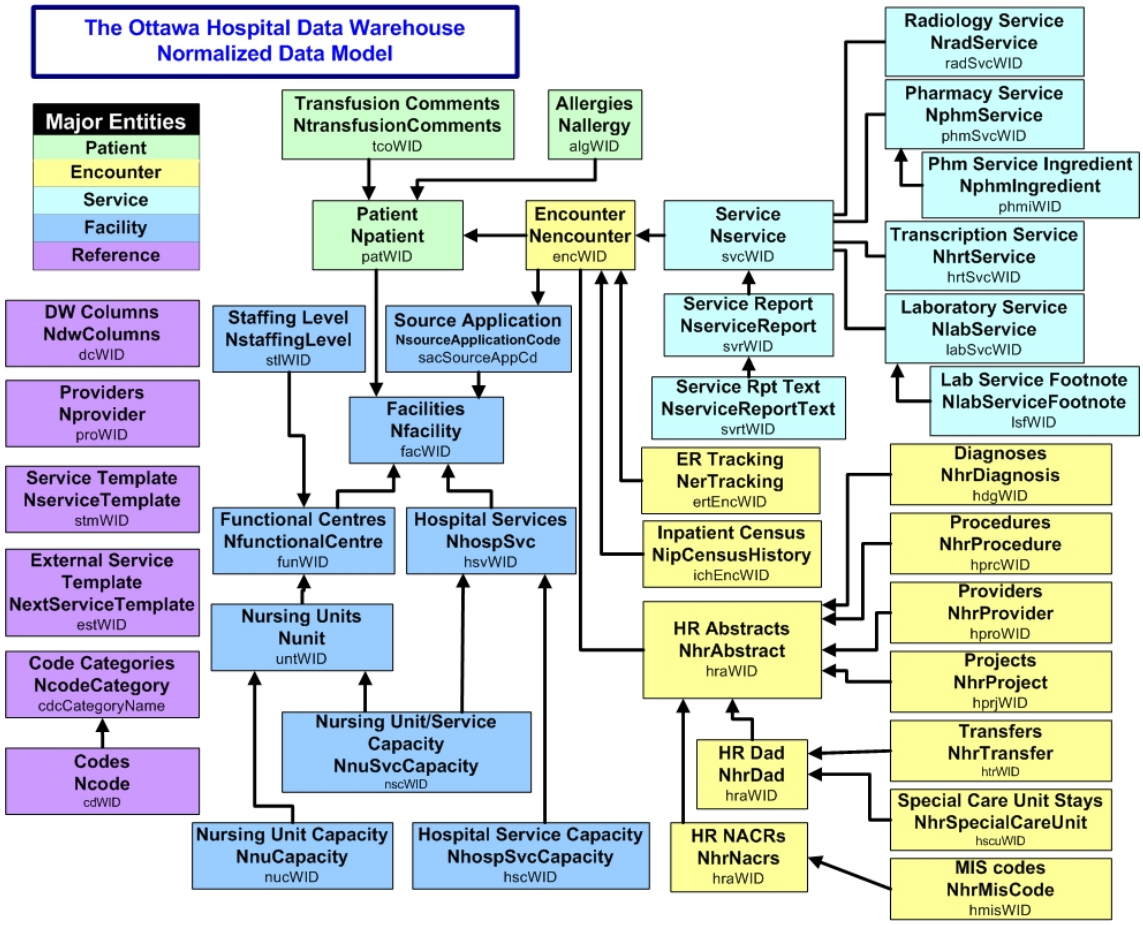


Figure 2.1: Schematic representation of The Ottawa Hospital Data Warehouse demonstrating the relationship of main entities and sub-sub-entities. Tables connected by an arrow are linked by numerical patient or encounter identifiers. The arrows represent the relationship of table keys.

2.5 Creating the Analytical Dataset

In order to extract, clean, and sort data from the OHDW I developed a computer program using the Statistical Analysis Software (SAS) (version 9.2) programming language. I used this program to identify hospitalizations meeting the inclusion criteria and developed additional programs to find and link study variables and outcomes with their associated hospitalizations. This process is described in detail below. Appendix A.3 contains the

data dictionary for all variables collected and analyzed in this study.

2.5.1 Identifying Relevant Hospital Encounters

Using the Encounter and Abstract tables, I identified all adult emergency department encounters that occurred between January 1^{st}, 2004 and December 31^{st}, 2012. From this group, I used a variable describing ED disposition status to select encounters where patients were admitted to hospital (n = 393,612 encounters). Among these encounters, I used an automated text search algorithm to determine which patients presented with fever, and or cough, and or shortness of breath, based upon their documented presenting complaint in the ER Tracking table (n = 24,567 encounters). This formed our baseline dataset of hospitalizations.

Using the unique encounter identification numbers we selected patient demographics (age at the time of admission, and gender), death status, admission to intensive care, length of stay (days), and admission and discharge dates from the Abstract and Encounter tables. We linked these variables to the dataset of hospitalizations to form our base dataset.

2.5.2 Identifying NP Swab Records

Using the Service table, the code for NP swab tests was identified and cross referenced with the electronic medical record to ensure the code accurately represented a viral respiratory test. I searched for all encounters in the base dataset during which an NP swab was performed. Given that the swab could have been performed just prior to admission, while the patient was in the ER, I created an admission *window* to account

for the 24 hour period prior to admission. I searched for NP swabs performed in this 24 hour window and during the hospitalization to ensure complete data capture. I linked the NP swab code to the Service Report table to obtain the full text report of the NP swab result (as it would appear in the electronic medical record). The text reports were then linked to the base dataset.

2.5.3 Categorizing NP Swab Results

I developed a unique text search algorithm to identify key words in the NP swab reports that would identify the swab as *Positive*, *Negative*, or *Unsuitable*. Unsuitable NP swab specimens were those that could not be tested due to a technical problem with the way a swab was collected, stored, or transported (for example: unsuitable transport media or incorrect labelling). We manually reviewed 500 NP swab reports to validate the performance of the text search algorithm on NP swabs between 2004 and 2012. We ran the algorithm on our baseline dataset and created the variable *swab status* to describe encounters where a swab was performed, and *swab result* to describe the results of the swab as positive (1) or negative (0).

2.5.4 Measuring Patient Co-morbidity: Elixhauser Score and Kaiser Permanente Inpatient Risk Adjustment Methodology

We used two main measures of adult inpatient co morbidity in this study: the Elixhauser comorbidity summary score and the Kaiser Permanente mortality risk.[52–54]

The Elixhauser summary score is a validated scoring system which summarizes comorbid

illness and can predict the patients risk of death in hospital.[52] It was derived and validated using data from TOH, and was based upon the original 30 comorbidity diagnosis groups in the Elixhauser comorbidity classification system.[1,52] Appendix A.4 shows the 30 Elixhauser comorbidity groups.[1] The Elixhauser summary score ranges from a minimum of -19 to +89, which is associated with a 0.37% and 99.41% risk of in-hospital death, respectively.[52] We obtained the relevant Elixhauser baseline comorbidities for each encounter from the Abstract table in the OHDW and applied the validated Elixhauser scoring system to obtain the summary score. This summary score was used to adjust for confounding based upon severity of illness at time of admission to hospital.

Secondly, I determined the baseline risk of death for each encounter using a validated model which incorporates patient data available at the time of admission. The model was initially derived and internally validated by Escobar and colleagues, and subsequently externally validated by van Walraven and colleagues using data from The Ottawa Hospital.[53,54] This model accounts for patient age, gender, urgency of admission, admitting service (medical or surgical), illness severity based on laboratory values, admission diagnosis, and chronic Elixhauser comorbidities.[53,54] I extracted the required variables for this model from the OHDW and ran the model to determine the baseline risk of in-hospital death for each encounter in the dataset.

2.5.5 Defining Influenza Season

Using the admission and discharge dates, we flagged each hospital encounter which occurred during an influenza season. We used data from FluWatch Canada, a national influenza surveillance program, which identified influenza season to be October to April inclusive.[55] For the 2009 pandemic influenza season, we categorized the influenza season

to include both waves of the pandemic in April to August 2009, and September 2009 to February 2010.[55]

2.5.6 Identifying Isolation Precautions for Infection Control

When a patient in hospital is placed under isolation precautions their status is updated in the electronic patient information system (SMS) to reflect the use of isolation. Using the Encounter and Inpatient Census tables the in the OHDW, we identified isolation codes for general isolation precautions, droplet, airborne, and contact precautions for all encounters in our baseline dataset. Encounters were flagged as *1* or *0* based upon their isolation status in hospital. The translation of these codes from SMS to the OHDW repository was reviewed and confirmed with a health records analyst at TOH to ensure accurate representation of isolation status in the OHDW.[56]

To determine the duration of isolation precautions, I identified the date and time at which the first isolation code was applied for each encounter. I calculated the time (in seconds) until the code was changed to reflect a non-isolation status, and accounted for multiple periods of isolation use in this calculation. The value was transformed to reflect the number of days under isolation precautions.

2.5.7 Collecting Process of Care Variables

I developed a coding algorithm to extract the required process of care variables for all encounters in the dataset. The same algorithm was applied to the Service, Diagnosis, Radiology, and Pharmacy tables to obtain variables of interest. Variables of interest included white blood cell counts, neutrophil counts, chest radiographs, computed to-

mography scans, bronchoscopies, and antibiotic and antiviral prescriptions.

We limited our selection of antimicrobials to those that would be appropriate for a respiratory bacterial or fungal infection, and the final list of antibiotic types and routes of administration were reviewed electronically and manually to ensure the capture of the appropriate data. With regard to antiviral medications, we searched only for Oseltamivir and Zanamivir, as we felt these to be the most relevant antiviral medications.

2.5.8 Identifying Encounters with Pulmonary Infections for Post-Hoc Subgroup Analysis

Using the Abstract table, I obtained the most responsible discharge diagnosis for all encounters in the dataset. This yielded 1402 unique diagnoses. All diagnoses were manually reviewed to obtain those related to a pulmonary infection or exacerbation ($n = 75$). The list of selected ICD-10-CM codes is presented in Appendix A.5.

A subset of our original dataset was created to include encounters with a discharge diagnosis related to a pulmonary infection or exacerbation. A post-hoc analysis (Section 2.6) was performed on this dataset.

2.6 Analysis

All analyses for this study were conducted using SAS software, Version 9.2 of the SAS System for Windows.

The unit of analysis in this study was the hospital encounter. Study variables were compared between encounters with and without an NP swab, and between those with

positive and negative swab results. The difference of means and standard deviations (SD) for continuous variables were analyzed using a one-way analysis of variance test (ANOVA). Differences between proportions for binary variables were compared using a chi-squared test. All p-values were considered significant at a level of $p < 0.05$.

2.6.1 Primary Analysis: NP Swabs and Death, ICU Admission, Length of Stay In Hospital

We used unadjusted and adjusted logistic regression modelling to investigate the association between having an NP swab in hospital (NP swab status), and death and ICU admission.

We used univariate and multivariate linear regression with transformation to determine the change in length of stay in hospital when an NP swab was performed during the encounter. A description of model building strategies is described below.

2.6.2 Adjusted Logistic Regression Modelling

Selection of Candidate Variables

We selected candidate variables for the logistic regression models based upon their significance in univariate association with the outcomes (death and ICU admission). Significance was confirmed if the confidence interval around the odds ratio did not include a value of 1, and if the p-value associated with the parameter estimate for each variable was $p < 0.05$.

Investigation for Effect Modification and Confounders

Based upon clinical plausibility, I determined a list of variables *a-priori* which could potentially modify the relationship between NP swab status and the outcome. All pre-selected variables were tested for effect modification using an interaction term with NP swab status. If an interaction term was significant (parameter estimate p-value < 0.05, it was kept in the adjusted model to account for effect modification.

We also generated a list of potential confounding variables *a-priori*. Variables were considered to be confounders if they met three criteria. First, the confounder must have a significant association with the dependent variable. To test this, the candidate multivariate logistic regression model was run with the confounder variable as an independent variable. If the parameter estimate was significant ($p > 0.05$), the confounding variable met the first criteria. Secondly, the confounder must have a significant association with the independent variable of interest, in this case, NP swab status. I tested this by running a multivariate regression model with the confounding variable as the dependent variable, and NP swab status as the independent variable. Finally, the parameter estimate of the main predictor had to change by at least 10% when the confounder was removed from the model. We determined this by comparing the parameter estimate for NP swab status in a model with and without the confounding variable. We then used the following calculation:

$$n = \frac{full\,model\,parameter\,estimate - partial\,model\,parameter\,estimate}{full\,model\,parameter\,estimate} \tag{2.1}$$

In Equation 2.1, if $n \geq 10\%$, the third criterion for a confounder variable was satisfied.

Examination for Collinearity

We created a Pearson correlation matrix of all candidate variables, including confounders and effect modifiers, to address the issue of collinearity. We determined *a-priori* that a Pearson correlation coefficient greater than 0.7 would represent significant collinearity. Any two candidate variables meeting this criteria were examined in a univariate and multivariate model to determine their relationship with the dependent variable. If one collinear variable became insignificant in the multivariate model, we decided to drop the insignificant variable, unless it was a statistical or clinically important confounder.

Variable Selection Methods

Once all candidate variables including confounders and effect modifiers were included in the multivariate model, we used forwards, backwards, and stepwise variable selection techniques to create the final model. The main predictor (NP swab status) and confounders were kept in the model prior to application of variable selection. The final model was chosen based upon the variable selection technique that yielded the most parsimonious model.

Goodness of Fit Tests

We used the receiver operating characteristic curve and the c-statistic as a *goodness of fit* measure for the final adjusted regression model. The c-statistic provides a measure of how well the model discriminates between the encounters with and without the outcome. We considered a c-statistic of ≥ 0.7 as acceptable model discrimination. We did not use the Hosmer-Lemeshow or Likelihood Ratio tests in this analysis.

2.6.3 Adjusted Linear Regression Modelling

Linear regression modelling was used to investigate hospital length of stay when an NP swab was performed. We ran both a univariate and multivariate model to determine the change in length of stay (days) when an NP swab was performed.

Transformation of the Outcome

One assumption of linear regression is that the dependent variable is normally distributed. To evaluate our data against this assumption, I created a histogram to demonstrate the distribution of length of stay. I used several mathematical transformations, including the natural logarithm function, to determine the transformation that produced the least skewed distribution. The transformed outcome variable was used as the dependent variable in the model.

Creating the Adjusted Model

Candidate variables for the multivariate model were chosen based on clinical significance and statistical association in univariate analysis with the outcome. I ran the candidate model with a selection procedure that maximized the adjusted r^2 value in the final adjusted model.

Model Diagnostics

To test the assumptions of linear regression modelling, we created a boxplot of studentized residual values against the independent variable categories, examined the distribu-

tion of studentized residual values with a histogram, and created a quantile-quantile plot of observed versus expected values for the model.

The boxplot of residual values against the independent variable (swab status) tests the linear model assumption of homoscedasticity, which states that the *error* in the model has a constant variance. The *error* in the model refers to the portion of the dependent variable that is not explained by the independent variable. If the boxplot demonstrated an equal distribution across both categories of the independent variable, we were satisfied that there was no significant heteroscedasticity present.

The histogram of studentized residual values tested the assumption that the *error* in the model has a normal distribution.

The quantile-quantile plot of the observed versus expected values in the model also addressed the model assumption of normality in the *error*. If there were no serious deviations from a linear relationship in the quantile-quantile plot, we felt this assumption was satisfied.

2.6.4 Secondary Analysis: NP Swab Results and Death, ICU Admission and Length of Stay In Hopsital

Using the primary analytical dataset, I created a subgroup of encounters where NP swabs were performed. Within this subgroup, encounters with a positive and negative NP swab result were compared on multiple factors including patient demographics, comorbidities, process of care variables, and outcomes. Differences in means and proportions were compared using the same statistical tests as used in the primary analysis.

We used logistic and linear regression analyses to determine the association between NP

swab result (positive versus negative), and death, ICU admission and length of stay. The model building strategies and model diagnostics were the same as used in the primary analysis.

2.6.5 Post-Hoc Analysis

As described above, a subgroup of encounters was created from the analytical dataset to represent a diagnosis of pulmonary infection or exacerbation.

Amongst this subgroup, I conducted an identical analysis to that of the primary analysis. We compared means and proportions of study variables, and determined the association between NP swab status and death, ICU admission, and length of stay. This analysis was conducted in a post-hoc fashion, and was not planned *a-priori*.

Results

3.1 Study Cohort Characteristics

3.1.1 Demographics

During the 8 year study period between January 1^{st}, 2004 and December 31^{st}, 2012, we identified 24,567 hospital admissions from the emergency room of adult patients with a chief presenting complaint of fever *and/or* cough *and/or* shortness of breath. These hospital admissions represented 17,327 unique patients. An NP swab was performed in 2722/24,567 admissions (11%). Baseline characteristics of the study cohort are described in Table 3.1. The mean and standard deviation (SD) of patient age in the study cohort was 67.5 ± 17.3 years. The mean age among admissions where an NP swab was done was statistically younger when compared with admissions where no swab was done ($p < 0.001$). Among hospital admissions where an NP swab was done, 52.2% were female (1420/2722), which was a statistically larger proportion compared with the admissions where no NP swab was done ($p = 0.023$). The largest number of admissions took place in 2011 (3269 admissions, 13.3%), while the least occurred in 2004 (1882, 7.7%). The majority of hospital admissions (61.8%) occurred during influenza season, as defined above.

