Cost-Utility Analysis of Oral Antiseptic Chlorhexidine in decreasing Ventilator-Associated Pneumonia in Intensive Care Units

by

So Jung Lee

A thesis submitted in conformity with the requirements for the degree of Masters of Science in Dental Public Health Graduate Department of Dentistry University of Toronto

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Abstract

Purpose: To evaluate the cost-utility of chlorhexidine (CHX) mouthrinse (0.12-2%) as compared to placebo/usual care in preventing ventilator-associated pneumonia (VAP), among ventilated intensive care unit (ICU) patients.

Methods: A cost-utility (and its sensitivity) analyses were performed using a state transition model. We assumed a daily cycle, lifetime horizon, third party payer perspective, 2015 Canadian Dollars adjusted costs, and a 5% discounted benefits. We performed a meta-analysis to obtain CHX effectiveness in preventing VAP and associated survival.

Results: Use of CHX was associated with 0.008 life-years, 0.005 Quality-adjusted life-years (QALYs) lived, and a cost savings of $804.53/patient. Sensitivity analyses showed that an increased mortality risk or reduced effectiveness associated with CHX, or reduced number of prolonged ICU days results in reduced life-years lived and QALYs.

Conclusions: CHX oral antiseptic in ICU for preventing VAP as compared to the care without CHX resulted in comparable health outcome, yet it was cost saving.
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<td>CEA</td>
<td>Cost-effectiveness analysis</td>
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<td>CUA</td>
<td>Cost-utility analysis</td>
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<td>CHX</td>
<td>Chlorhexidine</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<td>ICUR</td>
<td>Incremental cost-utility ratio</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>CAP</td>
<td>Community-acquired pneumonia</td>
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<td>HAP</td>
<td>Hospital-acquired pneumonia</td>
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<td>HCAP</td>
<td>Healthcare-associated pneumonia</td>
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<tr>
<td>MDR</td>
<td>Multidrug-resistant</td>
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<td>MV</td>
<td>Mechanical ventilation</td>
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<td>P. aeruginosa</td>
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<td>PSA</td>
<td>Probabilistic sensitivity analysis</td>
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<td>QALYs</td>
<td>Quality-adjusted life-years</td>
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<td>QoL</td>
<td>Quality of life</td>
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<td>S. aureus</td>
<td><em>Staphylococcus aureus</em></td>
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<td>VAP</td>
<td>Ventilator-associated pneumonia</td>
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Chapter 1 Introduction

1 Introduction

Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring after at least 48 hours of endotracheal intubation and mechanical ventilation (MV) (ATS, 2005). An average of 8-28% of patients on mechanical ventilators in the intensive care unit (ICU) develop VAP (Timsit et al., 2011), but its incidence can be as high as 78% (Rello et al., 2002). Consequently, VAP is associated with increased morbidities, mortality, economic burden, and reduced quality of life (QoL). Yet, a number of strategies have proven effective in preventing VAP. Increasing evidence in the literature suggests a strong link between colonization of dental plaque, respiratory pathogens and VAP (Munro et al., 2006). Anti-septic chlorhexidine (CHX) is one preventive strategy that targets oral pathogens. Topical CHX application, as a part of oral hygiene care, has been shown to reduce the odds of VAP by 40%, i.e. for every 15 mechanically ventilated patients in ICU daily CHX application will prevent one patient from developing VAP (Shi et al., 2013). On the other hand there are meta-analysis reporting possible increase in mortality rate from CHX use (Price et al., 2014). Despite numerous studies suggesting the effectiveness of CHX in preventing VAP, the knowledge gap in the cost-effectiveness and cost-utility of CHX warranted further study. The main objective of this study is to evaluate the cost-utility of CHX application for VAP prophylaxis in ICU. From a health care perspective, it is important to understand the cost-effectiveness and cost-utility of clinically effective treatments so that the health resource can be distributed more efficiently. This study provides valuable information for policymakers and stakeholders with respect to budget planning and policy implementation. Furthermore, the findings will have a global impact because VAP is a common condition around the world. It will be particularly beneficial to resource limited countries that suffer fiscal strains.
1.1 Statement of the problem

VAP is highly preventable with appropriate preventive care, yet a high proportion of patients on mechanical ventilators in ICU still develop VAP. This is problematic because VAP is associated with adverse health outcomes resulting in reduced QoL, as well as high costs that constitute a burden on the health care system. In concordance with published studies on effectiveness of CHX in preventing VAP, clinical practice guidelines indicate the use of CHX. However, possibility of mortality associated with CHX is of a rising concern. Therefore, this conflicting evidence on CHX justifies the need for further research on its clinical and economical aspects, hence its degree of cost-effectiveness and cost-utility.

1.2 Purpose of the study

The purpose of this study is to determine the magnitude of the cost-utility of CHX applications in preventing VAP in the ICU as compared to standard/usual care that does not include CHX therapy. This study shall provide an insight to the cost associated with VAP and ICU stay for health professionals, decision makers, and policy administrators. Depending on the results of the study, CHX use may or may not be encouraged as standard of care for all intubated patients in ICU. This study will provide a framework to make informed decisions regarding the prevention of VAP using CHX based on the cost-effectiveness and cost-utility of CHX on the prevention of VAP.
1.3 Central research question

What is the cost-utility of CHX in preventing VAP in mechanically ventilated patients in ICU compared to standard care that does not include CHX?

1.4 Implication of research

Despite numerous studies suggesting the effectiveness of CHX in preventing VAP, the knowledge gap in the cost-effectiveness of CHX warrants further study. Cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) are designed to evaluate the adequacy of resource use in terms of costs and effectiveness of an intervention. The results from our CUA will inform decision-makers by providing general information on the relative costs and health benefits of CHX application in preventing VAP; this information can contribute through multiple channels to a more informed debate on resource allocation priorities. In essence, the results may suggest replacing a less efficient intervention aimed at a particular condition with a more efficient alternative (Drummond et al., 2005; Edeje et al., 2012).

Those who are interested in conducting health economic evaluations include parties with limited funding. With this information, hospitals will be able to allocate their budgets more efficiently. For health care providers, this information will be useful in determining clinical guideline recommendations as to whether CHX application should be maintained in the protocol for day-to-day care. In addition, this study will emphasize the cost-effectiveness and cost-utility of CHX in the prevention of VAP.
1.5 Knowledge translation plan

The knowledge translation goal for this study is to provide and promote evidence-based decision-making in policy development for VAP prevention programs. The results obtained from this study will be disseminated to stakeholders involved in the development of ICU patient management programs locally and nationally, and it may also be applicable to hospitals in low-income countries. Further this knowledge dissemination will be done through multiple channels including publication in a peer-reviewed journal that target the main audience in hospitals and presentations at provincial- and national-level conferences.

1.6 Background

1.6.1 Definition of pneumonia

Pneumonia is an infection caused by the invasion and overgrowth of microorganisms in pulmonary parenchyma that induces inflammation provoking intra-alveolar exudates (Alcón et al., 2008; Mandell & Wunderink 2011). It is commonly associated with a sharp, shooting pain aggravated by inspiration or coughing (Longo et al., 2011). Pathophysiology, etiology, and signs and symptoms of pneumonia will be discussed in detail in a later section of this review.