3.1.2 Description of Patient Comorbidities

Table 3.1 shows the mean (± SD) baseline probability of death among all hospitalizations was 0.14 (± 0.15), or 14%. This was not significantly different between hospital admissions where an NP swab was and was not performed ($p = 0.65$). The individual Elixhauser comorbidities and Elixhauser Scores in the study cohort are shown in Appendix B.1. A total of 5553 admissions (22.6%) scored in the highest quartile of elixhauser scores. The proportion of admissions in the third and fourth quartile of elixhauser scores was significantly less in the group with an NP swab ($p < 0.001$), demonstrating less comorbidity burden among the hospital admissions where an NP swab was done. With regards to individual comorbidities there was significantly less congestive heart failure ($p < 0.001$) and significantly more chronic pulmonary disease ($p < 0.001$) among the hospital admissions where an NP swab was done.

3.1.3 Process of Care: Use of Laboratory, Radiology, Antimicrobial Prescriptions, and Procedures

Process of care variables are shown in Table 3.2. Antibiotics and Oseltamivir were administered during 18,232 (74.2%), and 569 (2.3%) of hospital admissions, respectively. Blood cultures and chest radiographs were performed in half of the hospitalizations (53.6%, 49.9%, respectively), while CT scan of the chest was completed in 19.3% of hospitalizations. Among hospital admissions during which an NP swab was performed, patients received statistically more antibiotics, antivirals, blood cultures, sputum cultures, bronchoscopies, computed tomography scans of the thorax, and chest radiographs ($p < 0.001$).

Table 3.1: Baseline characteristics of hospital admissions for respiratory symptoms between 2004 and 2012. $n = 24{,}567$ hospitalizations

Variable	**No Swab**	**NP Swab**	**Total**	**P-Value**
Age (mean ± SD)	67.7 ± 17.14	65.99 ± 18.31	67.48 ± 17.28	<0.001
Female N (%)	10,891 (49.9%)	1420 (52.2%)	12,311 (50.15)	0.023
Year 2004	1818 (8.3%)	64 (2.4%)	1882 (7.7%)	<0.001
2005	2328 (10.7%)	186 (6.8%)	2514 (10.2%)	
2006	2226 (10.2%)	119 (4.4%)	2345 (9.5%)	
2007	2284 (10.5%)	263 (9.7%)	2547 (10.4%)	
2008	2391 (10.9%)	319 (11.7%)	2710 (11.0%)	
2009	2408 (11.0%)	767 (28.2%)	3175 (12.9%)	
2010	2637 (12.1%)	303 (11.2%)	2940 (12.0%)	
2011	2849 (13.0%)	420 (15.4%)	3269 (13.3%)	
2012	2904 (13.3%)	281 (10.3%)	3185 (13.0%)	
Influenza Season N (%)	12,958 (59.3%)	2221 (81.6%)	15,179 (61.8%)	<0.001
Risk of Death (mean ± SD)	0.14 ± 0.15	0.14 ± 0.14	0.14 ± 0.15	0.65

Table 3.2: Laboratory, prescription, radiology, and procedure use among hospitalizations with and without a NP swab. Statistical differences in categorical variables were computed using the chi-squared test.

Variable	**No Swab** $n = 21{,}845$	**Swab** $n = 2722$	**Total** $n = 24{,}567$	**P-Value**
Antibiotics	15,631 (71.6%)	2601 (95.6%)	18,232 (74.2%)	<0.001
Antiviral	98 (0.4%)	471 (17.3%)	569 (2.3%)	<0.001
Blood Cultures	11,011 (50.4%)	2153 (79.1%)	13,164 (53.6%)	<0.001
Sputum Cultures	4091 (18.7%)	1146 (42.1%)	5237 (21.3%)	<0.001
Bronchoscopy	631 (2.9%)	167 (6.1%)	798 (3.2%)	<0.001
CT Thorax	4071 (18.6%)	682 (25.1%)	4753 (19.3%)	<0.001
Chest Radiograph	10,743 (49.2%)	1522 (55.9%)	12,265 (49.9%)	<0.001

Table 3.3: Description of laboratory, prescription, radiology, and procedure use among hospitalizations with a positive and negative NP swab result. Statistical differences in categorical variables were computed using the chi-squared test.

Variable	**Negative Swab** $N = 2302$	**Positive Swab** $N = 420$	**Total** $N = 2722$	**P-Value**
Antibiotics	2204 (95.7%)	397 (94.5%)	2601 (95.6%)	0.265
Antiviral	305 (13.2%)	166 (39.5%)	471 (17.3%)	<0.001
Blood Cultures	1813 (78.8%)	340 (81.0%)	2153 (79.1%)	0.309
Sputum Cultures	979 (42.5%)	167 (39.8%)	1146 (42.1%)	0.291
Bronchoscopy	147 (6.4%)	20 (4.8%)	167 (6.1%)	0.202
CT Thorax	599 (26.0%)	83 (19.8%)	682 (25.1%)	0.006
Chest Radiograph	1293 (56.2%)	229 (54.5%)	1522 (55.9%)	0.532

Table 3.3 also describes process of care variables stratified by the NP swab result ($n = 2722$ hospitalizations). When comparing hospitalizations with a positive and negative NP swab, there was no statistical difference in the use of antibiotics, blood cultures, sputum cultures, bronchoscopy, or chest radiographs (all $p < 0.05$). There was however, more Oseltamivir use among encounters with a positive NP swab ($p < 0.001$), and less use of computed tomography scans ($p = 0.006$).

3.1.4 NP Swabs, Respiratory Viruses, and Isolation for Infection Control

A total of 2722 NP swabs were completed at The Ottawa Hospital during the study period, with 420 positive NP swabs (15.4%) identifying a respiratory virus. Figure 3.1 demonstrates the trend in absolute number of swabs per year during the study period at The Ottawa Hospital. Figure 3.2 demonstrates the proportion of positive NP swabs performed annually at The Ottawa Hospital.

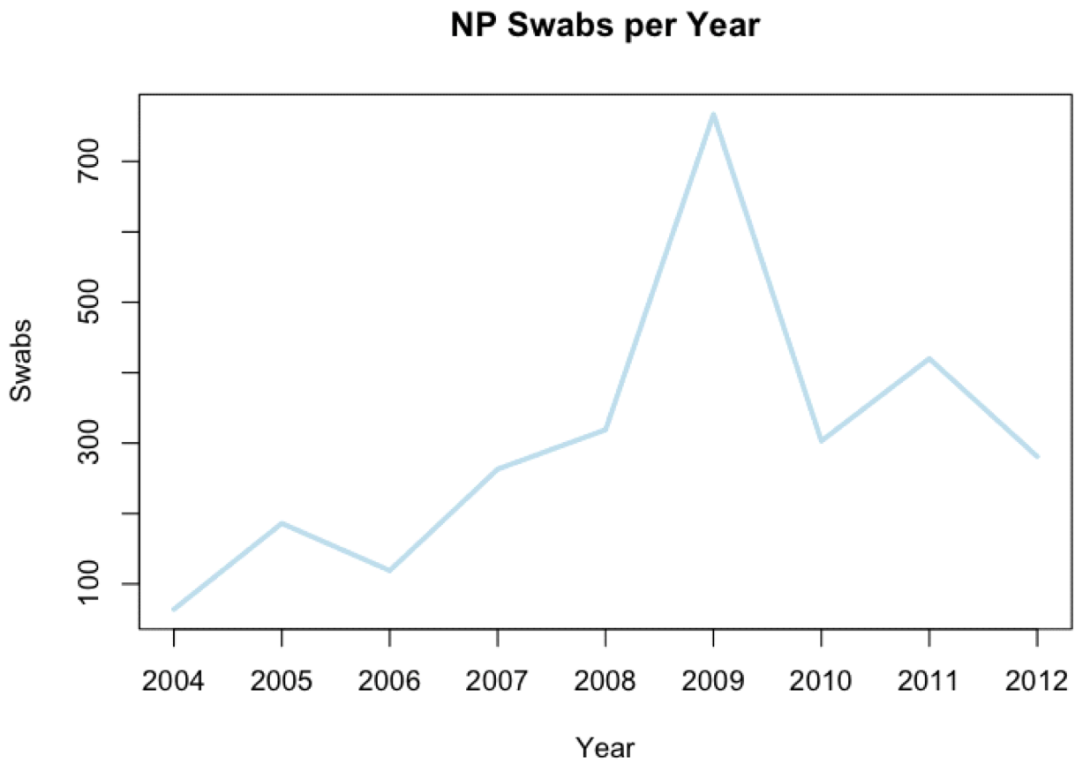


Figure 3.1: Proportion of positive NP swabs completed annually at The Ottawa Hospital. The peak in number of NP swabs during 2009 was due to the H1N1 influenza pandemic.

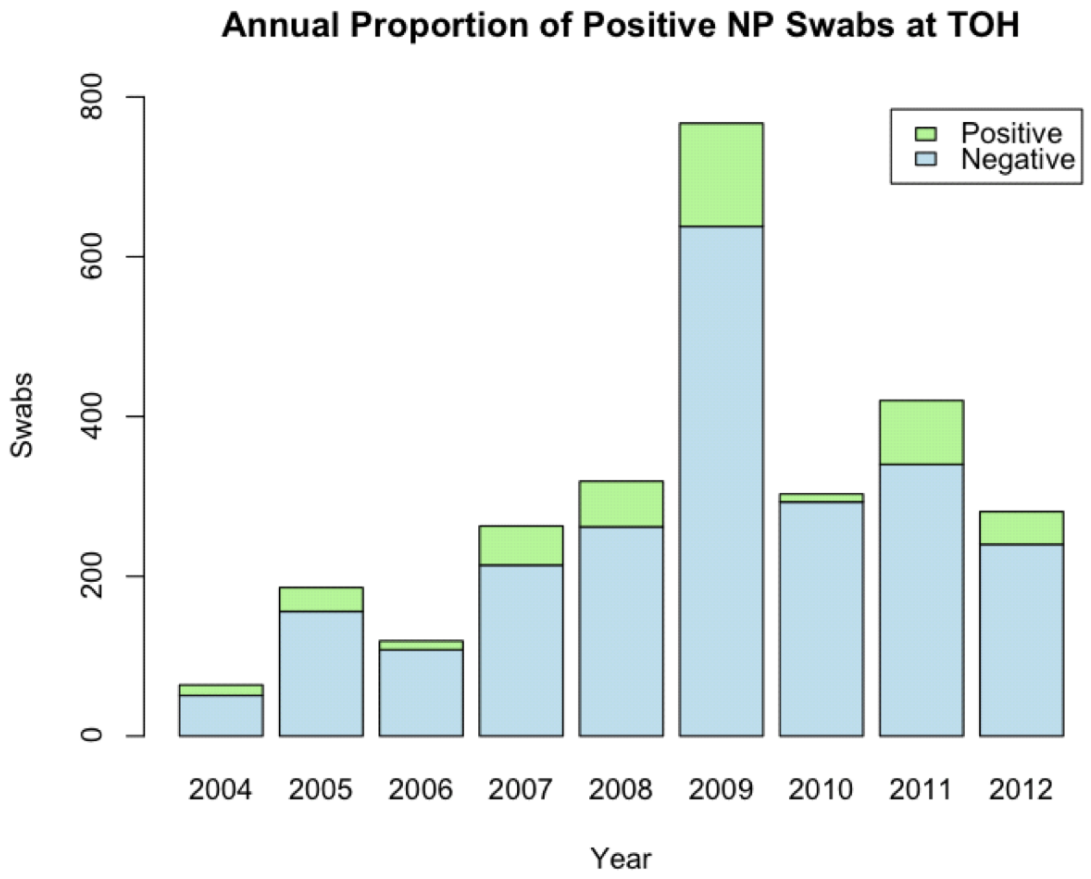


Figure 3.2: Proportion of positive and negative NP swabs per year at The Ottawa Hospital between 2004 and 2008. The mean number of swabs performed per year is 303.

Overall, 30.5% (7487/24,567) of hospital encounters had isolation precautions for infection control during the course of hospitalization (Table 3.4). Isolation precautions were used in 87.8% (2389/2722) of encounters where an NP swab was done, and 23.3% (5098/21, 845) of hospital encounters without an NP swab. The mean ($\pm$ SD) number of days under isolation precautions was 1.79$\pm$6.79 days in the study cohort. The hospitalizations receiving an NP swab had a statistically longer period of isolation (4.79$\pm$7.35 days) when compared to the admissions without an NP swab (1.41 ± 6.63), $p < 0.001$.

Table 3.4: Description of hospital outcomes among patients hospitalized for cough, and/or shortness of breath, and/or fever between 2004 and 2012. Differences of means for continuous variables were computed with the ANOVA test, and differences in categorical variables were computed using the chi-square test. [a]ICU admission occurred anytime during hospitalization. [b]Isolation precautions refer to droplet, airborne, or contact isolation precautions.

Variable	**No NP Swab** $n = 21{,}845$	**NP Swab** $n = 2722$	**Total**	**P-Value**
Death	2271 (10.4%)	279 (10.2%)	2550 (10.4%)	0.814
ICU Admission[a] (mean ± SD)	1590 (7.3%)	417 (15.3%)	2007 (8.2%)	<0.001
Days in ICU (mean ± SD)	7.60 ± 9.79	11.30 ± 12.99	8.37 ± 10.64	<0.001
Hospital Isolation[b]	5098 (23.3%)	2389 (87.8%)	7487 (30.5%)	<0.001
Days Under Isolation (mean ± SD)	1.41 ± 6.63	4.79 ± 7.35	1.79 ± 6.79	<0.001
Hospital Length of Stay (mean ± SD)	9.52 ± 14.97	11.68 ± 21.64	9.76 ± 15.86	<0.001

3.2 Description of Outcomes in Study Cohort

Table 3.4 describes the relevant hospital outcomes, stratified by NP swab status. There was no statistical difference in in-hospital mortality in those patients who had NP swabs compared to patients who were not tested with NP swabs (10.4% vs 10.2% in-hospital mortality respectively, $p = 0.81$). However, hospital encounters where an NP swab was performed had statistically more ICU admissions (15.3% vs 7.3%, $p < 0.001$), longer duration of ICU admission (11.3 days vs 7.6 days, $p < 0.001$), greater use of isolation precautions (87.8% vs 23.3%, $p < 0.001$), longer duration of isolation (4.8 days vs 1.4 days, $p < 0.001$), and longer length of stay in hospital (11.7 days vs 9.5 days, $p < 0.001$) compared with admissions where an NP swab was not done.

3.3 Primary Analysis: Association between Use of an NP Swab and Death, ICU Admission, and Length of Stay

Table 3.5 demonstrates the results of univariate and multivariate logistic regression analysis describing the association between use of an NP swab during hospitalization and death, and ICU admission. Table 3.6 demonstrates the results of univariate and multivariate linear regression analysis describing the change in length of stay in hospital when an NP swab is performed. These results are described in detail below.

Variables in the adjusted model for Death include: *Swab status, baseline risk of death, admission during influenza season, isolation status, age, antibiotic use, antiviral use,*

chronic pulmonary disease, metastatic cancer, solid tumor without metastasis, and complicated diabetes

Variables in the adjusted model for ICU admission include: *Swab status, isolation status, isolation status* x *swab status (interaction term), baseline risk of death, admission during influenza season, age, antibiotic use, antiviral use, chronic pulmonary disease, renal disease, metastatic cancer, complicated diabetes*

Table 3.5: Odds of Death and ICU admission among adult hospitalizations where an NP swab was performed. [a]There was a significant interaction term between isolation status and NP swab status in the regression model predicting ICU Admission.

Unadjusted

Outcome	β **Coefficient**	**Odds Ratio (95% CI)**
Death	-0.016	0.98 (0.86 – 1.12)
ICU Admission	0.840	2.31 (2.05 – 2.59)

Adjusted

Outcome	β **Coefficient**	**Odds Ratio (95% CI)**
Death	-0.110	0.90 (0.76 – 1.06)
ICU Admission		
Effect of NP Swab[a]	0.803	2.23 (1.609 – 3.098)
Effect of Swab and Isolation[a]	0.421	1.523 (1.30 – 1.79)
Effect of Isolation[a]	0.365	1.440 (1.283 - 1.616)

Table 3.6: Unadjusted and Adjusted Linear Regression Analyses Predicting Length of Stay in Hospital based upon NP Swab Status during Hospitalization. Model including deaths (n = 24,567) and excluding deaths ($n = 22,017$) are presented. The adjusted r^2 values for the multi-variate model are 0.1289, and 0.1528 respectively. 95% confidence intervals are calculated by 2 times the standard error of the parameter estimate. LOS is Length of Stay.

Unadjusted

LOS	**Estimate**	$e^{Estimate}$	**P-Value**
(inc. deaths)	0.19918	1.22 (1.17 - 1.27)	<0.0001
(ex. deaths)	0.16483	1.179 (1.13 – 1.23)	<0.0001

Adjusted

LOS	**Estimate**	$e^{Estimate}$	**P-Value**
(inc. deaths)	-0.01314	0.99 (0.95 – 1.03)	0.5455
(ex. deaths)	-0.04255	0.96 (0.92 - 1.00)	0.0536

3.3.1 Association between use of the NP Swab and Hospital Mortality

Univariate analysis (n = 24,567 hospitalizations) demonstrated no significant association between having an NP swab in hospital and death (odds ratio: 0.984; 95% CI: 0.863, 1.12).

Variables for the multivariate logistic regression model were chosen based upon clinical relevance and univariate association with death. They are shown in Appendix B.2. Testing for effect modification between NP swab status and isolation status, age, baseline risk of death, and antibiotic prescriptions was non-significant. Baseline risk of death, and isolation status in hospital were identified as statistically significant confounders. Admission during influenza season was not a statistical confounder, but this variable was kept in the model as it represented a clinically important confounder. No significant collinearity between candidate variables was identified (no pearson correlation coefficient

Table 3.7: Final adjusted logistic regression model output describing the association between having a NP swab in hospital and death. The last four items present the Elixhauser comorbidities.

Variable	**Odds Ratio (for Death)**	**95% Confidence Interval**
Swab Done (Yes vs No)	0.896	0.756 – 1.061
Age at Admission	1.014	1.010 – 1.017
Admitted during Flu Season	1.037	0.943 – 1.140
Isolation during Admission	1.052	0.943 – 1.174
Baseline Risk of Death	1.063	1.060 – 1.066
Antibiotics Given (Y vs N)	1.362	1.179 – 1.490
Antiviral Given (Y vs N)	1.694	1.267 – 2.265
COPD	0.880	0.796 - 0.972
Solid Tumor (no metastases)	1.388	1.203 – 1.601
Metastatic Cancer	1.220	1.036 – 1.437
Diabetes with Complications	0.635	0.563 – 0.716

≥ 0.7).

Backwards, forwards, and stepwise variable selection methods were performed on the candidate model, which specified inclusion of the NP swab status, isolation status, baseline risk of death and admission during influenza season. The results of variable selection methods are shown in Appendix B.2. The stepwise regression model was most parsimonious, and was chosen as the final adjusted model. Table 3.7 describes the odds ratio and 95% confidence intervals for the final adjusted model.

In the final multivariate logistic regression model, the odds of death during encounters where an NP swab was performed were 10.4% less when compared to encounters where an NP swab did not occur (odds ratio: 0.896; 95% CI: 0.756, 1.061), however this was not significant. The c-statistic for the final model was 0.821, suggesting excellent model discrimination. The receiver operating characteristic curve is shown in Figure 3.3.

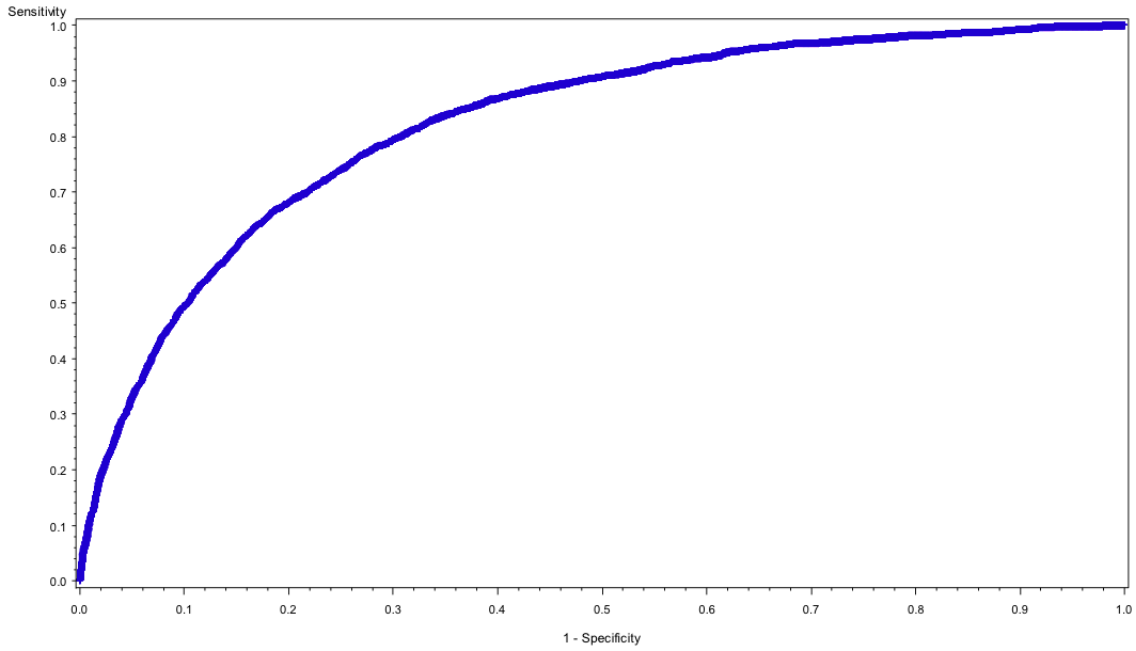


Figure 3.3: Receiver Operating Characteristic curve for the final adjusted logistic regression model describing the association between NP swab status in hospital and death. The c-statistic is 0.821, indicating *excellent* discrimination.

3.3.2 Association between use of the NP Swab and Admission to ICU

In univariate logistic regression analysis (n = 24,567 hospital encounters) the odds of ICU admission were 2.3 times greater during hospitalization if an NP swab was performed during the encounter (odds ratio: 2.31; 95% CI: 2.05, 2.59). This is described in Table 3.5.

Variables for the candidate multivariate regression model are shown in Appendix B.3.

During investigation for effect modification, a significant interaction term was identified between isolation status in hospital and NP swab status. Investigation for confounders

Table 3.8: Final multivariate model describing the association between having an NP swab and admission to ICU during hospitalization. There was a significant interaction term with NP swab status and isolation status in hospital.

Variable	**Adjusted Odds Ratio** (for ICU Admission)	**95% CI (Odds Ratio)**
Effect of NP Swab (No Isolation)	2.233	1.609 – 3.098
Effect of Isolation (No Swab)	1.440	1.283 – 1.616
Effect of Both (Swab and Isolation)	1.523	1.300 – 1.786
Baseline Risk of Death	1.062	1.058 – 1.065
Admit During Flu Season	0.919	0.829 – 1.019
Age	0.964	0.961 – 0.967
Antibiotic Prescription	3.764	3.132 – 4.523
Antiviral Prescription	3.054	2.432 – 3.834
COPD	1.224	1.102 – 1.359
Renal Disease	0.754	0.648 – 0.877
Metastatic Cancer	0.324	0.271 – 0.386
Diabetes with Complications	0.825	0.723 – 0.942

identified that the baseline risk of death, age, and admission during influenza season were not statistical confounders in the model. However, baseline risk of death and admission during influenza season were specified for inclusion in the model based on clinical relevance. No significant collinearity between predictor variables was identified (no pearson correlation coefficient > 0.7).

The results of backwards, forwards and stepwise variable selection are demonstrated in Appendix B.3. The model generated by stepwise regression was most parsimonious and chosen as the final multivariate model (Table 3.8).

In the final adjusted model, hospital encounters with an NP swab were 2.2 times more likely to have an ICU admission during hospitalization compared with encounters where an NP swab did not occur (odds ratio: 2.23; 95% CI: 1.61, 3.10).

Hospitalizations where an NP swab and isolation occurred together were 1.5 times more likely to have an ICU admission during the hospitalization (odds ratio: 1.52; 95% CI: 1.30, 1.79), while encounters with isolation precautions were 1.4 times more likely to

have an ICU admission during hospitalization (odds ratio: 1.44; 95% CI: 1.28, 1.61). The reference term for the interaction was an encounter where no NP swab and no isolation precautions occurred. The c-statistic for the final model was 0.783, suggesting acceptable model discrimination. The receiver operating characteristic curve is shown in Figure 3.4.

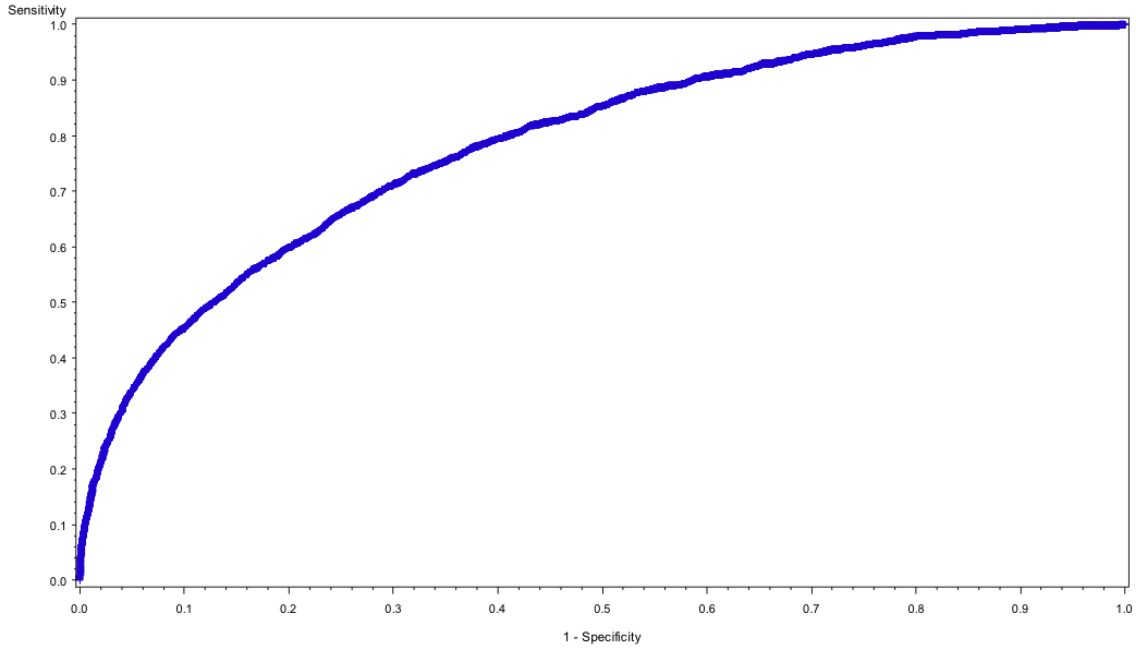


Figure 3.4: Receiver Operating characteristic curve for the adjusted logistic regression model describing the association between NP swab status and ICU admission. The C-Statistic is 0.783, suggesting *acceptable* discrimination.

3.3.3 Association between use of the NP Swab and Hospital Length of Stay

Univariate linear regression identified a significant increase in length of stay in hospital by 2.2 days when an NP swab occurred during the admission ($p < 0.0001$). The r^2

value for this model was 0.0018, or 0.18%, suggesting that only 0.2% of the variation in length of stay is explained by the model. However, the distribution of length of stay in hospital (days) was heavily right skewed (Figure 3.5) which violates the assumption of a normally distributed outcome variable in a linear regression model. A natural logarithm transformation of hospital length of stay was used in attempts to normalize the heavily right skewed distribution (Figure 3.6). Using the transformed length of stay variable, univariate linear regression demonstrates a 0.20 increase in the natural logarithm of length of stay. In other words, univariate linear regression showed a 1.22 day ($e^{0.19918}$) increase in length of stay when an NP swab was performed during admission ($p < 0.0001$) (Table 3.6). The r^2 value for this univariate model was 0.0038, or 0.38%.

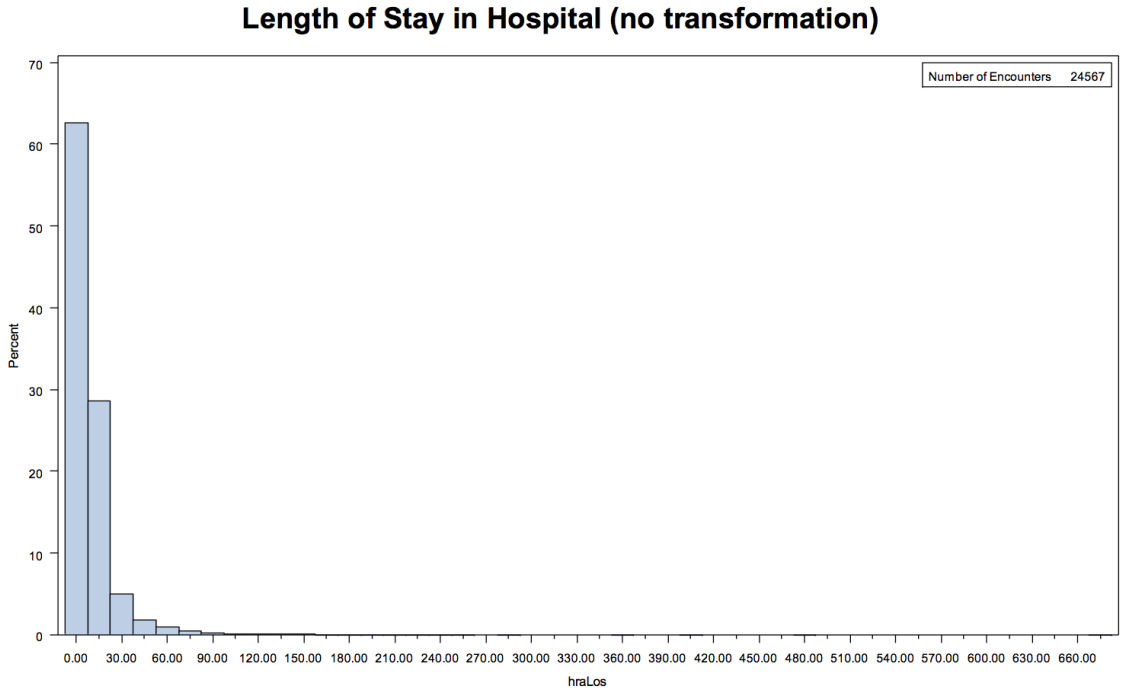


Figure 3.5: Distribution of the length of stay (days) in the study cohort (n = 24,567 encounters). This data is untransformed and is highly right skewed.

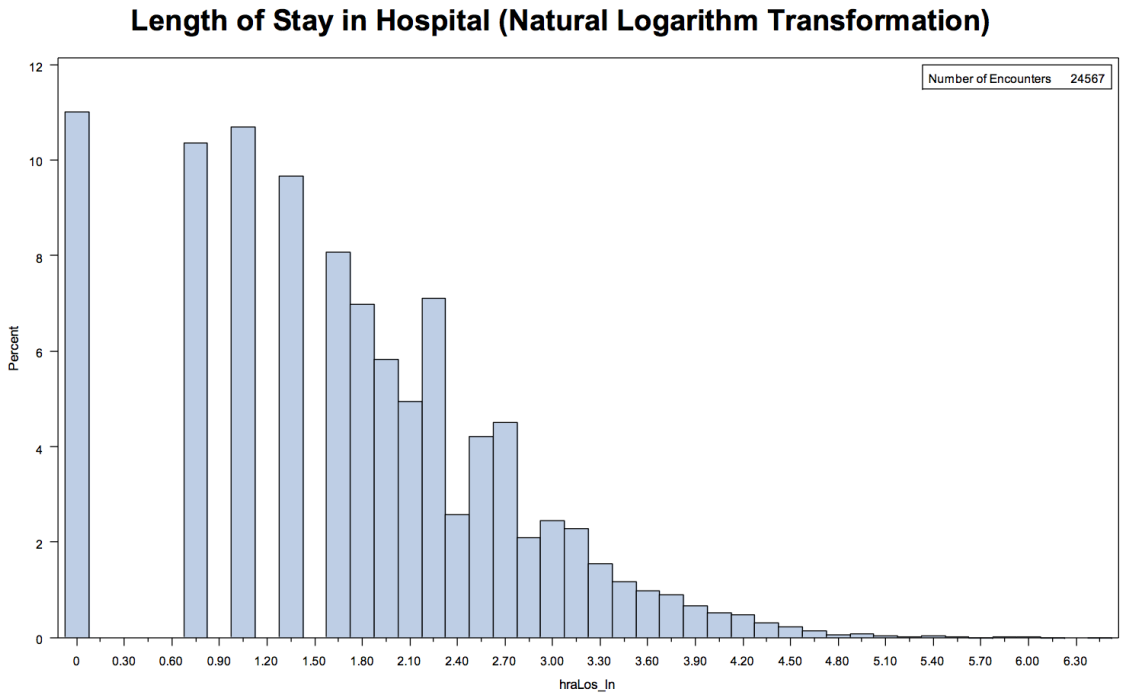


Figure 3.6: Distribution of the transformed length of stay (days) in the study cohort (n = 24,567 encounters). A natural logarithm transformation was used. The skewness is less severe when compared with the untransformed data.

In multivariate linear regression analysis, relevant candidate variables were tested in a univariate linear regression model with the transformed length of stay variable as the outcome (Appendix B.4). All candidate predictors were significantly associated with the natural logarithm of length of stay, except gender status and chronic pulmonary disease status. These two variables were removed from the candidate multivariate model.

From the candidate predictors identified through univariate association with the outcome, variables were selected for the multivariate model based upon the maximization of the adjusted r^2 value. Using this method, all candidate variables remained in the model with exception of antiviral prescriptions during hospitalization. In the final multivariate linear regression model, length of stay in hospital was increased by 1 day (95% CI: 0.95, 1.03)

Table 3.9: Multivariate linear regression model predicting the length of stay (Days) in hospital. There is a non significant increase in length of stay by one day (p=0.5455). Adjusted $r^2 = 0.13$.

Variable	**Estimate**	**Length of Stay** ($e^{Estimate}$)	**P Value**
NP Swab (Y vs N)	-0.01314	0.99	0.5455
Age	0.00510	1.01	<0.0001
Admission in Flu Season	0.04115	1.04	0.0011
Isolation in Hospital	0.18756	1.21	<0.0001
Baseline Risk of Death	0.00429	1.00	<0.0001
Antibiotic Prescription	0.43257	1.54	<0.0001
CHF	0.26872	1.31	<0.0001
Renal Disease	0.09349	1.10	<0.0001
Metastatic Cancer	0.24756	1.28	<0.0001
Cancer (No metastases)	0.08775	1.09	<0.0001
Diabetes with Complications	0.08381	1.09	<0.0001
ICU Admission	0.57309	1.77	<0.0001

when an NP swab was performed in hospital, but this was not statistically significant ($p = 0.55$). Results for all predictors in the final adjusted model are shown in Table 3.9. The adjusted r^2 value for this model was 0.1289, or 12.93%.