1.6.2 Different types of pneumonia

Pneumonia is an umbrella term that encompasses the different types of the disease, based on where it is acquired. It can be typically divided into community-acquired (CAP) and nosocomial
pneumonia (Mandell & Wunderink, 2011). Subgroups of nosocomial pneumonia are hospital-acquired pneumonia (HAP) and VAP (Weber & Salgado, 2013). Further auxiliary divisions include healthcare-associated pneumonia (HCAP) (Alcón et al., 2008; Mandell & Wunderink, 2011). These terms reflect the route through which pneumonia is acquired. For example, CAP refers to the pulmonary infection that is acquired in community settings outside the hospital, and HAP is defined as pneumonia identified after 48 hours of hospital admission in patients without evidence of an infection and/or incubation of pathogens at the time of admission (ATS, 2005). VAP is a type of pneumonia that arises more than 48 hours after a patient is intubated and mechanically ventilated (ATS, 2005). HCAP is a type of pneumonia found in hospitalized patients within 90 days of admission to an acute care or long-term care facility (ATS, 2005).

1.6.3 Epidemiology of pneumonia and VAP

Pneumonia is a common complication particularly in populations using MV in the ICU (Longo et al., 2011). The pooled cumulative incidence of VAP is reported as 22.8% (Safdar et al., 2005). This reported incidence of VAP coincides with the results reported by Timsit et al., (2011) which was determined from 4,802 patients in 51 control groups of randomized studies. In addition, a Canadian study with 1014 ventilated patients reported 17.4% of VAP (Heyland et al., 1999). Muscedere et al. (2008a) tabulated the mean incidence of 10.6 cases per 1000-ventilator days amongst medical and surgical patients in Canada. In comparison, the incidences of VAP according to the US National Nosocomial Infection Surveillance varied among different types of ICUs. The highest incidence of VAP cases was 15.2 per 1000-ventilator days in trauma ICU (NNIS, 2004).
The variation in the incidence rate of VAP in the literature is due to differences in diagnostic methods as well as prevention techniques (Eggimann et al., 2003; Timsit et al., 2011). VAP rates reported by the major hospitals in Ontario in the past decade dropped to approximately 1.09 per 1000-ventilator days (HQO, 2015). However, conclusion must be drawn carefully in terms of whether there has been an actual reduction in the number of VAP cases or if it appears to be reducing. The driver of the decreasing rates may be the variation of VAP definitions due to quality improvement initiatives and a systematic change to adjust VAP criteria (CDC, 2015; Timsit et al., 2011). Ventilator-associated events surveillance definition algorithm is one (CDC, 2015). Another possible reason for the decrease in the incidence of VAP is because VAP cases had to be reported as a quality indicator. However, this accounts for the definition of VAP with stricter criteria and subsequent under-reporting of VAP.

Literature reports that VAP is diagnosed with the highest frequency in the first five days of admission to the critical care unit, and shows a plateau in additional risk after two weeks (Cook et al., 1998; Longo et al., 2011). A Canadian study reported seven days for the median duration from ICU admission to the onset of VAP (Heyland et al., 1999). On average, patients with VAP are subject to an additional 4-9 days in the hospital and 4.3 days in ICU (Muscedere et al., 2014).

1.6.4 Global VAP rates

Gathering reliable data on the global burden of VAP is still a big challenge (Lev et al., 2015). However, it is generally accepted that VAP is associated with high morbidity including prolonged MV, ICU length of stays and often excessive antibiotics use (Lev et al., 2015; Edwards et al, 2009; O’Grady et al, 2012).
There are significantly different VAP rates between industrialized and resource limited countries. Recent publications report 1 to 4 VAP cases per 1000-ventilator days in North America and around 15 cases per 1000-ventilator days in resource limited countries (Rosenthal et al., 2012) (Table 1).

Although the numbers may seem low in industrialized countries such as Canada and US, Muscedere et al. suggested that data from the new surveillance system may be underestimating the reality (Morrow et al., 2006; Drees et al., 2010). The reduced reported VAP rates may be a reflection of a new surveillance system itself and not a true estimate of improvement (Kollef, 2014). This argument in turn speaks to the fact that VAP is still a burden on the health care system and that the appropriate prevention strategies must be applied and evaluated even in industrialized countries. However, a reduction in VAP rate is being reported globally. For example in Saudi Arabia, the VAP rate decreased from 19.1 in 2003 to 6.3 per 1,000 ventilator-days in 2009 (Al-Doriz et al., 2012). The study reports that this improvement is a pooled effort from surveillance, and the practice of evidence-based prevention focused on identified modifiable risk factors (Al-Doriz et al., 2012).

1.6.5 Etiology and pathophysiology of pneumonia

Pneumonia is triggered by microbial proliferation and the host’s defensive response to those pathogens once microbial pathogens reach alveoli (Alcón et al., 2008; Longo et al. 2011). Amongst several different ways bacteria intrude into the lower tract of the respiratory system, the most common way is aspiration from the upper respiratory tract, specifically the oropharynx (Alcón et al., 2008; Longo et al. 2011). Patients with decreased levels of consciousness are at a
higher risk of aspiration, particularly during their sleep (Longo et al., 2011). The host defense system is usually sufficient for preventing lung infections and pneumonia in healthy adults and the type of pathogens encountered are less virulent (Alcón et al., 2008); however, patients admitted to hospital have significantly impaired host defense systems for a number of reasons.

Host defense mechanisms include mechanical factors such as hairs and turbinates of nares, which prevent large particles from reaching the lower respiratory tract. In addition, an intact gag and cough reflex protects patients from aspiration while the normal flora in oropharynx prevents pathogens from colonizing and causing pneumonia (Longo et al., 2011). Risk factors for change in the normal flora of the upper respiratory tract include underlying disease, tracheal intubation, and systemic antibiotic treatment (Alcón et al., 2008).

Despite these defense mechanisms, microorganisms may find their way to the alveolar level. If they do, local proteins with antibacterial or antiviral properties assist resident alveolar macrophages in clearing pathogens (Longo et al., 2011). Microorganisms can then be either eliminated by the mucociliary elevator or through the lymphatics (Longo et al., 2011). When these defenses are absent, these organisms may successfully colonize the oropharynx and lungs. The clinical manifestation of pneumonia will become evident when alveolar macrophages exceed their capacity to engulf a microorganism and initiate an inflammatory response to trigger lower respiratory tract defenses (Longo et al., 2011). Fever is a reflection of inflammatory mediator release such as interleukin-1 and tumor necrosis factor, while peripheral leukocytosis and increased purulent secretion is a result of neutrophil reactions stimulated by chemokines (Longo et al., 2011).
1.6.6 Risk factors and pathology of VAP

It is important to understand the pathophysiology of VAP because doing so enables the design of preventive strategies. The pathogenesis of VAP consists of invading pathogen(s), risk factors, and host defenses.

There are three common risk factors in the pathogenesis of VAP: colonization, aspiration, and impairment of host defense mechanisms. First, pathogenic microorganisms may colonize the oropharynx, mainly through the colonization of dental plaque (Longo et al., 2011). Secondly, aspiration of these organisms into the lower respiratory tract may occur in intubated patients (Longo et al., 2011). Although the endotracheal tube may prevent aspiration of large volumes, micro-aspiration can occur. Further, it is the most common risk factor because it provides a pathway for pathogens to bypass the normal mechanical defense system (Longo et al., 2011). Microorganisms may also be introduced to the lung parenchyma via bacteremia and contaminated aerosols (Alcón et al., 2008). Fiberoptic bronchoscopy, a procedure using a tube-like instrument to assess the airways and lung tissue, can also introduce microorganisms as it is passed into the lungs. Lastly, the normal host defense mechanisms can be severely impaired during a critical illness (Longo et al., 2011). Other sources include nasogastric tubes, which do not improve gastroesophageal reflux or microaspiration, but rather give rise to lower oesophageal sphincter incompetence and thus increasing the risk of aspiration (Alcón et al., 2008). Additionally, the position of the patient in bed can increase the likelihood of gastric reflux and aspiration (Alcón et al., 2008). Other risk factors for VAP are advanced age, other comorbidities, and prolonged intubation or re-intubation (Weber & Salgado, 2013). In addition, damaged tracheal mucosa from the endotracheal tube and suctioning can facilitate the colonization of the lungs by pathogenic bacteria. Biofilms of bacteria can develop on the endotracheal tube and are
often protected from antibiotics and host defenses, and suctioning can dislodged bacteria (Long, 2011).