We ran the final multivariate model excluding all deaths from the study cohort ($n =$ 22,017). This analysis also found that length of stay increased by 1 day (95% CI: 0.92, 1.0) when an NP swab was performed in hospital, and this result was nearly significant ($p =$ 0.054). When deaths were excluded from the model, the adjusted r^2 value improved to 0.1528 (15.3%). This suggests that more of the variation in $ln(lengthofstay)$ is explained by the dataset excluding deaths. Results of the final multivariate model excluding deaths are presented in Table 3.10.

Diagnostic testing was performed on the final multivariate model to ensure there were no gross violations of linear regression assumptions. The models studentized residuals were calculated and plotted in a boxplot against the NP swab status (Figure 3.7). This demonstrated no significant skewness of the residual values. Distribution of the stu-

Table 3.10: Multivariate linear regression model predicting the natural logarithm transformed length of stay in hospital. There is a nearly significant increase in length of stay by one day ($p = 0.0536$). n = 22,017 hospitalizations, excluding all deaths in hospital. Adjusted $r^2 = 0.1528$

Variable	**Estimate**	**Length of Stay** ($e^{Estimate}$)	**P Value**
NP Swab (Y vs N)	-0.04255	0.96	0.0536
Age	0.00431	1.00	<0.0001
Admission in Flu Season	0.05722	1.06	<0.0001
Isolation in Hospital	0.16581	1.18	<0.0001
Baseline Risk of Death	0.01076	1.01	<0.0001
Antibiotic Prescription	0.36120	1.44	<0.0001
CHF	0.25226	1.29	<0.0001
Renal Disease	0.02701	1.03	0.1694
Metastatic Cancer	0.20595	1.23	<0.0001
Cancer (No metastases)	0.10019	1.12	<0.0001
Diabetes with Complications	0.05281	1.05	0.0017
ICU Admission	0.78886	2.20	<0.0001

dentized residual values appeared normal (Figure 3.8). The quantile-quantile plot of expected versus observed values in the final adjusted linear regression model were plotted, and showed a linear relationship, suggesting that there is no serious deviation from normality in either distribution (Figure 3.9).

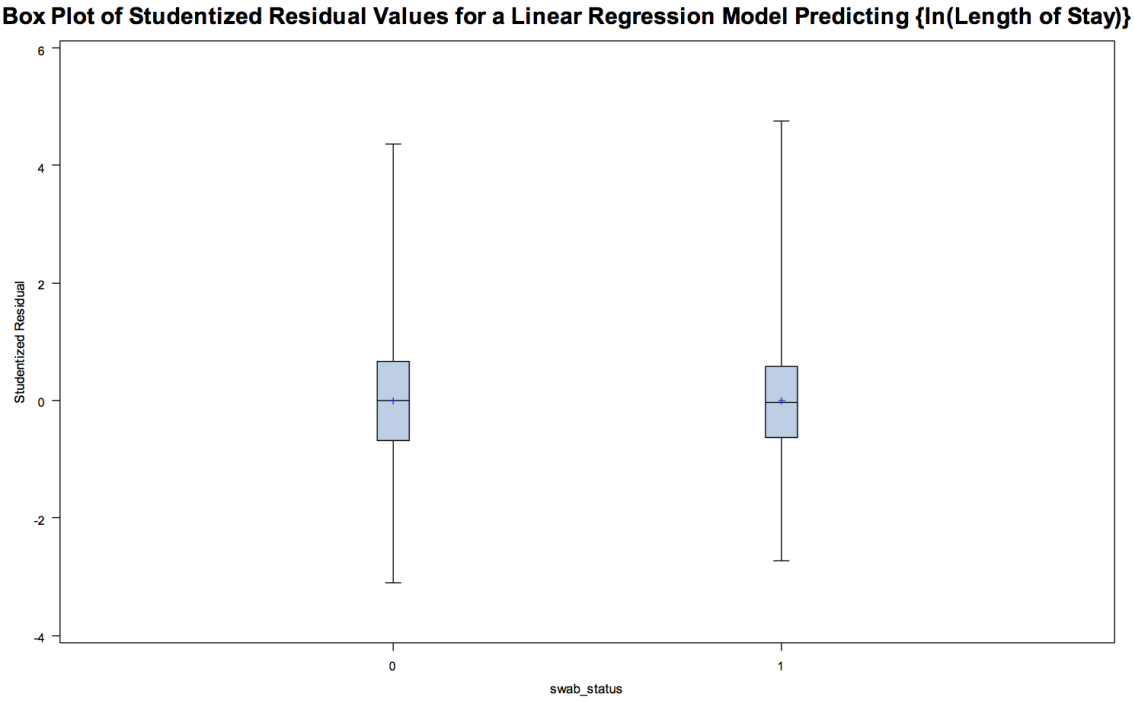


Figure 3.7: Boxplot representing distribution of studentized residual values for the multivariate linear regression model predicting ln(length of stay) outcomes in hospital encounters with and without an NP swab (n = 24,567). Distribution of residual values is uniform, and non-random. The horizontal line represents the median of residuals, the symbol (+) is the mean value of residuals, the error bar top and bottom represent the maximum and minimum residual values. The top and bottom of the box represents the 75^{th} and 25^{th} percentile residual values.

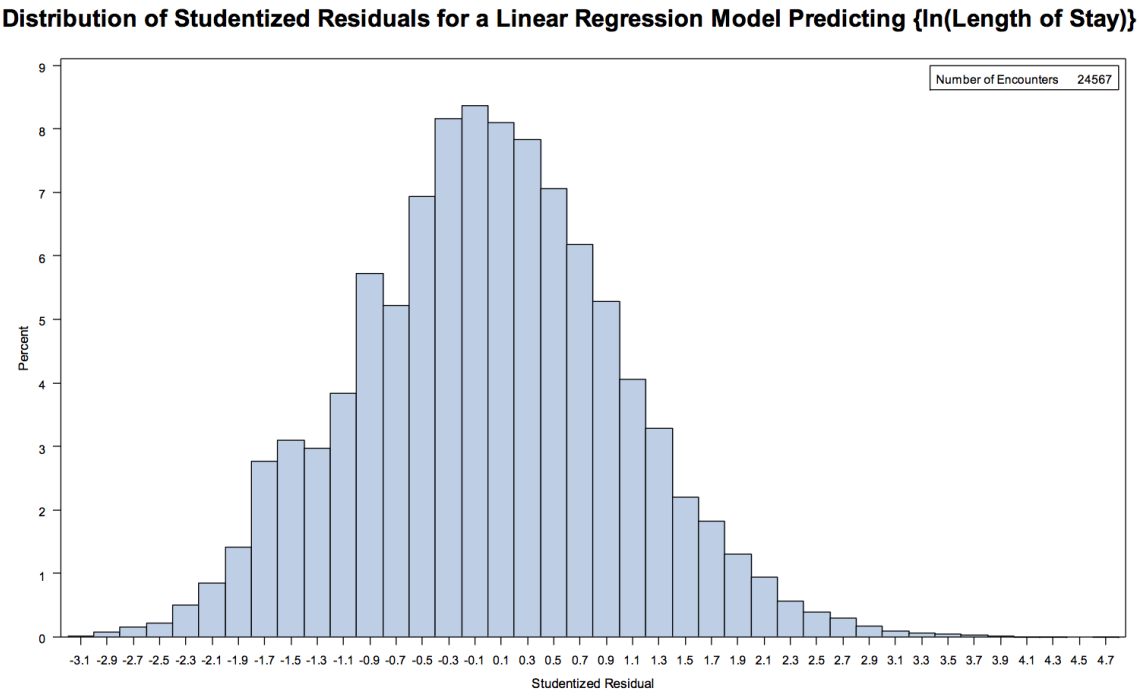


Figure 3.8: Distribution of the studentized residual values for the multivariate linear regression model predicting length of stay in hospital (n = 24,567 encounters). The distribution of residuals does not demonstrate significant skewness.

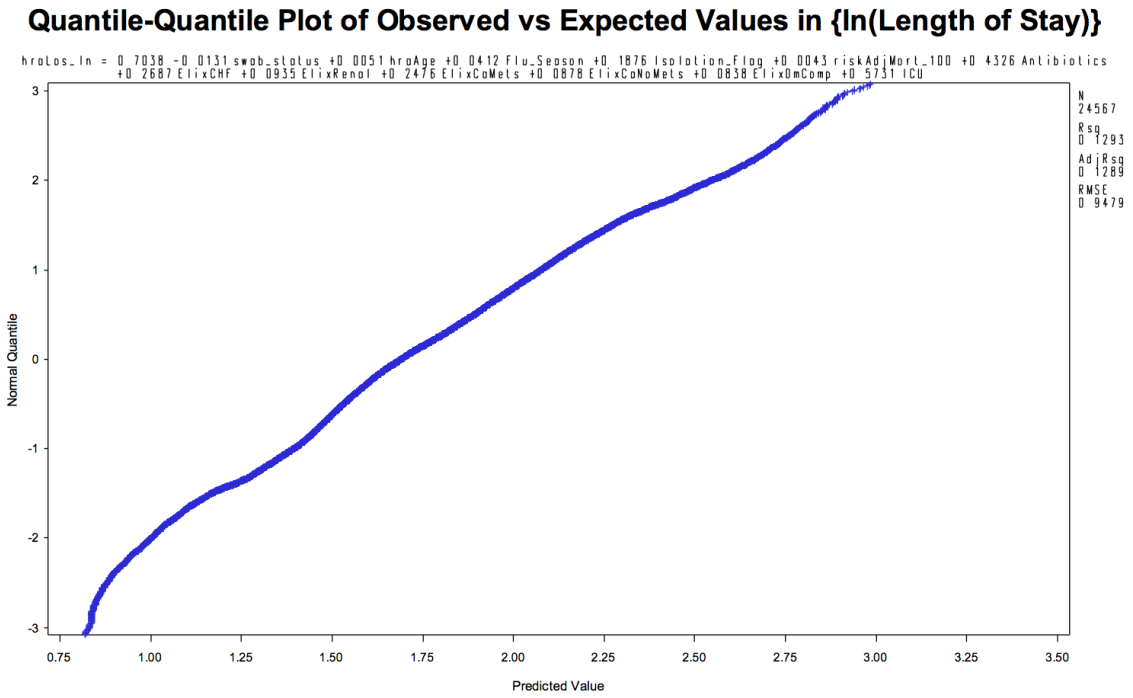


Figure 3.9: Quantile-Quantile plot of expected versus predicted values for the multivariate linear regression model predicting length of stay in hospital. The relationship is linear suggesting no gross violation of the linear regression model assumption of normality.

3.4 Secondary Analysis: Association between Positive NP Swab Results and Death, ICU Admission, and Length of Stay

3.4.1 Patient Characteristics Among Hospitalizations with Positive and Negative NP Swab Results

Table 3.11 describes the baseline characteristics in the subset of hospital admissions where an NP swab was performed ($n = 2722/24{,}567$ hospital encounters). There were 420 NP swabs positive for respiratory viruses (420/2722 swabs). The most commonly identified virus was influenza A. Patients with a positive NP swab were younger compared to those with a negative swab, however this was not statistically significant ($p = 0.223$). There were no significant differences between the positive and negative NP swab result groups with respect to individual elixhauser comorbidities, specifically congestive heart failure and chronic pulmonary disease. The baseline risk of death at admission was 14% ($\pm$ 14%) among encounters where an NP swab was done, and was not statistically different between positive and negative NP swab groups ($p = 0.087$).

3.4.2 Hospital Outcomes in Hospitalizations with Positive and Negative NP Swab Results

Descriptions of hospital outcomes stratified by NP swab results are shown in Table 3.12. There was no statistical difference in death or ICU admission between hospitalizations with positive or negative NP swab results ($p = 0.594$, $p = 0.086$, respectively). However,

Table 3.11: Baseline characteristics among hospitalizations where an NP swab was done, stratified by positive and negative results. The ANOVA test was used to test the difference between mean values, while the Chi-Square test was used for differences between proportions.

Variable	**Negative Swab** (N=2302)	**Positive Swab** (N=420)	**Total** (N=2722)	**P-Value**
Age at Admission	66.17 ± 18.03	64.99 ± 19.75	65.99 ± 18.31	0.223
Female Proportion	1201 (52.2%)	219 (52.1%)	1420 (52.2%)	0.991
Admission in Flu Season	1838 (79.8%)	383 (91.2%)	2221 (81.6%)	<.001
Baseline Risk of Death	0.14 ± 0.14	0.13 ± 0.14	0.14 ± 0.14	0.087
Chronic Pulmonary Disease	1005 (43.7%)	190 (45.2%)	1195 (43.9%)	0.548
Congestive Heart Failure	513 (22.3%)	99 (23.6%)	612 (22.5%)	0.561

admissions with a positive NP swab received more isolation precautions in hospital compared to admissions with a negative NP swab ($p < 0.001$). The mean number of days spent under isolation precautions was not statistically different between encounters with a positive and negative swab result ($p = 0.27$). There was a statistically longer mean length of stay in hospital among admissions with a positive NP swab compared with negative NP swab results ($p = 0.037$).

3.4.3 Modelling the Association between NP swab result and Death, ICU Admission, and Length of Stay

Among the 2722 swabs performed, there were 279 deaths (10.2%), 417 (15.3%) admissions to the ICU, and 2389 (87.8%) encounters where isolation was used. Table 3.13 shows the odds ratios and 95% confidence intervals describing the unadjusted and adjusted associations between a positive NP swab and death and ICU admission. Table 3.14 shows the unadjusted and adjusted parameter estimates and p-values describing the change in

Table 3.12: Hospitalization outcomes for patients during encounters where an NP swab was positive or negative ($n = 2722$ encounters). The ANOVA test was used to test the difference between mean values, while the chi-squared test was used for differences between proportions.

Outcome Variable	**Value**	**Negative Swab** ($n = 2302$)	**Positive Swab** ($n = 420$)	**Total** ($n = 2722$)	**P-Value**
Death	N (%)	239 (10.4%)	40 (9.5%)	279 (10.2%)	0.594
ICU Admission	N (%)	341 (14.8%)	76 (18.1%)	417 (15.3%)	0.086
Days in ICU	Mean ± SD	11.22 ± 12.77	11.70 ± 14.03	11.30 ± 12.99	0.771
Hospital Isolation	N (%)	1993 (86.6%)	396 (94.3%)	2389 (87.8%)	<0.001
Days Under Isolation	Mean ± SD	4.73 ± 7.65	5.16 ± 5.39	4.79 ± 7.35	0.27
Hospital Length of Stay	Mean ± SD	11.31 ± 20.11	13.71 ± 28.54	11.68 ± 21.64	0.037

length of stay when a positive NP swab occurs. The outcome event rates in the multivariate models predicting death and ICU admission allowed for adequate sample size, given 18 categories of predictor variables. This satisfied the model power requirements proposed by Peduzzi and colleagues to avoid significantly biased estimates.[57]

Table 3.13: Unadjusted and Adjusted Logistic Regression models evaluating the Association between a Positive NP Swab and Hospital Outcomes $n = 2722$. The odds ratio is computed with a confidence interval of 95%.

	Unadjusted		**Adjusted**	
	β **Coefficient**	**Odds Ratio**	β **Coefficient**	**Odds Ratio**
Death	-0.09658	0.909 (0.639 – 1.292)	-0.1129	0.893 (0.603-1.324)
ICU Admission	0.2395	1.271 (0.966 – 1.671)	-0.0313	0.969 (0.703-1.335)

Table 3.14: Unadjusted and Adjusted Linear Regression models evaluating the Association between a Positive NP Swab and length of stay. The adjusted r^2 value in the model including deaths is 0.1952, and is 0.2189 in the model excluding deaths. 95% confidence intervals were calculated based upon 2 x the standard error of the parameter estimate. $n = 2722$ (deaths included). $n = 2443$ (deaths excluded)

	Unadjusted			**Adjusted**		
Variable	**Estimate**	**Days**	**P-Value**	**Estimate**	**Days**	**P-Value**
Length of Stay (including deaths)	−0.0044	1.00 (0.90-1.11)	0.9338	-0.0014	0.999 (0.90-1.10)	0.978
Length of Stay (excluding deaths)	−0.0116	0.99 (0.89-1.10)	0.8308	-0.0133	0.987 (0.89-1.09)	0.789

3.4.4 Association between Positive NP swabs and Death

Candidate variables for the adjusted logistic regression model were selected based upon clinical relevance and statistical significance in univariate association with the outcome variable death. No significant effect modification of the relationship between NP swab result and death was detected after investigation of isolation status, age, baseline risk of death, and antibiotic use. Baseline risk of death was found to be a statistical confounding variable. Admission during influenza season and isolation status in hospital were specified for inclusion in the model based upon clinical significance (they were not statistical confounders). Variable selection methods were applied after inclusion of NP swab result, isolation status in hospital, baseline risk of death, and admission during influenza season. The results of variable selection methods are shown in Appendix B.5. In the final adjusted model (Table 3.15), there was no significant association between death and having a positive NP swab during hospitalization. Having a positive NP swab was associated with a 10.7% less chance of death, but this was not statistically significant (odds ratio: 0.893; 95% CI: 0.613, 1.363). The c-statistic for this model is 0.806, suggesting excellent

Table 3.15: Final adjusted logistic regression model investigating the association between a positive NP swab result and death during hospitalization ($n = 2722$ encounters). The c-statistic for the model is 0.806, suggesting *excellent* discrimination.