The main pathogenesis of VAP is from the leakage of colonized oropharyngeal secretions around the endotracheal tube cuff (Craven & Hjalmarson, 2010; Longo et al., 2011). Bacterial pathogens from these secretions cause microaspiration and an intraluminal bacteria biofilm in the endotracheal tube can enter the lower respiratory tract and colonize it (Craven & Hjalmarson, 2010). The progression seems inevitable as the endotracheal tube cuff and intraluminal biofilm make the clearance of bacteria and secretion difficult without manual suctioning. Together with the given condition, local trauma and inflammation from the lower respiratory tract and the failure of host lung defenses will result in the development of VAP in some patients.

Host lung defenses fight these bacterial pathogens and help prevent the progression of the disease from colonization to VAP. This defense system consists of cilia, mucous, polymorphonuclear leukocytes, and macrophages and their respective cytokines, antibodies (IgM, IgG, and IgA), and complements (Longo et al., 2011). Many critically-ill intubated patients have pathogenic bacteria instead of normal flora in the oropharynx (Longo et al., 2011). The risk factors for this change are exposure to antibiotics, contaminated instruments, cross-infection from other patients, and malnutrition (Longo et al., 2011). For example, *P. aeruginosa* causes infection almost only through antibiotic exposure. Some specific pathogens such as *Stenotrophomonas maltophilia* are markers for poor immune systems and therefore are associated with a higher mortality rate. In some cases involving immune-compromised patients where fungal and viral pathogens may be associated with VAP.

Etiological agents of VAP are multidrug-resistant (MDR) and non-MDR pathogens. The spectrum ranges between species of both gram-negative bacilli and gram-positive cocci (Rotstein
et al., 2008). The MDR pathogens are associated with the highest attributable mortality compared to any other causative pathogens (Brusselaers et al., 2011). The most common MDR pathogens found in VAP patients are *Pseudomonas aeruginosa* (*P. aeruginosa*), methicillin-resistant *S. aureus*, *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumoniae* (Craven & Hjalmarson, 2010). The non-MDR pathogens, for example *S. pneumoniae*, *Haemophilus influenzae* and Gram-negative bacilli, are similar to those found in severe CAP (Longo et al., 2011). The virulence of the pathogens vary by institution and the relative frequency of each often varies significantly both within and among hospitals (Longo et al., 2011).

In summary, the development of VAP involves a number of factors including oropharyngeal colonization, microaspiration and an overwhelmed host defense system. Therefore, alterations in types of pathogens in the oropharynx, host factors, and use of antibiotics may influence the colonization of microbes associated with VAP (Longo et al., 2011).

1.6.7 Diagnosis

Both radiographic and clinical evidence must be present to diagnose VAP in patients who have been intubated for at least 48 hours. Radiographic signs include new or progressive and persistent infiltrations or cavitation on an antero-posterior chest radiograph (Craven & Hjalmarson et al., 2010; Weber & Salgado, 2013). Although the sensitivity and specificity of chest radiographs are not high, the absence of abnormality can be helpful in excluding VAP (Amanullah et al., 2013).
Clinical signs and symptoms include fever (> 38 degrees Celsius), leukocytosis (>11,000 leukocytes/mm$^3$) or leukopenia (<3,500 leukocytes/mm$^3$), and a decline in oxygenation (Amanullah et al., 2013; Craven & Hjalmarson, 2010; Rotstein et al., 2008; Weber and Salgado, 2013). An additional indicator is purulent sputum, which can be either newly formed or already present, but with a change in characteristics and an increase in the volume of sputum that can affect suctioning requirements (Rotstein et al., 2008).

In addition, a positive microbiological sample from the lower respiratory tract is another indication of the condition (Rotstein et al., 2008; Weber & Salgado, 2013). A positive sample includes a protected specimen brush (PSB), bronchoalveolar lavage, or an endotracheal aspirate with a positive gram stain and polymorphonuclear leukocytes, with or without bacteria (Craven & Hjalmarson, 2010). However, microbiological sampling may be of no benefit in the absence of any clinical indicator, and rather cause harm (Weber & Salgado, 2013). It may induce unnecessary treatment such as antibiotic therapy and expose patients to side effects and drug-resistance issues without clinical benefit (Weber & Salgado, 2013).

Altogether, it is difficult to diagnose VAP (Timsit et al., 2011). Some studies report that invasive microbiological sampling techniques such as bronchoscopic examination, bronchoalveolar lavage, and the protected specimen brush are more specific in diagnosing VAP than a regular clinical or non-invasive exam. However, supporting evidence is lacking and these procedures may be subject to the introduction of unnecessary pathogens. Although quantitative bacterial cultures are preferred over non-quantitative cultures, the results from endotracheal aspirates are sufficient for a diagnosis of suspected VAP (Amanullah et al., 2013; Muscedere et al., 2014).

According to Centre for Disease Control and Prevention diagnostic criteria, initial treatment of VAP starts on the suspicion of VAP using chest x-ray and clinical parameters. However, the
confirmation of VAP with positive cultures may take up to 48 hours to come back. Therefore, during this time, patients are at risk of being over-treated and subject to antibiotics overuse.

1.6.8 Prognosis and outcomes

Mortality is the most significant outcome of VAP. Some studies report the mortality in VAP patients is doubled compared to those without (Amin, 2009; Safdar et al., 2005). Amin (2009) reported a pooled odds ratio of 2.03 (95% CI 1.16-3.56; p=0.05) for ICU mortality in VAP patients compared to ICU patients without VAP. But patients who develop VAP often have underlying diseases that may result in death from other causes, and so VAP may be more of an marker of overall disease severity and an immunocompromised state. Therefore, it is important to distinguish deaths directly attributable to VAP from those that are not. Mortality rates for VAP vary among the type of patients and underlying diseases that brought them to ICU. Overall rates can range from 24% to 50%, and can be as high as 76% (Chastre & Fagon, 2002; Lev et al., 2015). In addition, geriatric patients appear to have one of the highest mortality rates from VAP with 30.6%. (Lizza et al., 2014).

There are considerable variations in the reported VAP mortality rates in the literature. In Canada, the attributable mortality associated with VAP is 5.8% (95% CI -2.4% - 14.0%) (Heyland et al., 1999). This rate is consistent with the attributable mortality rate of 4-6% (Bekaert et al., 2011; Timist et al., 2011). Attributable mortality refers to the death directly caused by VAP. For example, if the risk of death increased from 10 to 20% due to VAP, the attributable mortality would be 10% (Timsit et al., 2011). However, in most cases, it is defined by the difference in
mortality rates between patients with and without VAP without considering confounders (Timsit et al., 2011).

Some of the clinical characteristics that may influence the variation of VAP mortality rates include the severity of an underlying illness, the type of microbial pathogen and its resistance, and the provision of appropriate antibiotic treatment (Timsit et al., 2011). As one might expect, comorbidities such as chronic renal failure increase the risk of mortality (Timsit et al., 2011). Studies have found that the mortality rate is higher in general surgical and non-traumatic patients than in medical and trauma patients. This is likely due to the fact that many trauma patients are assumed healthy without any comorbidities or predisposing factors. For some patients that have multiple comorbidities and consequently a poor prognosis, it is often impossible to determine the attributable mortality of VAP.

Increased costs associated with prolonged ventilator days and ICU stays varied amongst hospitals. Amin (2009) reported 6.10 additional mean number of ICU days (95% CI 5.32-6.87 days) in VAP patients. These additional costs are associated with ICU beds, antibiotic regimens for VAP treatment, and physician and nurse fees (Amin 2009). Total reported costs range between $10,000 – 40,000 per VAP case (Amin, 2009). In Canada, it is estimated that the total cost of VAP per year is approximately $46 million per year with a range of $10 million to $82 million based on 4000 cases of VAP per year (Muscedere et al., 2008a).

These outcomes from many studies highlight the clinical impact and economic burden of VAP, which in turn emphasizes the importance of preventions that are cost-effective (Kolleft et al., 2012). Based on these findings, aggressive preventive strategies have been developed and are being implemented worldwide.
The impact of reducing VAP is not only about decreasing the economic burden on hospital from reducing the length of stays in ICUs and hospitals, and improving the QoL for patients, but also potentially decreasing the use of antibiotics, which in turn can have a positive impact on the worldwide antibiotic resistant problem. To achieve this, we need to focus on prevention, and early diagnosis and treatment.

1.6.9 Prevention

VAP continues to be common in ICUs. This is problematic because it is associated with increased length of ICU stays, which in turn is associated with greater hospitalization costs, higher mortality rates, and compromised patient QoL (Longo et al., 2011; Nussenblatt et al., 2014). These negative outcomes of VAP justify the need for more effective protocols that can prevent the occurrence of VAP and hence reduce both the costs and complications associated with mechanical ventilation (Bowton et al., 2013).

Risk factors must be addressed when determining the most appropriate prevention strategies. A retrospective matched-cohort study by Rello et al. identified non-modifiable risk factors associated with VAP development in ICU patients as male sex (adjusted OR, 1.58), admission to the trauma unit (adjusted OR, 1.75), and the severity of the underlying illness at hospital admission (adjusted OR, 1.47–1.70). Other risk factors include age over 60, multi-organ failure, prolonged invasive ventilation, history of neurosurgery, coma and previous antibiotic exposure (Maselli & Restrepo, 2011; O’Grady, 2012).

Aggressive early prevention is the most effective way of preventing VAP and is commonly practiced in North America. However, variations in clinical guidelines exist that include
preventive interventions in terms of positional, pharmacologic and non-pharmacologic measures. The following have been proposed to decrease the incidence of VAP and its complications in a number of studies (Longo et al., 2011; Lorente et al., 2007; Muscedere et al., 2008b).

1) Elevate head of bed to 30-45 degrees, preferably 45 degrees i.e. place a patient in a semi-recumbent position to prevent micro-aspiration of stomach contents.

2) Decontaminate the oropharynx regularly with CHX with mechanical cleaning of oral cavity to prevent colonization of mouth with pathogens.

3) Daily sedation vacation and assess readiness to extubate daily to minimize the duration of ventilation and reduce overall time-at-risk.
   a. Sedation vacation is a medical term referring to a scheduled interruption of sedation in ICU patients

4) Perform additional endotracheal tube and ventilator specific preventive measures:
   a. Endotracheal Tube:
      i. Use endotracheal tube with subglottic secretion drainage to prevent aspiration of secretions above the endotracheal tube cuff
      ii. Use oral intubation instead of nasal approach
   b. Ventilator:
      i. Use closed suctioning system to avoid aerosolization of pathogens
      ii. Use passive humidifiers or heat moisture exchangers as they reduce colonization of the ventilator circuit
         1. Change heat and moisture exchangers every 5-7 days
      iii. Change ventilator circuit with every new patient to prevent cross-contamination
   c. PEEP
d. Change closed endotracheal suctioning system for every new patient and as needed clinically.

e. Use non-invasive ventilation when feasible.

Health professionals should be mindful of the fact that the guidelines should be followed on the basis of each individual case and that they are subject to modifications.

Although positioning a patient’s bed in a semi-recumbent position is an easy and cost-effective intervention for VAP prevention, this is often limited to certain types of ICU patients e.g. trauma patients who are on spine precautions and need to remain in a horizontal supine position (Table 2) (Alexiou et al., 2009).

As discussed earlier, the aspiration of colonized oropharyngeal secretions is a major factor in the pathogenesis of VAP. A tapered-cuff endotracheal tube has been demonstrated to reduce aspiration around the cuff. Whether these properties are efficacious in reducing VAP is not yet known (Bowton et al., 2013). For example, in the study where there was high adherence to a VAP prevention bundle, the use of a tapered-cuff endotracheal tube was not associated with a reduction in VAP rates (Bowton et al., 2013).

Prevention strategies in European guidelines coincide with recommendations in the Ontario guideline. Oral care protocols in the Critical Care Manual of Clinical Procedures and Competencies, endorsed by the British association of critical care nurses (Mallett et al, 2013) include:

• Mechanical toothbrushing at least twice a day.

  o Use of small-headed toothbrush that allows for better maneuvering inside the mouth of the intubated patient.
• The complete removal of toothpaste from the oral cavity to prevent it from drying there.
• Use of antiseptic 0.12% CHX gluconate.

Since the discovery of the oral-systemic link between intraoral microbiome and respiratory infections, oral flora have been paid attention to as a reservoir for VAP pathogens with a potential for colonizing on the ventilator (Avila et al., 2009). In turn, efforts, such as routine oral hygiene care in the ICU, have been made to reduce oral flora with the aim to ultimately reduce VAP.

VAP is one of the most common hospital-acquired infections in intensive care units (Lawless et al., 2012). There have been initiatives to prevent VAP across the world. For example, a VAP surveillance program in Ontario, Canada requires hospitals to report VAP rates and instituting a universal guideline on evidence-based practices in critical care has been proposed to help reduce VAP incidences. The four principles of this guideline include quality improvement initiatives, surveillance and audit, best practices for VAP prevention, and services and tools that can be utilized (Lawless et al., 2012).

1.6.10 Chlorhexidine

One simple approach to reduce the risk of pneumonia, as has been identified by systematic reviews, is oral hygiene care (Azarpazhooh & Leake 2006; El-Rabbany et al., 2014; Shi et al., 2013). Effective oral hygiene care is important for ventilated patients in ICUs (Azarpazhooh & Leake 2006; El-Rabbany et al., 2014; Shi et al., 2013). Oral hygiene care not only refers to mechanical brushing but also the use of additive materials such as a mouth rinse. In spite of some
studies that report a possible increase in the mortality rate from CHX use, VAP prevention guidelines still recommend the use of CHX. Muscedere et al., (2008b) indicated that CHX is preferable in terms of its safety, feasibility and cost considerations. These results are supported by the most recent Cochrane review by Shi et al. (2013). This review reported that CHX mouthwash or gel was associated with a 40% reduction in the odds of developing VAP in critically ill patients. In other words, for every 15 mechanically ventilated patients in the ICU, the use of CHX will prevent one patient from acquiring VAP (Shi et al., 2013). A recent review also suggested that CHX rinses, gels and swabs may be effective in disinfecting the oral cavity in patients at high risk of acquiring VAP (El-Rabbany et al., 2014).

1.6.11 Mechanism of CHX, pathophysiology

A widely used topical bactericidal agent, CHX is frequently found in oral products such as CHX solutions, gels, and/or varnishes at different concentrations and formulations (Weinstein et al., 2008).