Variable	**Adjusted Odds Ratio** (For Death)	**95% CI (Odds Ratio)**
NP Swab Result (positive)	0.893	0.603 – 1.324
Admission During Flu Season	1.052	0.733 – 1.508
Isolation During Admission	1.002	0.650 – 1.544
Baseline Risk of Death	1.063	1.054 – 1.072
Age	1.015	1.005 – 1.024
Gender	1.404	1.068 – 1.847
Antiviral Given During Admission	1.614	1.134 – 2.297
Cancer (No metastasis)	2.081	1.333 – 3.251
Metastatic Cancer	0.542	0.298 – 0.985
Complicated Diabetes	0.481	0.328 – 0.705

model discrimination.

3.4.5 Association between Positive NP swabs and ICU Admission

Candidate variables for the adjusted model, along with results of variable selection methods are shown in Appendix B.6. No significant effect modification was identified, specifically, the interaction term between isolation status and NP swab result was not significant. Baseline risk of death, admission during influenza season, and isolation status were specified for inclusion in the model as they were significant confounders (as above in the adjusted regression model predicting death). Final results of the adjusted model investigating the association between a positive NP swab result and ICU admission are shown in Table 3.16. There was no significant association between having a positive NP swab and ICU admission, evidenced by an odds ratio of 0.969 (95% CI 0.703, 1.335). Encounters with a positive NP swab were 3.1% less likely to have ICU admission during

Table 3.16: Final adjusted logistic regression model investigating the association between a positive NP swab result and ICU admission during hospitalization ($n = 2722$ encounters).

Variable	**Adjusted Odds Ratio** (for ICU Admission)	**95% CI (Odds Ratio)**
NP Swab Result (positive)	0.969	0.703 – 1.335
Admission During Flu Season	0.923	0.684 – 1.245
Isolation During Admission	0.657	0.460 – 0.938
Baseline Risk of Death	1.069	1.060 – 1.078
Age	0.957	0.950 – 0.964
Antibiotics Given During Admission	10.797	2.597 – 44.89
Antiviral Given During Admission	3.431	2.603 – 4.521
COPD	1.507	1.178 – 1.929
Metastatic Cancer	0.417	0.251 – 0.693
Complicated Diabetes	0.706	0.508 – 0.981

hospitalization, although this was non-significant. The c-statistic for this model is 0.781, suggesting acceptable model discrimination.

3.4.6 Association between Positive NP swabs and Length of Stay in Hospital

Figures 3.10-3.11 illustrate the distributions of the untransformed and transformed length of stay variable. Using a natural logarithm function to transform the length of stay values resulted in less rightward skewness (Figure 3.11).

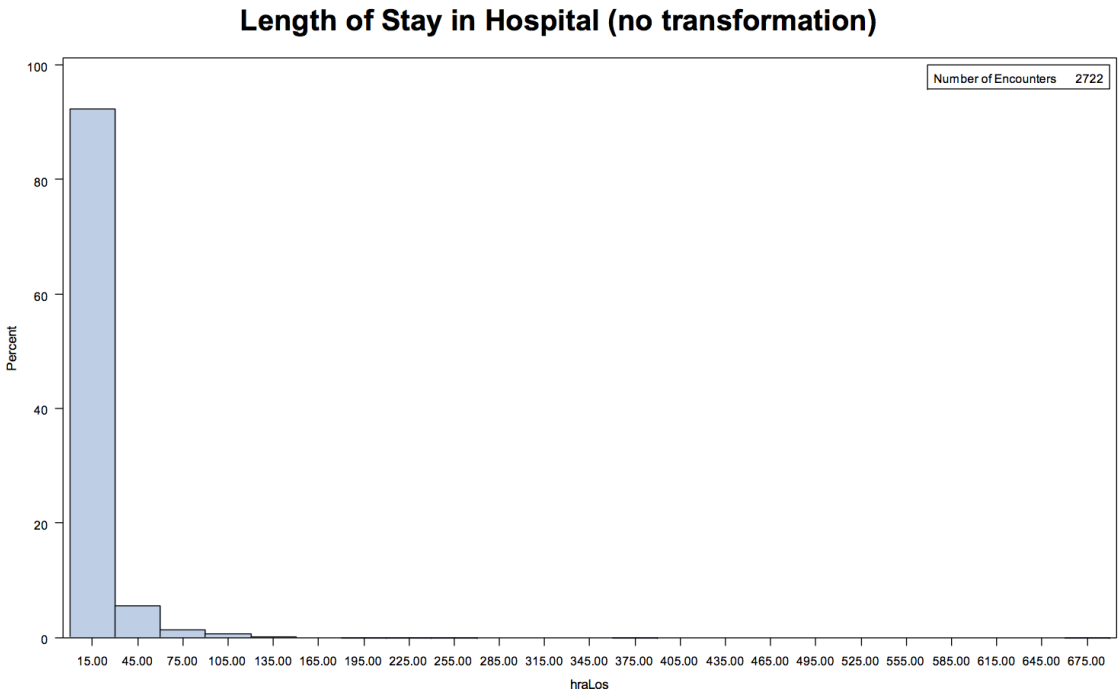


Figure 3.10: Distribution of the untransformed length of stay among hospitalizations where an NP swab occurred ($n = 2722$).

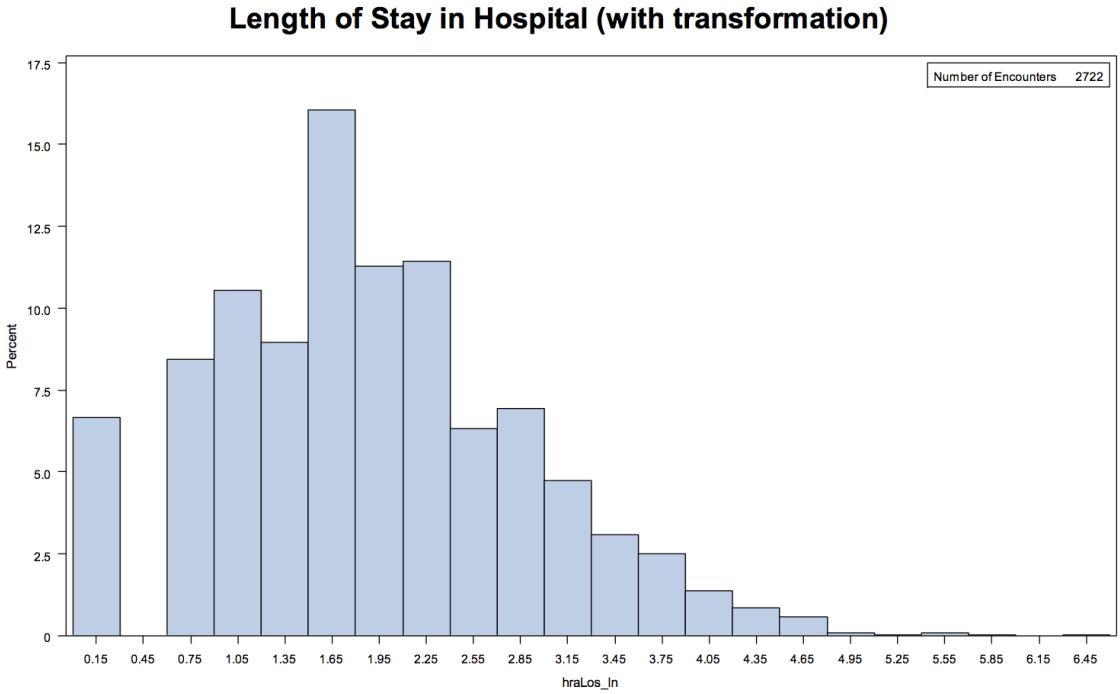


Figure 3.11: Distribution of length of stay in hospital transformed with a natural logarithm function. There is less right-ward skewness when compared with the distribution of the untransformed length of stay. ($n = 2722$)

Variables in the final adjusted linear regression model were selected based upon maximization of the adjusted r^2 values. Table 3.17 describes the parameter estimates with p-values for all variables in the final adjusted model ($n = 2722$ encounters). In this model, there was an increase in length of stay by 1 day (95% CI: 0.9, 1.1 days) among encounters with a positive NP swab, compared to those with a negative NP swab. However, this was non-significant ($p = 0.9778$). The adjusted r^2 value for this model was 0.1952, or 19.5%.

The same adjusted linear regression model was applied to the dataset where deaths were removed. This dataset contained a total of 2443 / 2722 hospital encounters with NP swabs performed. In the multivariate linear model excluding deaths, length of stay

Table 3.17: Final adjusted linear regression model describing the association between a positive NP swab result and length of stay in hospital. The adjusted r^2 value for this model is 0.1952. $n = 2722$

Variable	**Estimate**	**Days** (e^{PE})	**P-Value**
NP Swab Result (positive)	-0.00138	0.999	0.9778
Admission During Flu Season	0.05685	1.058	0.2051
Isolation During Admission	0.15812	1.17	0.0034
Baseline Risk of Death	0.00963	1.01	<0.0001
Age	0.00486	1.00	<0.0001
Antiviral Given During Admission	-0.07637	0.93	0.1183
Antibiotics Given During Admission	0.67120	1.96	<0.0001
CHF	0.13529	1.14	0.0028
Metastatic Cancer	0.16933	1.18	0.0177
ICU Admission During Hospitalization	0.87025	2.39	<0.0001
Complicated Diabetes	0.05866	1.06	0.2385

increased by 1 day (95% CI, 0.9, 1.1 days) with a positive NP swab result compared to encounters with a negative NP swab result. This was again insignificant ($p = 0.7891$). The adjusted r^2 value in this model excluding deaths was 0.2189, or 21.9%, suggesting that more of the variation in length of stay was explained by this model, compared to the model where deaths were included.

The final adjusted linear regression model diagnostics including the studentized residuals boxplot, distribution of studentized residual values, and quantile-quantile plots of observed versus expected values in ln(length of stay) are shown in Figures 3.12, 3.13, and 3.14, respectively. As seen in the primary analysis, there were no serious violations of the model assumptions of normality and homoskedasticity.

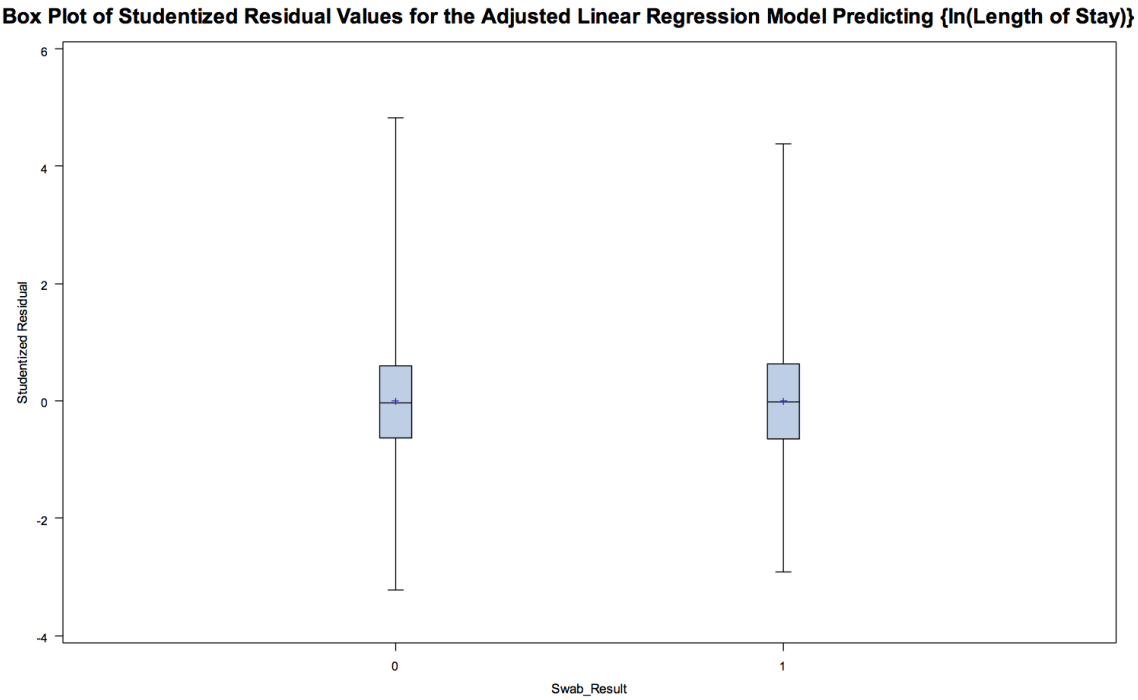


Figure 3.12: Boxplot of studentized residual values for the adjusted linear regression model investigating the relationship between NP swab result and hospital length of stay. The residual values appear to be non-random and equally distributed around the value 0 for each group (NP swab positive = 1, NP swab negative = 0).

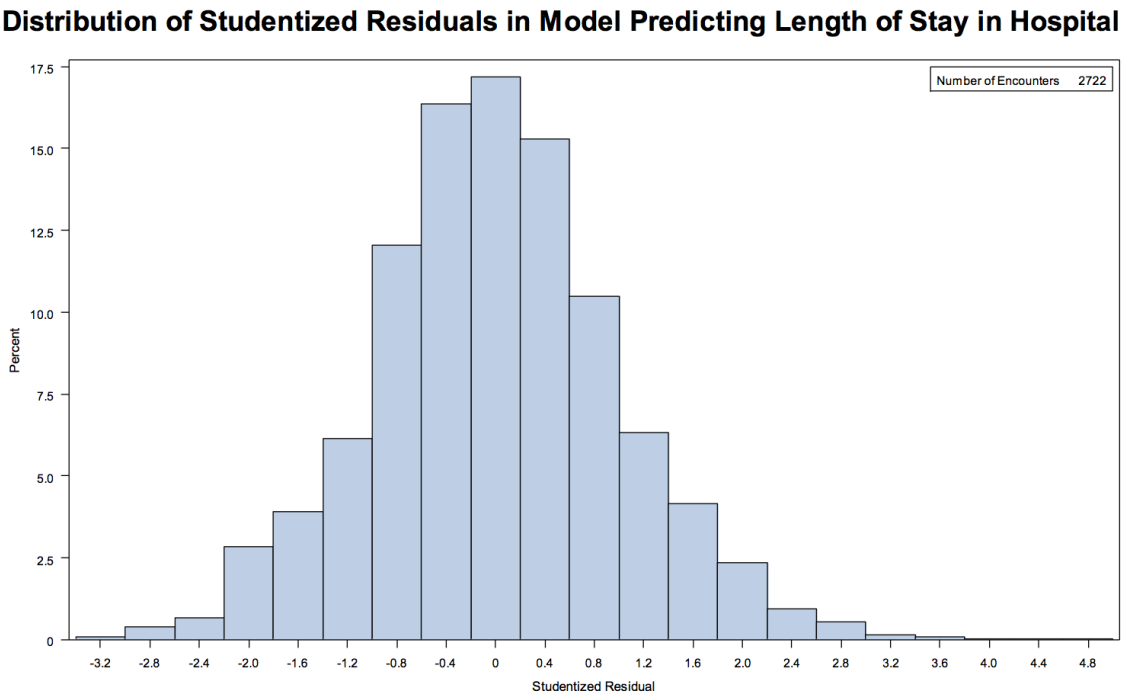


Figure 3.13: Distribution of studentized residual values for the adjusted model investigating the association between NP swab result and length of stay in hospital. $n = 2722$

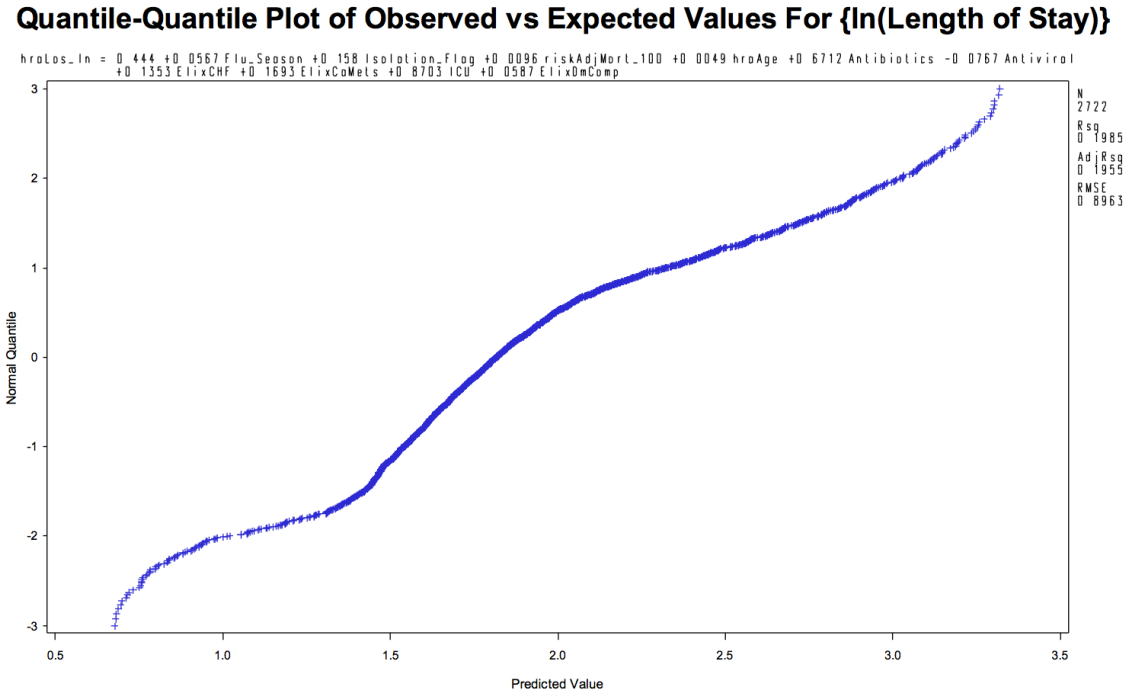


Figure 3.14: Quantile-Quantile plot of observed versus expected values in the final adjusted linear model investigating the association between NP swab results and length of stay in hospital. This plot demonstrates no serious deviations from a linear relationship. $n = 2722$

3.5 Post Hoc Analysis

The results of the post-hoc analysis restricted to hospitalizations where a pulmonary infection was recorded as the most responsible discharge diagnosis ($n = 7459$ hospitalizations) are shown in Appendix B.7 - B.12. The final adjusted logistic and linear regression models used in the planned primary and secondary analyses were applied to the post hoc dataset containing hospitalizations for pulmonary infections. Testing of the adjusted linear regression model assumptions are demonstrated in Appendix B.1 - B.3. Among hospitalizations for pulmonary infection, an NP swab during hospitalization was not significantly associated with increased mortality in a multivariate logistic

regression model (Appendix B.7), which is congruent with the results in the primary analysis. There was a statistically significant association with increased ICU admissions (OR 2.6, 95% CI 1.7, 4.0), and a one day increase in hospital length of stay ($p = 0.04$) in multivariate logistic regression and linear regression models respectively (Appendix B.7, B.8). This is also similar to results from the primary analysis, with the exception that the 1-day increase in length of stay observed in the post-hoc analysis was not statistically significant in the primary analysis.