One of the indications of this antiseptic is that it has plaque growth inhibitor that will be an adjunct to oral care in medically compromised patients with difficulty in maintaining oral hygiene (Quirynen et al., 2001). It is known for its intraoral substantivity and wide spectrum bactericidal and bacteriostatic efficacy along with low irritation (McDonnell, 1999; Quirynen et al., 2001). It is effective in both gram-positive and gram-negative non-sporulating bacteria, and yeast (Quirynen et al., 2001). However, CHX has little effect on mycobacteria, sporulating bacteria, and has variable effects on virus (McDonnell, 1999). For example, studies report a rapid uptake of CHX occurring within 20 seconds by *E. coli* and *S. aureus* (McDonnell, 1999).
The antibacterial action of this cationic biguanide works by disrupting the integrity of a negatively charged bacterial cell membrane (Quirynen et al., 2001) resulting in a leakage and a change in the osmotic equilibrium of the bacterial cell (Weinstein et al., 2008). CHX can damage the outer cell layer of bacteria, but this action itself will not usually induce cell death. A bactericidal effect of CHX starts with affecting the integrity of the cytoplasmic inner membrane at low concentrations and when the agent crosses the cell wall through diffusion (McDonnell, 1999). At high concentrations, CHX can cause intracellular precipitation of proteins and nucleic acids, and congealment of cytoplasm at high concentrations, resulting in decreased leakage and cell death.

1.6.12 Side effects of CHX

CHX has disadvantages. It can cause irritation in oral mucosa, contact dermatitis and rarely hypersensitivity and severe allergic reactions (Weinstein et al., 2008). Further, staining of the pellicle and tongue and adverse effects on the intensity and quality of taste have been reported (Quirynen et al., 2001). However, there have been no reported adverse consequences in patients of all ages and no data to suggest that trace levels have clinical importance (Weinstein et al., 2008, Shi et al., 2013).

1.6.13 Current CHX recommendations in Ontario

Oral care is provided to everyone in ICUs in Ontario as per Ontario’s oral assessment guide in the University Health Network Policy & Procedure Manual for critical care nursing. There are three levels of care: basic, advanced or extensive. All intubated patients receive advanced oral
care, which includes the use of CHX.

Directly Adopted from the *University Health Network Policy and Procedure Manual* (Lawless et al., 2012)

**Procedure for Basic Oral Care: Score 5 (to include tracked patients)**

1. Independent Care: Brush teeth q 12 hours.
   - Provide patient with the following items:
     a. toothbrush
     b. toothpaste
     c. towel – to protect gown and to wipe face
     d. cup of room temperature water
     e. kidney basin or Yankauer and suction source

2. Non-independent Care:
   - Brush teeth q 12 hours with a soft brush.
   - Oral freshening q 2-4 hours with foam stick and water.
   - Suction excess secretions with oral Yankauer.
   - Ice Chips P.R.N. after consultation with physician or speech pathologist.
   - Encourage patient to wear dentures when possible, and remove them during evening care.

   **Note:** Brush off any debris before soaking over night.

**Advanced Oral Care: Score 6-8 (and to include all intubated patients)**

1. Brush teeth with soft toothbrush twice a day (i.e., 06/18 or 08/20 or 10/22 hours).
2. CHX 0.12% mouth rinses q bid.

   · Pour 15 mL of CHX 0.12% into a medicine cup.

   · Soak foam stick in CHX 0.12% until saturated.

   · Rub soaked foam stick along buccal, gingival, tongue and tooth surfaces in a circular motion. · Discard foam stick after each use.

   · Avoid any other oral agents for 30 minutes after CHX rinse.

3. Mouth freshening every 2-4 h and P.R.N. with either

   a. foam stick and water

   b. foam stick and 1.5 % hydrogen peroxide

4. Lubrication of lips and oral mucous every 2-4 hours with a water-soluble ointment.

5. Do not use nystatin two hours before or after the use of CHX solution.

CHX 0.12% may stain teeth, but this can be reversed by professional dental cleaning.

Extensive Oral Care: Score 9 or greater (individualized based on assessment, diagnosis or physician-specific directives)

1. Dry mucosa/tongue: obtain order for artificial saliva replacements.

2. Excessive bleeding: gentle mouth rinses with foam stick and water every hour and prn.

3. Assess for pain, ulceration, infection, bleeding gingival or altered saliva consistency.

Although CHX application is a strongly recommended procedure in preventing VAP, it is unclear how much of which concentration is best for which use. As well, the practice of oral decontamination for MV patients is variable among different countries. There is not enough evidence available on the effectiveness of other mouth care rinses such as water, saline or
triclosan (Shi et al., 2013; El-Rabbany et al., 2014). Questions remain about its cost-effectiveness, cost-utility long-term safety, and the generalizability of the efficacy of CHX (Weinstein et al., 2008). Further, there has been an ongoing debate on downgrading CHX use in response to a trend of increased mortality rate, though the rate is not statistically significant. Therefore, this study aims to determine the cost-effectiveness and cost-utility of CHX intervention in preventing VAP in mechanically ventilated patients in ICU.
Table 1. Mean VAP rates globally

<table>
<thead>
<tr>
<th>Location</th>
<th>Mean VAP rate (per 1000 ventilator days in ICU patients*)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>1.6 – 7.3 per 100,000 persons</td>
<td>Lizza et al., 2014</td>
</tr>
<tr>
<td>US</td>
<td>1.27</td>
<td>Kollef et al., 2012</td>
</tr>
<tr>
<td>US</td>
<td>1-4</td>
<td>National Healthcare safety network NHSN Edwards et al., 2009</td>
</tr>
<tr>
<td>US</td>
<td>15.2</td>
<td>National Nosocomial Infectious Surveillance (NNIS), 2004</td>
</tr>
<tr>
<td>Canada</td>
<td>10.6</td>
<td>Muscedere et al., 2008d</td>
</tr>
<tr>
<td>Ontario, Canada</td>
<td>2.8</td>
<td>Health Quality Ontario website – source MOHLTC</td>
</tr>
<tr>
<td>Multicenter Canada</td>
<td>9</td>
<td>Sinuff et al., 2013</td>
</tr>
<tr>
<td>Europe</td>
<td>13.5</td>
<td>European Centre for Disease Prevention and Control (ECDC) 2011 – National Health Service</td>
</tr>
<tr>
<td>Japan</td>
<td>12.6</td>
<td>Suka et al., 2007</td>
</tr>
<tr>
<td>Brazil</td>
<td>24.7</td>
<td>da Rocha et al., 2008</td>
</tr>
<tr>
<td>China</td>
<td>5.7 - 21.4 baseline</td>
<td>Tao et al., 2012</td>
</tr>
<tr>
<td>Resource limited countries</td>
<td>8.1 - 11.7 baseline</td>
<td>Rosenthal et al., 2012</td>
</tr>
<tr>
<td>Resource limited countries</td>
<td>13.6</td>
<td>Rosenthal et al., 2010</td>
</tr>
<tr>
<td>36 Resource limited countries</td>
<td>15.8</td>
<td>Rosenthal et al., 2012b</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>15.9</td>
<td>Al-Dorzi et al., 2012</td>
</tr>
</tbody>
</table>

* Ventilator days are the number of days spent on a ventilator by patients in ICU. The number of VAP cases per 1000 ventilator days indicates the total VAP, and is commonly used when reporting VAP. The VAP rate is number of new cases of VAP in the ICU per 1,000 ventilator days. The numerator equals the total number of VAP cases in the ICU after 48 hours of mechanical ventilation in the ICU. The denominator equals the total number of ventilator days for patients 18 years and older (Health Quality Ontario, 2014).
### Table 2. Effectiveness of various preventive strategies in NNT, OR and/or RR