Appendix B.9 demonstrates the baseline characteristics among hospitalizations for pulmonary infections, stratified by NP swab status. Patients who received an NP swab during hospitalization were statistically younger ($p < 0.001$). Gender distribution was equal among those with and without an NP swab, and 67% of the hospitalization in this cohort occurred during influenza season. Baseline risk of death was 12% (± 11.3) in this cohort, and was no different between encounters with and without an NP swab ($p = 0.84$). Isolation precautions for infection control were used in 47% of this cohort, and the mean (± SD) length of isolation was 2.4 (± 6.4) days. The duration of isolation was statistically greater for encounters where an NP swab occurred, compared to encounters without an NP swab ($p < 0.001$).

The overall mortality rate in this cohort was 8.6%, while 10% of the hospitalizations required admission to the ICU during hospitalization. The mean (± SD) number of days spent in ICU was 9.6 (± 11.5), while the mean (± SD) number of days in hospital was 8.8 (± 14.1).

Appendix B.10 describes the use of laboratory and radiographic tests, procedures, and antimicrobial prescriptions among hospitalizations for pulmonary infections. Overall, 94% of hospitalizations received antibiotics, while only 5% received Oseltamivir. Blood and sputum cultures were performed in 60%, and 36% of hospitalizations, respectively.

Chest radiographs were performed in 46% of encounters, while computed tomography scans of the chest were performed in 21% of encounters. Among encounters where an NP swab was performed, the use of antibiotics, antivirals, blood cultures, sputum cultures, and chest radiographs was significantly greater when compared with encounters where an NP swab did not occur ($p < 0.001$).

Appendices B.11 and B.12 describe the baseline characteristics, outcomes, and use of diagnostic tests stratified by NP swab results, among hospitalizations for pulmonary infections ($n = 1711$). Eighteen percent of all swabs done identified a virus. Patient with a positive swab were younger ($p = 0.02$), and mean baseline risk of death was no different between groups with a positive and negative NP swab ($p = 0.24$). Isolation precautions were used in 89% of encounters where an NP swab occurred, and the mean ($\pm$ SD) number of days under isolation was no different between encounters where a swab was positive or negative ($p = 0.264$). This was also identified in the secondary analysis. Hospitalizations with a positive NP swab stayed statistically longer in hospital ($p = 0.02$). Encounters with a positive NP swab used more antivirals and blood cultures ($p < 0.002$), but did have statistically less computed tomography scans of the chest and sputum cultures performed ($p < 0.01$).

Discussion

4.1 Summary of Major Findings

In this section, I will review the main findings from this study. Respiratory viral testing during hospitalization was not associated with significant reduction in patient mortality. Viral testing, however, was associated with increased ICU admission but not with increased overall length of hospital stay. It is possible that this failure to have any observable beneficial impact on health outcomes is a result of a failure by health care providers to adjust care processes based upon the results of the testing. Our study demonstrates that respiratory viral testing during hospitalization does not lead to significant reduction in antibiotic use, chest imaging, bronchoscopy, or microbiological cultures among patients with infectious respiratory symptoms. Most importantly, a *positive* viral test result did not lead to significant reductions in antibiotic use, chest radiographs, and blood cultures.

As anticipated, our study showed significantly more isolation precautions used in patients with a positive NP swab compared to those with a negative NP swab (94% versus 87%, $p < 0.001$). However, the result of the viral test did not influence the duration of isolation precautions as there was no statistical difference in the mean number of isolation-days between patients with positive and negative viral test results (5.2 days versus 4.7 days, $p < 0.001$). There are two potential reasons for this: first, health care providers may

not be using the test results to appropriately discontinue isolation, or secondly, infection control directives are not in place for front line staff to discontinue isolation precautions when appropriate. As a result, patients remain under isolation precautions for the standard five days, as per policy, regardless of the NP swab result.[31]

In a post-hoc secondary analysis, we limited our cohort to hospital encounters with a final discharge diagnosis of respiratory exacerbation or infection (Appendix B.7 - B.12). We observed the same results in this cohort.

What do these results mean? While I will fully explore implications in a later subsection, our results suggest that respiratory inpatients do not appear to benefit from viral testing. Viral testing does not achieve the goals of reducing diagnostic testing and timely discontinuation of isolation precautions. This implies that hospital imaging, laboratory, and pharmacy resources are not being used to optimal efficiency in these patients. Further, hospitalized patients may be subject to harm and sub-standard care from longer duration of isolation precautions when they do not have a viral infection.[41,42] These results also imply that the value proposition for viral testing in hospitals is poor, whereby *value = benefit/cost*. We observed no benefits to testing, but observed increased use of resources which imply increased hospital costs. Lastly, since the duration of isolation precautions is not guided by the viral test result, one has to question whether the process of viral testing is actually reducing viral infection transmission in hospital.

While this is only an observational study, it does capture the real-world care experience for a large population of patients. Our results should lead clinicians and policy makers to question whether viral testing should be used routinely in patients with infectious respiratory symptoms.

4.2 How Do Our Results Compare with Other Studies

4.2.1 Viral Testing and Impacts on Antibiotic Use and Clinical Outcomes

There have been relatively few studies that have evaluated the impact of respiratory viral testing on process of care and clinical outcomes in hospitalized adults. Most of these studies were performed on children in the emergency department.[43–46] However, recently Hernes and colleagues prospectively studied the impact of respiratory viral PCR testing on antibiotic treatment and length of stay among 147 hospitalized patients over 65 years with respiratory infections.[49] Patients with respiratory symptoms were swabbed for respiratory viruses within the first 24 hours of admission. The authors found no difference in antibiotic use or length of stay between patients with a positive and negative viral test.[49] They concluded that early knowledge of a viral diagnosis did not impact antibiotic prescriptions or length of stay in hospital. An earlier study in 2005 by Oosterheert and colleagues found similar results among 107 adult patients admitted for antibiotic treatment of lower respiratory tract infection.[47] Early knowledge of the viral test result did not significantly reduce the duration of antibiotics when compared to a group in which the viral test results were not made available.[47]

The results of these two small prospective studies are congruent with our results. Compared to our study, these studies were much smaller and they did not examine the impact of viral test results on additional process of care variables such as antiviral use, blood and sputum cultures, procedures, radiographic tests, and isolation precautions. More

importantly, they did not examine patient related outcomes such as inpatient mortality, duration of patient isolation, and ICU admission. Data collection in these studies occurred in only one influenza season, while our study encompassed eight influenza seasons, including the 2009 pandemic H1N1 influenza season. As we observed in our study, there have been changes in how viral testing was used over time, which in theory might influence test utilization. Other studies could not evaluate this, but we did not see this effect.

One retrospective study ($n = 574$ patients) published in 2000 examined the impact of viral testing on a broader range of outcomes. The authors used a before and after design to evaluate whether viral testing results using the rapid DFA method as compared to delayed viral culture method led to improved antibiotic stewardship, inpatient mortality, length of stay in hospital, and improved patient related costs.[48] Unlike our study, they found there was an association between viral testing and these processes of care. There are several reasons why these results might not be valid. First, Barenfangers study used data over two separate and consecutive historical cohorts ($n_1 = 293$, $n_2 = 281$ patients). It is entirely possible that secular trends may have contributed to the improvement in outcomes in the second year of the study. Second, the number of viral samples included in each historical cohort was less than 300, and important confounding variables such as underlying comorbidity were not adjusted for when examining length of stay and mortality outcomes. The positive samples in each year represented only 11 and 28 patients respectively. While our study was also retrospective, we studied a large number of hospitalizations with data spanning eight consecutive years as opposed to two years. We also accounted for multiple confounding variables including admission during influenza season, isolation status, and baseline risk of death in adjusted regression models to determine the association between viral testing and mortality and length of stay. Most

importantly, our investigation included a single cohort in which all patient data were collected the same way.

4.2.2 Viral Testing Associated with Greater Chance of ICU Admission

We found a greater chance of ICU admission among hospital encounters where an NP swab was done, after adjustment for important confounders including admission during influenza season, isolation status, and baseline risk of death. There are several potential explanations for this observation.

First, residual confounding may have influenced this association. Although we measured the baseline risk of death in patients admitted to hospital, it is possible this was not a complete measure of the patients illness severity. Patients with greater illness severity may have been more likely to have an NP swab, which would have resulted in a biased positive association between NP swabs and ICU admission during hospitalization (confounding by indication).

Secondly, temporal confounding could have also biased this association. We did not assess the temporal relationship between the performance of the NP swab and the ICU admission. It is possible that the majority of ICU admissions could have been swabbed at the time of entry to the intensive care unit, which would again result in a biased positive association.

Finally, it is possible that this association represents a signal of patient harm. It is not reasonable to think that an NP swab itself leads to increased ICU admission, but an NP swab is done in patients who are already under droplet isolation (according to

policy). Therefore, it is possible that factors associated with isolation itself are driving the increased risk of ICU admission.

While this may seem implausible at first, there is evidence that isolation precautions may pose harm to patients. In a systematic review of this topic, Abad and colleagues demonstrated that isolation precautions are associated with greater adverse drug events, less physician and nurse care, and increased patient scores for anxiety and depression.[42] In a prospective study, Stelfox and colleagues demonstrated that isolated patients were twice as likely to experience a preventable adverse event in hospital, more likely to formally complain to the hospital about their care, more likely to have no vital signs done when ordered, and more likely to have days with no physician progress note written, when compared to non-isolated controls.[41]

We did not evaluate the effect of isolation status on clinical outcomes in this study, as we did not monitor preventable adverse events and other relevant clinical care variables.

4.2.3 Use of NP Swabs in Hospitalized Patients

During an eight year period between 2004 and 2008, 420 / 2722 (15%) NP swabs yielded a positive result. This demonstrates that the majority of NP swabs performed on inpatients are negative. NP swabs are associated with significant costs as they require valuable laboratory resources, nursing time, and subsequent use of isolation precautions for the patient. The fact that a majority of NP swabs performed are negative implies that our current process to select patients for NP swab testing is not cost efficient, and is leading to unnecessary use of isolation precautions.

Currently, health care institutions in Ontario are required to use infection screening tools

such as the febrile respiratory illness screening tool (FRI) to identify patients with respiratory symptoms who are likely to have a transmissible viral illness. Having a positive FRI screen is a signal to perform a viral test, according to current infection control policy. There are many published studies in the literature that suggest these symptom based screening tools have poor sensitivity and specificity for identifying patients with viral illness.[39,58–62] Most notably, a systematic review by Ebell and colleagues in 2011 summarized many of the previously developed multivariate models and clinical decision rules for influenza diagnosis.[39] The studies were too heterogeneous to generate a summary statistic for screening tool accuracy, however the sensitivities were relatively poor across the board, ranging from 27% – 80%. The review called for the development of prospectively validated prediction models with thresholds for viral testing and empiric treatment in order to better assist clinician decision making at the bedside.[39]

Improved syndromic screening methods may better target the correct population in which to perform NP swabs. This would improve efficiency with respect to costs and use of isolation precautions.

4.3 Study Strengths

Our study has several strengths. This study is the largest study conducted in adult patients to evaluate the impact of respiratory viral testing on clinical outcomes in hospitalized patients. Given the 24,567 hospitalizations in our dataset, all adjusted logistic regression models were adequately powered to evaluate mortality, and ICU admission outcomes, according to the requirements set forth by Peduzzi *et al.*[57] This held true for the secondary and post hoc analyses as well.

No study to date has evaluated viral testing and infection control practices in a real-world setting over a span of eight years. In this context, we developed and validated a text search algorithm for NP swab text reports with the OHDW which could accurately identify tests that were classed as negative, positive, and unsuitable. This enabled us to evaluate a much greater sample than any other study. The infrastructure will also enable us to monitor and track NP swab results in the future for hospital quality measures, and infection control purposes.

In addition to studying process of care and patient outcomes, we also examined the impact of testing on isolation precautions, which have a significant impact on patient care and hospital costs. The previous studies in adult patients have not looked at the impact of viral testing on use or duration of isolation measures.

4.4 Study Limitations

Our study also has several limitations.

The retrospective nature of this study makes the results vulnerable to unmeasured confounding. We accounted for temporal confounding due to influenza seasonality, and for confounding by indication using validated measures of baseline mortality risk and co-morbidity in the adjusted regression models. However, we did not capture acute vital signs and other non-laboratory clinical data at the time of presentation, which may have influenced the outcomes we studied. It is possible that we did not obtain a true measure of illness severity. If patients having NP swabs were less sick compared to those without NP swabs, then this could have biased the results towards less death and reduced length of stay among the swabbed group.

Secondly, our population inclusion criteria were very broad, including patients with cough, fever, and shortness of breath. Many of these patients went on to have a non infectious diagnosis, which in turn could have biased our clinical outcomes in either direction (depending on the nature and severity of the final diagnosis). To address this issue, we conducted the post hoc analysis limited to encounters with a final diagnosis related to a respiratory infection or exacerbation (viral or bacterial). Given that the results in the post-hoc analysis did not deviate from the main findings in the primary cohort, it is unlikely that our broad inclusion criteria greatly biased the results. Also, the fact that many patients with non-infectious respiratory illness are being tested implies that having broad inclusion criteria was the correct approach.

Finally, we used a linear regression model with natural logarithm transformation to assess the length of stay outcome. While the transformed length of stay variable demonstrated less skewness, the distribution was not entirely normal. This may have biased the model, although our model diagnostic tests of linear regression assumptions (presented in the results) did not reveal any gross violations of normality. We did consider use of a generalized linear model and a cox proportional hazards model, but given the lack of temporal sequence in the data, it would have been inappropriate to use survival analysis.

4.5 Implications of Study Results

Our study is the largest adult study to examine the impact of viral testing in hospitalized patients. Our results strengthen the existing literature in both children and adults that knowledge of a positive viral test does not lead to reduction in antibiotic use or length of stay in hospital. Further, our study has added that viral testing and the results of testing do not lead to reductions in other diagnostic testing, such as radiological tests,

performance of microbiological cultures, and procedures. Perhaps most importantly, our study has also shown that viral testing does not guide the duration of isolation precautions in hospital, as one would expect it to.

These results are important because they highlight a large gap in quality of care from the individual and health system perspective. Our findings should encourage hospital administrators and infection control practitioners to re-evaluate and reform the process of screening and testing patients presenting with febrile respiratory illness, so that the intended goals of viral testing are being met. For example, hospitals should consider creating directives for nurses, physicians, and allied health professionals to discontinue isolation precautions based upon set criteria including the results of the viral test. Currently this decision lies with infection control practitioners only. Hospitals should develop systems to prompt physicians regarding the decision to continue antibiotics in patients with a positive viral test. Finally, the process of screening patients with symptom based screening tools should also be improved to avoid unnecessary testing and isolation for patients with respiratory symptoms but *very little risk of infection*. This may include the adoption of rapid viral point of care tests for respiratory viral illnesses, or the inclusion of chest imaging and laboratory results in the initial viral screening process.

4.6 Future Research: Next Steps

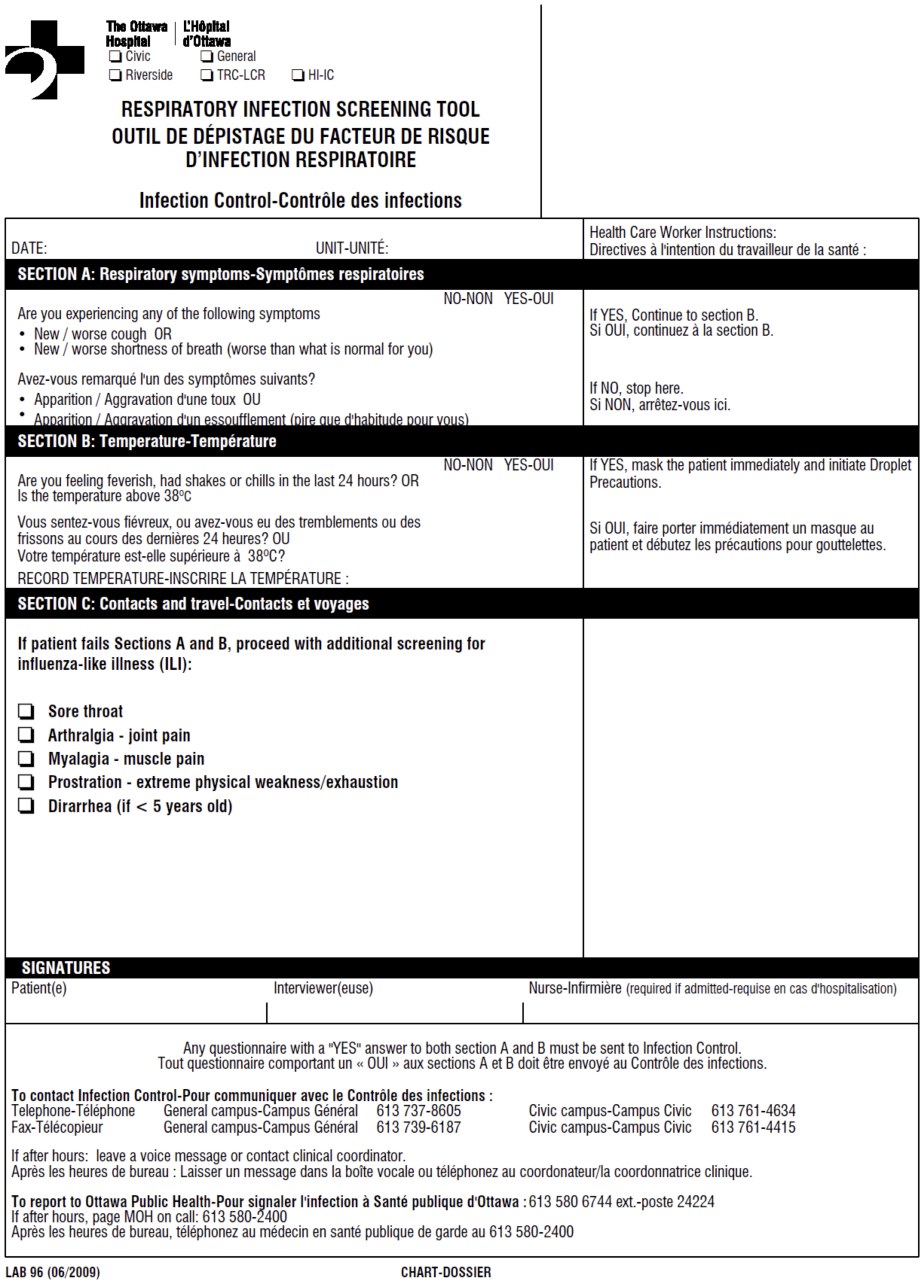
This study sets the foundation for prospective evaluation of our government mandated infection control policy for febrile respiratory illness. Understanding how this policy impacts the individual patient is important, but one of the most important remaining questions is whether viral testing and isolation precautions prevent transmission of respiratory viral illness between patients and health care workers in a non-outbreak setting.

Other questions surrounding the cost of isolation to hospitals remain unanswered.

Future research to address these questions will guide the evidence based reform of our current infection control policies, and contribute to safer and more cost efficient care for patients with respiratory infections.

Method Appendix

A.1 Febrile Respiratory Illness Symptom Screening Tool



The Ottawa Hospital | L'Hôpital d'Ottawa
❑ Civic ❑ General
❑ Riverside ❑ TRC-LCR ❑ HI-IC

RESPIRATORY INFECTION SCREENING TOOL
OUTIL DE DÉPISTAGE DU FACTEUR DE RISQUE D'INFECTION RESPIRATOIRE

Infection Control-Contrôle des infections

DATE: UNIT-UNITÉ:

Health Care Worker Instructions:
Directives à l'intention du travailleur de la santé :

SECTION A: Respiratory symptoms-Symptômes respiratoires

NO-NON YES-OUI

Are you experiencing any of the following symptoms
- New / worse cough OR
- New / worse shortness of breath (worse than what is normal for you)

Avez-vous remarqué l'un des symptômes suivants?
- Apparition / Aggravation d'une toux OU
- Apparition / Aggravation d'un essoufflement (pire que d'habitude pour vous)

If YES, Continue to section B.
Si OUI, continuez à la section B.

If NO, stop here.
Si NON, arrêtez-vous ici.

SECTION B: Temperature-Température

NO-NON YES-OUI

Are you feeling feverish, had shakes or chills in the last 24 hours? OR
Is the temperature above 38ºC

Vous sentez-vous fiévreux, ou avez-vous eu des tremblements ou des frissons au cours des dernières 24 heures? OU
Votre température est-elle supérieure à 38ºC?

RECORD TEMPERATURE-INSCRIRE LA TEMPÉRATURE :

If YES, mask the patient immediately and initiate Droplet Precautions.

Si OUI, faire porter immédiatement un masque au patient et débutez les précautions pour gouttelettes.

SECTION C: Contacts and travel-Contacts et voyages

If patient fails Sections A and B, proceed with additional screening for influenza-like illness (ILI):

- ❑ **Sore throat**
- ❑ **Arthralgia - joint pain**
- ❑ **Myalagia - muscle pain**
- ❑ **Prostration - extreme physical weakness/exhaustion**
- ❑ **Dirarrhea (if < 5 years old)**

SIGNATURES

Patient(e) | Interviewer(euse) | Nurse-Infirmière (required if admitted-requise en cas d'hospitalisation)

Any questionnaire with a "YES" answer to both section A and B must be sent to Infection Control.
Tout questionnaire comportant un « OUI » aux sections A et B doit être envoyé au Contrôle des infections.

To contact Infection Control-Pour communiquer avec le Contrôle des infections :

Telephone-Téléphone	General campus-Campus Général	613 737-8605	Civic campus-Campus Civic	613 761-4634
Fax-Télécopieur	General campus-Campus Général	613 739-6187	Civic campus-Campus Civic	613 761-4415

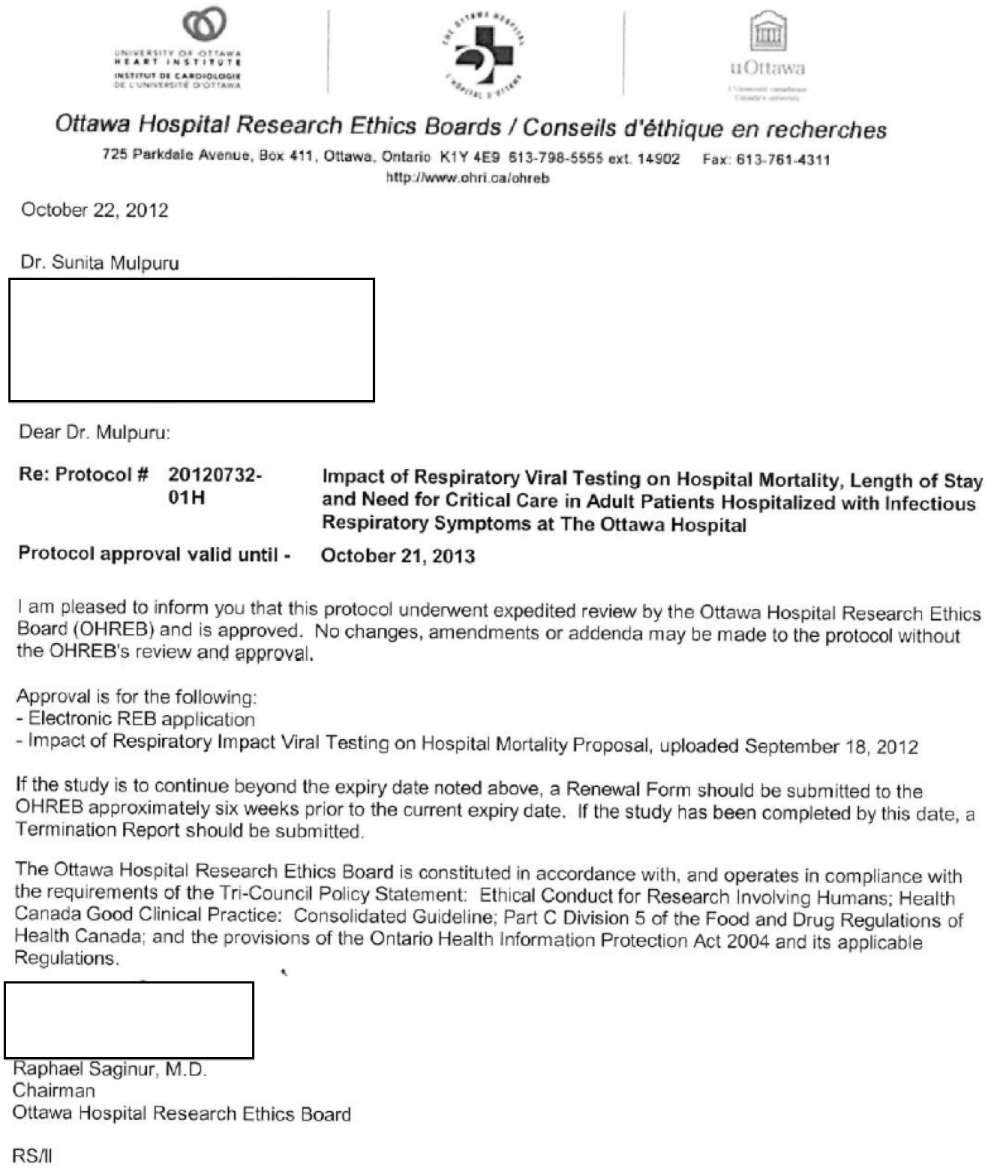
If after hours: leave a voice message or contact clinical coordinator.
Après les heures de bureau : Laisser un message dans la boîte vocale ou téléphonez au coordonateur/la coordonnatrice clinique.

To report to Ottawa Public Health-Pour signaler l'infection à Santé publique d'Ottawa : 613 580 6744 ext.-poste 24224
If after hours, page MOH on call: 613 580-2400
Après les heures de bureau, téléphonez au médecin en santé publique de garde au 613 580-2400

LAB 96 (06/2009) CHART-DOSSIER

Figure A.1: Febrile Respiratory Illness symptom screening tool used at The Ottawa Hospital.

A.2 Research Ethics Board Approval Letter



Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

725 Parkdale Avenue, Box 411, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax: 613-761-4311
http://www.ohri.ca/ohreb

October 22, 2012

Dr. Sunita Mulpuru

[redacted]

Dear Dr. Mulpuru:

Re: Protocol # 20120732-01H **Impact of Respiratory Viral Testing on Hospital Mortality, Length of Stay and Need for Critical Care in Adult Patients Hospitalized with Infectious Respiratory Symptoms at The Ottawa Hospital**

Protocol approval valid until - October 21, 2013

I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol without the OHREB's review and approval.

Approval is for the following:
- Electronic REB application
- Impact of Respiratory Impact Viral Testing on Hospital Mortality Proposal, uploaded September 18, 2012

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

[redacted]

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

RS/ll

Figure A.2: TOH Research Ethics Board study approval letter. Data collection and analysis completed by the termination date of this letter.

A.3 Data Dictionary

Table A.1: Data dictionary for all study variables and outcomes in the analytical cohort.

Variable Name	**Definition**
Nasopharyngeal Swab	Was swab performed, or not performed during hospitalization (Y/N). Method of Viral Testing (DFA, PCR, Viral Culture)
Age, Gender	Patient age at admission (years) Patient gender (female, male)
Risk of In-Hospital Death	Probability score between 0-1, validated in TOH patient population.[52,54]
Most responsible discharge diagnosis	Diagnosis listed on the final clinical discharge summary and abstracted from the chart into the DW
Elixhauser Individual Comorbidity & Elixhauser Comorbidity Summary Score	Collection of the 30 individual Elixhauser Comorbidities, according to the original Elixhauser Classification System.[1] Calculation of the summary score based upon the methodology by van Walraven and colleagues.[52]
Laboratory Tests at Admission	White blood cell count, Neutrophil count at admission
Blood Cultures & Sputum Cultures	Blood cultures ordered by physician during hospital admission (Yes or No) Sputum sample ordered by physician during admission (Yes or No)
Chest Radiograph	Chest x-ray ordered by physician (Yes or No)
Computed Tomography	CT thorax ordered during admission (Yes or No)
Bronchoscopy	Bronchoscopy ordered and performed during admission (Y/N)
Antibiotics Prescribed Antiviral Prescribed	Relevant antibiotic prescribed during admission (Y/N) Oseltamivir or Zanamivir prescribed during admission (Y/N)
Influenza Season	Patient presents during Influenza Season (October – April) (Y/N) 2009: Influenza season from April – August 2009, Sept – February 2010

A.4 Elixhauser Commorbidity Diagnoses

Table A.2: List of the original 30 co-morbidities defined by Elixhauser *et al.*[1]

Elixhauser Comorbidity Diagnoses
Congestive Heart Failure
Cardiac Arrhythmia
Valvular Heart Disease
Pulmonary Circulation Disorders
Peripheral vascular Disease
Hypertension, Uncomplicated
Hypertension, Complicated
Paralysis
Other Neurological Disorders
Chronic Pulmonary Disease
Uncomplicated Diabetes
Complicated Diabetes
Hypothyroidism
Renal Failure
Liver Disease
Peptic Ulcer Disease (excluding bleeding)
HIV/AIDS
Lymphoma
Metastatic Cancer
Solid Tumor Without Metastasis
Rheumatoid Arthitis/Collagen Vascular Disease
Coagulopathy
Obesity
Weight Loss
Fluid and Electrolyte Disorders
Anemia (due to deficiency)
Blood Loss and Anemia
Alcohol Abuse
Drug Abuse
Psychoses
Depression

A.5 ICD-10-CM Codes

Table A.3: ICD-10-CM Codes of most responsible discharge diagnosis, identified for post-hoc subgroup analysis.

ICD-10-CM Codes
A1501, A151, A1520, A1530, A160, A1620, A1621
A169, A1690, A1691, A199, A310, A403, A492
B012 , B349 , B371 , B392 , B402 , B409 , B441 , B59 E840
J020, J029 J039 , J040 , J09 , J100 , J101 , J110 , J111 , J121 , J128 , J129 , J13 , J14
J150, J151, J152, J153, J154
J155, J156, J157, J158, J159
J168 , J180 , J181 , J188 , J189
J208, J209, J210
J22 , J40 , J411 , J42
J440, J441
J448, J449
J4580 , J4591 , J80
J850, J851, J852
J860 , J960 , J969
R091

Results Appendix

B.1 Supplemental Tables

Table B.1: Proportion of Elixhauser comorbidities and Elixhauser scores among adult hospitalizations for cough, shortness of breath, or fever. P-values were obtained using the chi-squared test.

Variable	**No Swab** (N=21845)	**NP Swab** (N=2722)	**Total** (N=24567)	**P-Value**
Elixhauser Quartile (0^{th})	5636 (25.8%)	981 (36.0%)	617 (26.9%)	<0.001
Elixhauser Quartile (1^{st})	5877 (26.95%)	762 (28.0%)	639 (27.0%)	
Elixhauser Quartile (2^{nd})	5200 (23.8%)	558 (20.55%)	5758 (23.4%)	
Elixhauser Quartile (3^{rd})	5132 (23.5%)	421 (15.5%)	5553 (22.6%)	
Liver Disease	606 (2.8%)	55 (2.0%)	661 (2.7%)	0.022
Lymphoma	866 (4.0%)	183 (6.7%)	1049 (4.3%)	<0.001
Metastatic Cancer	2670 (12.2%)	182 (6.7%)	2852 (11.6%)	<0.001
Solid Tumor (No Metastasis)	4271 (19.6%)	340 (12.5%)	4611 (18.8%)	<0.001
Complicated Hypertension	1046 (4.8%)	69 (2.5%)	1115 (4.5%)	<0.001
Congestive Heart Failure	7587 (34.7%)	612 (22.5%)	8199 (33.4%)	<0.001
Obesity	231 (1.1%)	29 (1.1%)	260 (1.1%)	0.97
Complicated Diabetes	4238 (19.4%)	443 (16.3%)	4681 (19.1%)	<0.001
Peripheral Vascular Disease	934 (4.3%)	91 (3.3%)	1025 (4.2%)	0.022
Renal Failure	2887 (13.2%)	272 (10.0%)	3159 (12.9%)	<0.001
Pulmonary Circulation Disorders	1558 (7.1%)	106 (3.9%)	1664 (6.8%)	<0.001
Chronic Pulmonary Disease	7074 (32.4%)	1195 (43.9%)	8269 (33.7%)	<0.001
Coagulopathy	691 (3.2%)	90 (3.3%)	781 (3.2%)	0.688

Table B.2: Variables chosen for candidate logistic regression model predicting death, based upon clincal relevance and univariate association with death. The stepwise variable selection results were chosen as final most parsimonious model. *Specifies pre-inclusion in the model prior to variable selection method.

Candidate Variables	Backward	Forward	Stepwise
Swab_status*	x	x	x
RiskAdjustedMortality*	x	x	x
Flu_Season*	x	x	x
Isolation_Status*	x	x	x
HraAge	x	x	x
Gender_Code		x	
Antibiotics	x	x	x
Antiviral	x	x	x
elixCHF		x	
elixCOPD	x	x	x
elixRenal		x	
elixCaMets	x	x	x
elixCaNoMets	x	x	x
elixDmComp	x	x	x

Table B.3: Candidate variables selected for multivariate logistic regression model predicting ICU admission during hospitalization. The results of variable selection methods are described. The model chosen by stepwise variable selection was used as the final model. *Specifies pre-inclusion in the model prior to variable selection method.