<table>
<thead>
<tr>
<th>Type</th>
<th>NNT/OR/RR*</th>
<th>Benefits/ Side-Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12 – 0.2% CHX + Toothbrushing</td>
<td>NNT = 15</td>
<td>Discolouration and taste alteration.</td>
<td>Shi et al., 2013</td>
</tr>
<tr>
<td></td>
<td>OR = 0.60</td>
<td>However, medically not significant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.47-0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5% Hydrogen Peroxide + Antibiotics + Moisturizer + Toothbrushing</td>
<td>8.9% developed VAP compared to 33.3% in control</td>
<td>Lev et al., 2015</td>
<td></td>
</tr>
<tr>
<td>Head of bed 45 degree position</td>
<td>OR = 0.47 (0.27-0.82)</td>
<td>Easy and cost-effective intervention, however not always feasible</td>
<td>Alexiou et al., 2009</td>
</tr>
<tr>
<td>ETT with subglottic secretion drainage</td>
<td>RR = 0.55 (0.46, 0.66)</td>
<td>No effect on mortality or ICU LOS</td>
<td>Muscedere et al., CCM 2011</td>
</tr>
<tr>
<td>Toothbrushing</td>
<td></td>
<td></td>
<td>Alhazzani et al., 2013</td>
</tr>
<tr>
<td>Prevention bundle in resource limited countries</td>
<td>Reduction rate 31%</td>
<td></td>
<td>Rosenthal et al., 2012</td>
</tr>
</tbody>
</table>

NNT = Number needed to treat  
OR = Odds ratio  
RR = Relative risk
Chapter 2 Methods

2 Methods

2.1 Basic principles of economic evaluations

The fundamental concept of economics lies on the scarcity of resources and choice. Health economics utilize different methods to evaluate how resources are distributed in health care system and how they can be allocated (Haddix et al., 2003; Elliott et al., 2005). Economic evaluation is one example, which is largely based to the concepts of CEA, CUA and cost-benefit analysis. Each measure the difference in resource consumed and effectiveness generated between alternative intervention strategies (Haddix et al., 2003; Elliott et al., 2005).

While cost-benefit analysis measures both treatment costs and benefits in monetary terms, CEA compares the treatment costs with effects of treatments in naturally-occurring units for example life-years. Similarly, CUAs measure the treatment costs, but its health outcomes associated with treatment are measured in terms of both quantity and quality of life, for example QALYs (Petitti, 1999).

2.1.1 Components of economic evaluations

Economic evaluations are characterized by a number of components that are shared across the three forms. These include the concepts of the time horizon, the perspective and discounting. Time horizon of the analysis is the length of time that is expected to be sufficient in order to capture all health and economic outcomes of the treatment alternatives (Petitti, 1999). Defining the perspective of the analysis, typically societal or individual, is important because costs and
outcomes are measured differently (Petitti, 1999). It dictates the kind of costs and benefits that are included in the analysis based on who is paying the cost (Petitti, 1999). Therefore, type of costs incurred will vary with different perspectives. For example, when the perspective of the Ontario Ministry of Health is taken (i.e. the “payer” perspective in Ontario, since the Ontario Ministry of Health covers most of the healthcare expenditure), the focus is on the costs of providing health care service, hospitalization, labour and material; whereas in perspective of a patient, costs are those associated with their pocket expenditure for receiving health care service, wage loss/loss of time from work, and transportation. Societal perspective, which combines all of the above costs, is generally accepted for cost analysis studies conducted by public health agencies (Petitti, 1999). Discounting is a type of time preference adjustment in health-related economic evaluations, which devalues the future values by a constant annual change in cost and outcomes (Bonneux and Birnie, 2001). Discounting accounts for individual and society preferences for receiving benefits early and paying costs later. For example, discounting of 5% refers to the fact that the health outcomes are devalued by 5% in the first year. Devaluation will be 40% in 10 years, 65% in 20 years and so on. The relationship is that the greater the number of years ahead, the larger the discounting factor and the lower the current value will be (Bonneux and Birnie, 2001). Economic evaluations account for the increase in treatment and associated costs by adjusting costs according to the inflation rate – the health component of the consumer price index (CPI) at specific time, so that they are measured in current currency values (Petitti, 1999).
2.1.2 Costing in economic evaluations

In all types of economic evaluations, costs of treatment are measured in the same way, through identification and valuation of all costs associated with the treatments. Identification of costs includes determining direct, opportunity and/or productivity/indirect costs depending on the perspective of the analysis (Petitti, 1999). Determination of individual cost can be challenging and therefore, macro-costing is more commonly used in practice than micro-costing methodologies (Petitti, 1999). This approach counts amount of inputs such as hospital days and assigns costs to each input based on market prices, for example Medicare fee schedule for cost of in-hospital physician services (Petitti, 1999).

2.1.3 Cost-utility analysis and quality-adjusted life years

The CUA incorporates the effects of treatments in means of both extension of life but also its effect on the patient’s QoL (Petitti, 1999). For example after a prolonged intensive care stay, a patient is often left severely debilitated having survived multiorgan failure and other complications. For this reason, survival alone may not be a sufficient endpoint in assessing resource allocation. Instead, other measures of outcome, such as health-related quality of life (HRQoL) that includes self-reported measures of physical and mental health, is equally important (Oeyen et al., 2010; Stricker et al., 2005).

The primary health outcome used in CUA is QALY (Petitti, 1999). It is a measure of health outcomes combining information on quantity or the number of years of life lived from the intervention and QoL into a single measure. Each year of life is assigned with an utility value representing the QoL of a patient. Perfect health is assigned a value of 1.0, while death has a
QoL of 0.0. If the number of years of life lived are not lived in perfect health, quality of these years would have values less than 1.0. These QoL values vary among disease states and health conditions that the individual is in during their lifetime. For example, if an individual is expected to live 2 years of life in perfect health because of receiving a particular intervention, then the QALY would be equal to 2 (2 life-years lived x 1 health value = 2 QALYs).

Instruments that measure varying dimensions of HRQoL include EuroQol, quality of wellbeing, health utility index, and SF-36. For the purpose of this research, a generic preference-based QoL measurement instrument, the EuroQol-5D (EQ-5D), will be considered. The EQ-5D consists of five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with three levels (Timmers et al., 2011).

2.1.4 Incremental cost-effective ratio and incremental cost-utility ratio

An overall economic outcome of CEA and CUA is the incremental cost-effectiveness ratio (ICER) or cost-utility ratio (ICUR) respectively. They can be calculated from equation (1) below and provide information on what is the cost of gaining an extra unit of health.

\[
ICUR = \frac{\text{Cost}_A - \text{Cost}_B}{\text{Effectiveness}_A - \text{Effectiveness}_B} \quad (1)
\]
2.1.5 Decision modeling

The ICER or ICUR can be estimated either directly from patient data or through decision modeling. The two most common ways of decision modeling include decision trees and Markov model.

Decision tree is a tool that depicts the problem and effects of interventions in the analysis, and estimates the probability of outcomes of different interventions (Petitti, 1999). It consists of decision and chance nodes, branches and outcomes that represent alternative options, transitions, and consequences of interventions.

A Markov model is another analytical structure that accounts for continuous risk, timing of events, and repeated events (Sonnenberg & Beck, 1993). The principle elements of the Markov model are mutually exclusive health states, constant or time-dependent transition probabilities among states, length of the cycle, and cost or QoL associated with each state (Drummond et al., 2005). There are assumptions specific to the Markov model. It assumes that the patient is in a single state at a given time and that the events are modeled as transitions among states during each cycle (Sonnenberg & Beck, 1993). These individual health states in this model are considered as memoryless because the model does not account for the previous health state that the cohort was in. Therefore, the transition probability depends on the current health state and not on past health states (Drummond et al., 2005). Therefore, this conceptual framework will be beneficial in evaluating costs and health benefits with respect to the current practice of CHX therapy in preventing VAP compared to usual care without CHX.
2.1.6 Sensitivity analysis

Sensitivity analysis is a method of handling parameter uncertainty and other types of uncertainty related to methodological assumptions (Petitti, 1999). It may be performed to assess the impact of uncertainty around input parameter estimates across a range and how parameter variation impacts the overall results of the model. There are several types of sensitivity analysis: univariate, multivariate, scenario analysis, threshold analysis, and probabilistic sensitivity analysis. Therefore, to account for uncertainties around input parameters and to determine the robustness of the intervention effects of CHX use, one-way analyses were performed.