Candidate Variables	**Backward**	**Forward**	**Stepwise**
Swab_Status*	x	x	x
Isolation During Admission*	x	x	x
Swab x Isolation*	x	x	x
Baseline Risk of Death*	x	x	x
Flu_Season*	x	x	x
Age	x	x	x
Gender		x	
Antibiotics	x	x	x
Antiviral	x	x	x
elixCHF			
elixCOPD	x	x	x
elixRenal	x	x	x
elixCaMets	x	x	x
elixCaNoMets		x	
elixDmComp	x	x	x

Table B.4: Candidate variables tested in univariate linear regression with the natural logarithm of length of stay {ln(length of stay)}. All variables were significantly associated with ln(length of stay) with the exception of gender and chronic pulmonary disease. They were not included in the candidate multivariate linear regression model.

Candidate Variables	**Significant**
Age at Admission	x
Gender	
Admission during Influenza Season	x
Isolation Used during Admission	x
Baseline risk of Death	x
Congestive Heart Failure	x
Chronic Pulmonary Disease	
Renal Disease	x
Metastatic Cancer	x
Cancer without Metastasis	x
Complicated Diabetes	x
Admission to ICU	x
Antibiotics Prescribed during admission	x
Antiviral Prescribed during admission	x

Table B.5: Variable selection methods for a multivariate logistic regression model investigating the association between NP swab result and the outcome of death. The model created by stepwise variable selection was kept as the final, most parsimonious, model. *Specifies variables that were selected for automatic inclusion in the model, prior to variable selection techniques.

Candidate Variables	**Backward**	**Forward**	**Stepwise**
Swab Result*	x	x	x
Isolation During Admission*	x	x	x
Admission During Flu Season*	x	x	x
Baseline Risk of Death*	x	x	x
Age	x	x	x
Gender	x	x	x
Antibiotics			
Antiviral	x	x	x
elixCHF			
elixCOPD			
elixRenal			
elixCaMets	x	x	x
elixCaNoMets	x	x	x
elixDmComp	x	x	x

Table B.6: Candidate variables and variable selection methods for the logistic regression model investigating the association between a positive np swab result and ICU admission during hospitalization. The model created by stepwise variable selection was kept as the final, most parsimonious, model. [a]Specifies variables that were selected for automatic inclusion in the model, prior to variable selection techniques.

Candidate Variables	**Backward**	**Forward**	**Stepwise**
Swab Result[a]	x	x	x
Isolation During Admission[a]	x	x	x
Admission During Flu Season[a]	x	x	x
Baseline Risk of Death[a]	x	x	x
Age	x	x	x
Gender		x	
Antibiotics	x	x	x
Antiviral	x	x	x
elixchf		x	
elixcopd	x	x	x
elixrenal		x	
elixcamets	x	x	x
elixcanomets		x	
elixdmcomp	x	x	x

Table B.7: Unadjusted and Adjusted Logistic Regression Analyses Predicting Death and ICU Admission among Hospitalizations where an NP Swab was Performed. $N = 7459$ hospitalizations for pulmonary infection related conditions. *Denotes an interaction term is present in the model, between NP swab status and isolation status.

Unadjusted

Outcome	**Odds Ratio** (95% CI)
Death	0.916 (0.753 – 1.114)
ICU Admission	1.594 (1.350 – 1.882)

Adjusted

Outcome	**Odds Ratio** (95% CI)
Death	0.844 (0.658 – 1.082)
ICU	
Effect of NP Swab*	2.6322 (1.7179 – 4.0331)
Effect of Swab and Isolation*	1.1043 (0.8637 – 1.4120)
Effect of Isolation*	1.2221 (0.9958 – 1.4999)

Table B.8: Unadjusted and adjusted linear regression analyses predicting length of stay in hospital based upon np swab status during hospitalization. $N = 7459$ hospitalizations for pulmonary infection related conditions. $N = 6814$ hospitalizations for pulmonary infection related conditions (excluding deaths).

	Unadjusted			**Adjusted**		
Outcome	**Estimate**	e^{PE}	**P-value**	**PE**	e^{PE}	**P-value**
LOS (including deaths)	0.18693	1.20554	<0.0001	0.05669	1.0583	0.0434
LOS (excluding deaths)	0.17237	1.1881	<0.0001	0.04829	1.0495	0.0886

Table B.9: Baseline characteristics among hospitalizations for pulmonary infection where an NP swab was performed ($N = 7459$).

Demographic Variables	**No Swab** ($N = 5748$)	**Swab** ($N = 1711$)	**TOTAL** ($N = 7459$)	**P-Value**
Age at Admission	70.45 ± 15.58	68.21 ± 17.55	69.93 ± 16.08	<0.001
Gender (Females)	2780 (48.4%)	788 (46.1%)	3568 (47.8%)	0.093
Influenza Season	3560 (61.9%)	1431 (83.6%)	4991 (66.9%)	<0.001
Baseline Risk of Death	12.06 ± 11.26	12.12 ± 11.45	12.08 ± 11.30	0.842
Isolation Precautions	1996 (34.7%)	1521 (88.9%)	3517 (47.2%)	<0.001
Days Under Isolation	1.76 ± 6.12	4.48 ± 6.73	2.39 ± 6.36	<0.001
ICU Admission	508 (8.8%)	229 (13.4%)	737 (9.9%)	<0.001
Days in ICU	9.07 ± 11.65	10.73 ± 10.93	9.59 ± 11.45	0.069
Death	506 (8.8%)	139 (8.1%)	645 (8.6%)	0.38
LOS in Hospital	8.43 ± 13.26	9.98 ± 16.51	8.79 ± 14.09	<0.001

Table B.10: Use of Laboratory tests, radiographic tests, and bronchoscopy among hospitalizations for pulmonary infection where an NP swab was performed ($N = 7459$).

Process of Care Variables	**No Swab** ($N = 5748$)	**Swab** ($N = 1711$)	**TOTAL** ($N = 7459$)	**P-Value**
Antibiotics	5317 (92.5%)	1655 (96.7%)	6972 (93.5%)	<.001
Antiviral	53 (0.9%)	315 (18.4%)	368 (4.9%)	<.001
Blood Cultures	3109 (54.1%)	1310 (76.6%)	4419 (59.2%)	<.001
Sputum Cultures	1910 (33.2%)	750 (43.8%)	2660 (35.7%)	<.001
Chest Radiographs	2551 (44.4%)	890 (52.0%)	3441 (46.1%)	<.001
CT Chest	1193 (20.8%)	389 (22.7%)	1582 (21.2%)	0.079
Bronchoscopy	245 (4.3%)	78 (4.6%)	323 (4.3%)	0.597

Table B.11: Baseline characteristics among hospitalizations for pulmonary infection stratified by NP swab result (N=7459).

Variable	**Negative Swab** $N = 1402$	**Positive Swab** $N = 309$	**TOTAL** $N = 1711$	**P-Value**
Demographics				
Age at Admission	68.66 ± 17.15	66.15 ± 19.17	68.21 ± 17.55	0.023
Gender (Females)	636 (45.4%)	152 (49.2%)	788 (46.1%)	0.222
Baseline Risk of Death	12.28 ± 11.56	11.43 ± 10.96	12.12 ± 11.45	0.242
Admission During Influenza Season	1150 (82.0%)	281 (90.9%)	1431 (83.6%)	<.001
Outcomes				
Isolation Precautions Used	1226 (87.4%)	295 (95.5%)	1521 (88.9%)	<.001
Days Under Isolation	4.39 ± 7.07	4.86 ± 4.89	4.48 ± 6.73	0.264
ICU No (%)	182 (13.0%)	47 (15.2%)	229 (13.4%)	0.298
Days in ICU	10.70 ± 9.92	10.87 ± 14.32	10.73 ± 10.93	0.923
Death No (%)	114 (8.1%)	25 (8.1%)	139 (8.1%)	0.981
Length of Stay in Hospital	9.56 ± 12.58	11.90 ± 28.08	9.98 ± 16.51	0.024
Admitting Service				
Internal Medicine (CTU)	956 (61.1%)	192 (62.1%)	1048 (61.2%)	<0.001
ICU	69 (4.9%)	17 (5.5%)	86 (5.0%)	
Respirology	178 (12.7%)	18 (5.8%)	196 (11.5%)	
Family Medicine	94 (6.7%)	22 (7.1%)	116 (6.8%)	
Other	105 (14.6%)	60 (19.5%)	265 (15.5%)	

Table B.12: Use of Laboratory tests, radiographic tests, antimicrobial prescriptions, and bronchoscopy among hospitalizations for pulmonary infection stratified by NP swab result ($N = 7459$).

Process of Care Variable	**Negative Swab** $N = 1402$	**Positive Swab** $N = 309$	**TOTAL** $N = 1711$	**P-Value**
Antibiotics	1356 (96.7%)	299 (96.8%)	1655 (96.7%)	0.968
Antiviral	187 (13.3%)	128 (41.4%)	315 (18.4%)	<0.001
Blood Cultures	1058 (75.5%)	252 (81.6%)	1310 (76.6%)	0.022
Sputum Cultures	639 (45.6%)	111 (35.9%)	750 (43.8%)	0.002
Chest Radiographs	729 (52.0%)	161 (52.1%)	890 (52.0%)	0.973
CT Chest	336 (24.0%)	53 (17.2%)	389 (22.7%)	0.01
Bronchoscopy	69 (4.9%)	9 (2.9%)	78 (4.6%)	0.125

B.2 Supplemental Figures

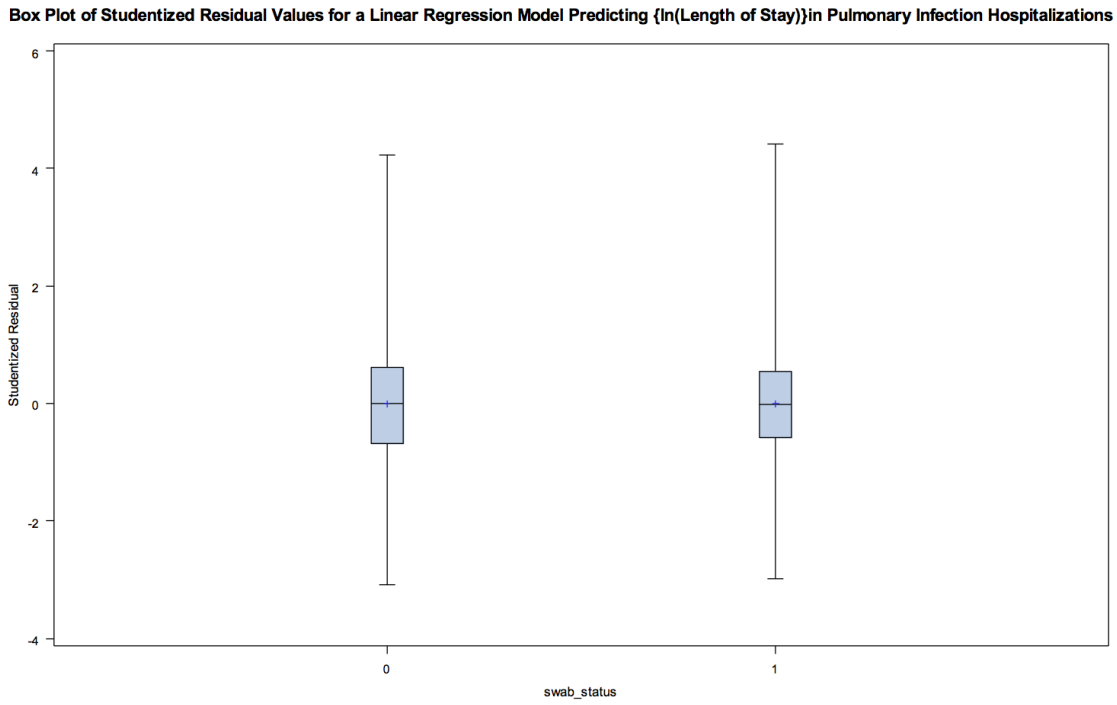


Figure B.1: A boxplot of studentized residual values for the adjusted linear regression model investigating the relationship between having an NP swab in hospital and length of stay. $N = 7459$ hospitalizations for pulmonary infection-related conditions.

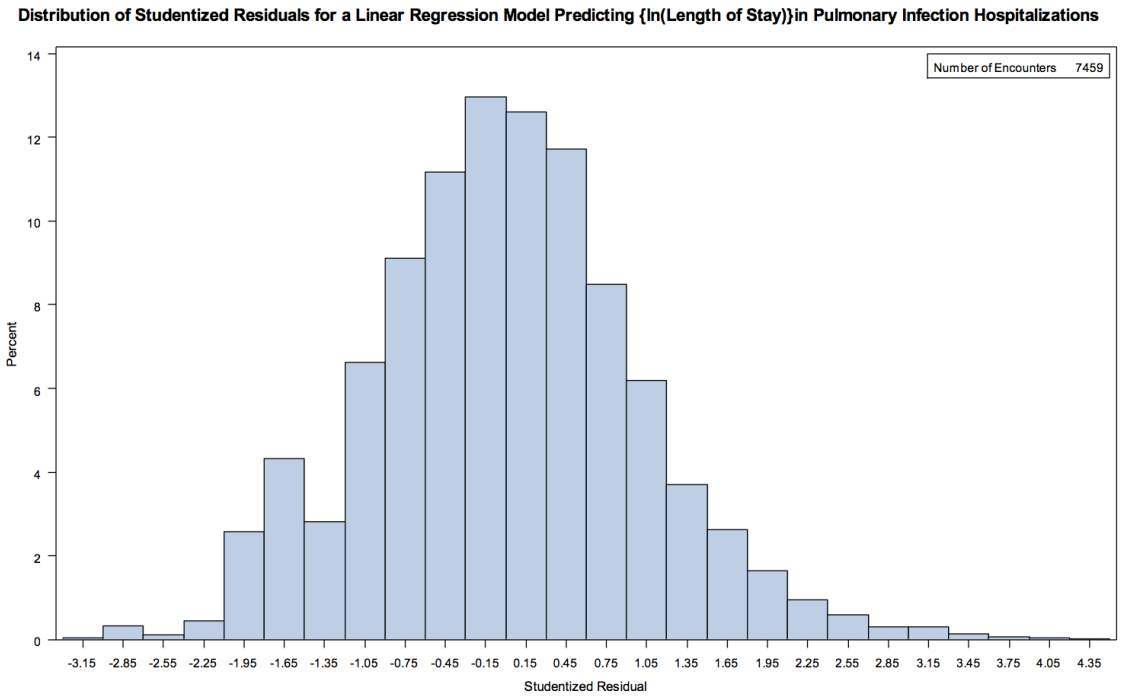


Figure B.2: Distribution of studentized residual values for the linear regression model investigating the relationship between having an NP swab in hospital and length of stay. $N = 7459$ hospitalizations for pulmonary-infection related conditions.

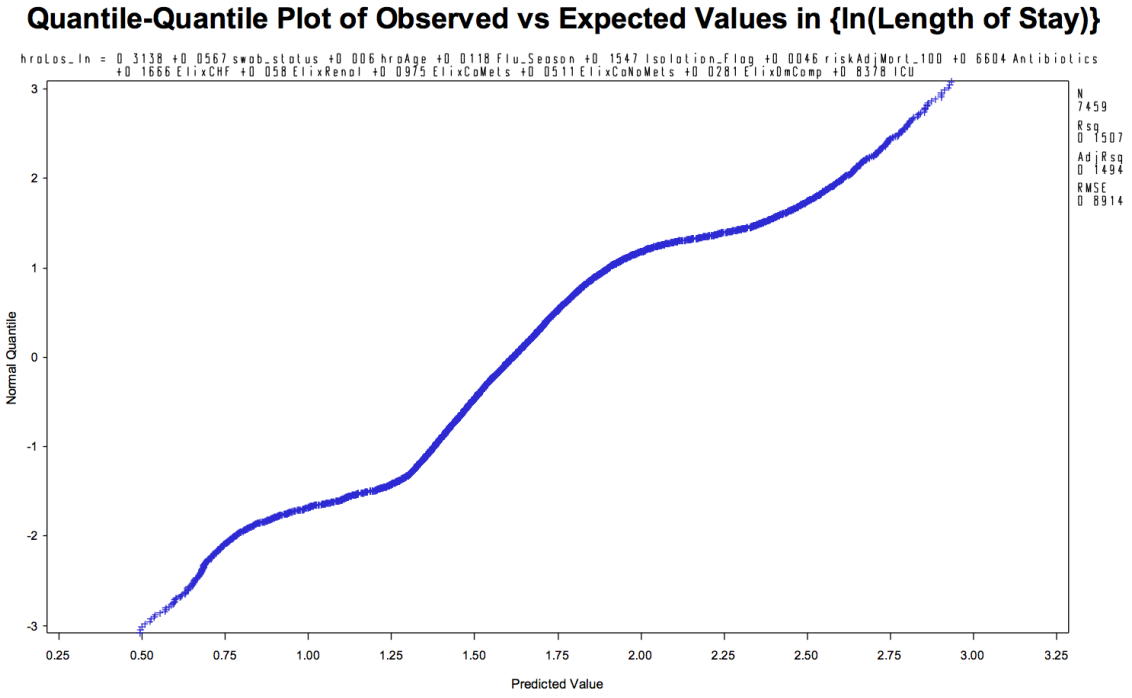


Figure B.3: Quantile-Quantile plot of observed versus expected values for the linear regression model predicting length of stay in hospital during encounters where an NP swab occurs. The linear relationship in this plot demonstrates no gross violations of the normality assumption.

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