2.2 Model

2.2.1 Data sources

The input parameters for each health state in the model were obtained from the literature and synthesis of published studies. Methods of combining primary studies included conducting meta-analysis. A literature search of PubMed, Cochrane and Scopus databases was conducted to identify studies that reported input parameters including the incidence of VAP in ventilated patients at least 48 hours after ICU admission, ICU and VAP mortality rates with and without CHX, VAP-associated health care costs and EQ-5D QoL measures in the context of the Canadian health care system where possible.
2.2.2 Study perspective

In Canada, healthcare is funded publicly under a universal health insurance system called Medicare. The perspective of this analysis was the Ministry of Health at the provincial level. The provision of VAP treatment has been assumed that is carried out in appropriate health care settings with equipment and competent health professionals.

2.2.3 Time horizon

Time horizon for this study was set at lifetime to take into account the long-term effects of ICU admission, VAP, and CHX preventive treatment.

2.2.4 Discounting

The recommended discounting rate by Canadian government agencies is 5% (CADTH, 2006). Therefore, for this study, discounting of 5% has been selected. The total cost in each group was discounted by 5% using the following equation (2-4).

\[
D_n = \frac{1}{(1+r)^n} \quad (2)
\]

\[
D_T = C_T \times D_n \quad (3)
\]

where \(D_n\) is the discount factor, \(r\) is the discount rate and \(n\) refers to the number of years ahead, \(D_T\) is the discounted total cost \(C_T\) is the total cost in present value.
For daily discounted cost at annual discounting factor of 5% the following equation was used.

\[ C_{5\%} = \frac{C_T}{1 + (0.05/365)^n} \] (4)

where \( C_T \) is the total cost in present value.

2.2.5 Patient Population

The population was general medical and surgical ICU patients with mechanical ventilation for 48 hours or more and free of pneumonia upon admission. Mean age for a hypothetical patient population in this model was set as 65 based on the mean age (64.5 ± 16.4 years) of critically ill patients in ICU from population-based analysis of all adult ICU care in Canadian province of Manitoba (Garland et al., 2013). Children were excluded because data on the effectiveness of CHX solution in children is limited. The primary reason for selecting ICUs for the study is that intubated patients are always found in the ICU setting. Surgical ICU is designed for providing care after elective or emergency surgical procedures in the hospital to stabilize health before transferring to a general ward, whereas general medical ICU specializes in treating medically critically ill patients. Both of these units can sometimes be combined in one institution to form a medical-surgical ICU.
2.2.6 Intervention

Intervention for this study is standard ICU care with CHX application of multiple concentrations at 0.12%, 0.2% and 2% (excluding antibiotic use) as a preventive therapy for VAP in ICU. The antibiotic therapies excluded from the studies refer to selective decontamination using topical antibiotics.

2.2.7 Control

Control for this study is standard ICU care without CHX application as a preventive therapy for VAP in ICU.

2.2.8 Outcomes

The lifetime cost of ICU patients with and without the use of CHX therapy, life-years, QALYs and incremental cost-utility ratios were determined from this study.

2.2.9 Theoretical framework of Markov model

A Markov model depicts the state of a system with a random variable that changes through time. We have constructed a model consisting of 5 health states and possible transition pathways, to evaluate the difference in the cost and health outcomes between standard care with and without the use of CHX for VAP prevention (Figure 1). Health outcomes were measured in both life-
years and QALYs, the cycle length was set at one day to reflect the dynamics of ICU admission and discharge rates, and costs were adjusted to 2015 prices, using the health component of the PCI, and were discounted at 5%. One-way sensitivity analyses were performed to test the uncertainties of these input parameters and their robustness. A cohort of 1,000 patients was entered into the model for cohort simulation. A cohort simulation was performed to assess the input parameters using a Microsoft Excel version 14.1.2 software program.

### 2.2.10 Selected health states, and transition pathways

Five health states are defined for the Markov model for CUA: 1) ventilated without VAP, 2) ventilated with VAP, 3) ventilated after VAP, 4) discharged from ICU after discontinuation of ventilation and without VAP, and 5) dead. The transition between states is described in Figure 1. The number of cohorts moving from states to another was determined by the transition probability associated with each state.

It is assumed that the all patients enter the model through the ‘ventilated without VAP’ state, which refers to the state where the patient is under ventilation upon entry to the ICU and is free of VAP. This is a non-absorbing state because patients can move out of this state and transfer to the state of either ‘ventilated with VAP’, ‘discharged from ICU’, or ‘dead’, or remain in the same state for the cycle.

The state of ‘ventilated with VAP’ refers to the state when a ventilated patient acquires VAP in the ICU. Once patients are in this state, they could now either remain in the same state, be transferred to ‘ventilated after VAP’, or ‘dead’ states.
Furthermore, ‘ventilated after VAP’ state is where patients who recover from VAP yet remain in the ICU with ventilation would reside. In case of recurrent VAP, patients will return to ‘ventilated with VAP’ state, otherwise, patients are to remain in the same state, be transferred to ‘discharged from ICU after discontinuation of ventilation and without VAP’ or ‘dead’ states.

The state of ‘discharged from ICU after discontinuation of ventilation and without VAP’ consists of patients being discharged from the ICU and therefore in absence of ventilation and VAP. It should be noted that the patient may still be on antibiotics for VAP on discharge but sufficiently treated active infection. The only outgoing transition from ‘discharged from ICU after discontinuation of ventilation and without VAP’ state is to ‘dead’ and the rest are incoming transitions.

A final absorbing state of ‘dead’ is modeled as a state where all members of the cohorts will reach from all other states. Once patients arrive in this state, there is to be no further distribution of patients and therefore, allowing a termination of the whole Markov process upon absorption of the entire cohort.

### 2.2.11 Transition probabilities

Probabilities in the Markov model represent the probability of cohort moving from one state to another at that specific time. All the transition probabilities used in the Markov model are summarized in Table 3. These values have been extracted from the literature.

The probability of acquiring VAP in intubated patients was based on a prospective cohort study from 16 ICUs in Canada (Cook et al., 1998). The probability of a patient being discharged from
the ICU in the control group was estimated based on in-ICU mortality rate. The probability of death in ventilated patients was derived from a meta-analysis on the mortality rate in ICU patients without VAP based on 20,059 patients (Muscedere et al., 2010).

The probability of death in ventilated patients in CHX group was calculated based on the risk of mortality associated with CHX (Figure 2). Please refer to Section 2.2.12 for further explanation. The probability of death after ICU discharge is determined based on reported values of Brinkman et al., 2013 and mortality rate of general population in Section 2.2.13. The probability of developing VAP in ventilated patients in CHX group was determined based on the incidence of VAP in control group and the effectiveness of CHX from meta-analysis conducted on a subgroup of studies identified by a previous systematic review (Figure 3). Please refer to Section 2.2.14 for further explanation.

The probability of ventilated patients with VAP dying was calculated by taking into account that the VAP attributable morality rate is 5.8% as reported in Heyland et al., (1999) to the mortality rate in ventilated ICU patient (Table 3). The probability of patients with VAP returning to ‘ventilated after VAP’ state was estimated based on the sojourn time in Section 2.2.15.

Furthermore, the probability of patients in the ‘ventilated after VAP’ state re-acquiring VAP in the control group was derived from Combes et al., (2007) while it was calculated based on effectiveness of CHX for patients in the CHX group. Combes et al., (2007) reported similar probabilities of discharge from ICU or death between patients who had VAP vs. never had VAP. Therefore, the same probability was used for patients in ‘ventilated after VAP’ being discharged and/or dying, as with the patients in ‘ventilated without VAP’ state being discharged and/or dying.
2.2.12 Transition probability of death in ventilated patients receiving CHX intervention

Relative survival with CHX was estimated through a meta-analysis of the relevant studies included in recent systematic reviews (Berry 2011; DeRiso 1996; Fourrier 2000; Fourrier 2005; Munro 2009; Scannapieco 2009).

Meta-analysis was conducted with dichotomous data, which included events and total number of participants in CHX and control groups, from the selected studies using Review Manager version 5.2.7. We used Mantel-Haenszel statistical method with random effects to estimate the pooled odds ratio. The results show that compared to the control group, the CHX intervention group has 1.05 times (95% CI 0.65-1.70) higher odds of mortality (Figure 2). This inferred that the intervention increases the risk of mortality and has an undesirable effect but at a statistically non-significant level.

This value was then applied to the probability of death from ventilation without VAP in the control group using equation (5) to calculate probability of death in ventilated patients without VAP with CHX treatment.

\[
P_1 = \frac{\{\exp[\log(P_2/1-P_2)+\log(OR)]\}}{\{1+\exp[\log(P_2/1-P_2)+\log(OR)]\}}
\]

where \( P_1 \) is the probability of death in ventilated patients without VAP in CHX group and \( P_2 \) is the probability of death from ventilation without VAP in control group.
2.2.13 Transition probability of death after ICU discharge

Although mortality rate after ICU discharge varies amongst individual patients and their severity of illness, average ICU patients have higher mortality risk compared to the general population after the discharge (Brinkman et al., 2013). Mortality rates after ICU discharge was obtained from the Kaplan-Meier survival curve of ICU population for the first 3.5 years after the ICU discharge (Brinkman et al., 2013) to incorporate a higher mortality risk. It is estimated that 42% of patients would die after the ICU discharge. Thereafter, starting from 68.5 years, age specific probabilities of death for the general Canadian population extracted from Statistics Canada were used (Table 4).

2.2.14 Effectiveness of CHX in reducing VAP and transition probability of VAP in ventilated patients

Impact of CHX application on the prevention of VAP was estimated through a meta-analysis of the relevant published studies (Bellissimo-Rodrigues 2009; Berry 2011; Cabov 2010; DeRiso 1996; Fourrier 2000; Fourrier 2005; Munro 2009; Ozcaka 2012; Panchabhai 2009; Scannapieco 2009; Tantipong 2008). Further explanation for selection of studies can be found in discussion section.

Meta-analysis was conducted with dichotomous data, which included events and total number of participants in CHX and control groups, from the selected studies using Review Manager version 5.2.7. We used Mantel-Haenszel statistical method with random-effects to estimate the pooled
odds ratio. The results show that compared to the control group, the CHX intervention group has 0.54 times (95% CI 0.38-0.76) lower odds of incidence of VAP (Figure 3).

This value was incorporated into the calculation of the transition probability of a ventilated patient developing VAP in CHX group, using equation (5) where \( P_1 \) is the probability of a ventilated patient developing VAP in CHX group and \( P_2 \) is the probability of ventilated patient developing VAP in control group in this case.

### 2.2.15 Transition probability of VAP patients returning to ‘ventilated after VAP’ state

In order to determine the probability of VAP patients returning to ‘ventilated after VAP’ state, sojourn time was considered based on prolonged length of ICU stay (\( T \)).

\[
P_3 = [1 - \exp(-1/T)] - P_4 \quad (6)
\]

since the rate of sojourn time (\( r_s \)) is a reciprocal of time (\( T \)), this rate can be further converted to a probability of \( p_s = \{1 - \exp(-r)\} \) when determining the probability of VAP patients returning to ‘ventilated after VAP’ state (\( P_3 \)) using the probability of VAP to death (\( P_4 \)).

### 2.2.16 Daily transition probabilities

Conversions of probabilistic values to daily probabilities were necessary due to the daily cycle length. Probabilistic values were first converted to daily rates then to daily probabilities. The following equations were used:
\[ r = -\frac{\ln(1 - P)}{t} \quad (7) \]
\[ p = 1 - \exp(-rt) \quad (8) \]

where the rate \( r \) is the number of an event occurring in a given period of time \( (7) \); and
probability \( p \) of an event is the constant rate at which the event occurs in a given period of time \( (8) \) (Sonnenberg & Beck, 1993).

### 2.2.17 Costs

The costs of each health state in the Markov model associated with ICU stays with mechanical ventilation, VAP treatment, and CHX application were populated with the estimates from the literature (Table 5). These costs were converted to daily costs and adjusted to 2015 Canadian dollars.

Since this CUA was conducted from a Ministry of Health perspective only, direct medical costs were considered. When estimating the cost for the MV state, we decided to only consider the ICU bed cost and physician charge. The cost of CHX was included in the intervention group. For the cost of VAP, antibiotic therapy cost was considered on top of ICU bed and physician charge, but not CHX. It is assumed that costs for additional imaging, laboratory tests, equipment, nurse and other health professional care are included in the cost of ICU bed as outlined in a study by Muscedere et al., (2008). It was assumed that there is no cost associated with discharged and dead states.

The cost of an ICU bed was derived from Ontario Case Costing Initiative Data (Muscedere et al., 2008), antibiotic cost was extracted from Muscedere et al., (2010) and physician charge, specific
to the length of stay, was directly derived from the 2013 Ontario hospital fee guide. The cost of daily CHX application including supplemental materials such as swab was estimated based on the current market price of commercial CHX swabs.

2.2.18 Total Cost estimation

Total costs per cycle for both control and intervention groups were determined first by multiplying the cost of each state by the number of patients in that state and adding up the costs for MV and VAP states per cycle. The total cost was then calculated by aggregating together the cost of all cycles over life horizon.

2.2.19 Adjustments for inflation

The costs were adjusted for inflation using the CPI and using equation (10). The health component of CPI was derived from Statistics Canada for the current year (2015) and the corresponding base year of the cost used (Table 5).

\[
\text{Current Item Price (\$)} = \text{Base Year Price (\$)} \times \left( \frac{\text{Current Year CPI}}{\text{Base Year CPI}} \right)
\]  

(10)

2.2.20 Total life-years calculation

Life year is a common outcome measure used in CEA that refers to the number of years lived from one intervention (Evans et al., 2004). This value is not adjusted for HRQoL. Total life-
years for both control and intervention groups were determined by adding the number of patients in four states: ‘ventilated without VAP’, ‘ventilated with VAP’, ‘ventilated after VAP’ and ‘discharged’ state.

2.2.21 Quality of life

Information on QoL enables an understanding of the impact of ICU stay, VAP, and ventilation on patients’ well-being (Oeyen et al., 2010). There are limited studies on HRQoL upon and after ICU admission due to the unexpected and emergent nature of the patients’ condition upon admission (Dinglas et al., 2013; Hofhuis et al., 2009; Oeyen et al., 2010). QoL is difficult to measure among different patients even for the same disease state and subject to a wide variation due to different individual value, the measuring process can be labour intensive and time-consuming, and the results can be ambiguous for interpretation (Oeyen et al., 2010). Therefore, proxies were used for health utilities before and after ICU admission and health utility was estimated for the duration of a VAP state. The limitation in using a proxy is that it is subject to uncertainties and bias. To overcome such limitation, it is recommended to use health utility for the disease that has similar conditions, preferably of respiratory origin requiring MV such as respiratory distress syndrome (Solomkin, 2005). Furthermore, Granja et al. (2003) suggests that utility values of HRQoL among acute respiratory distress syndrome survivors are similar to other ICU survivors (Granja et al., 2003). In addition, studies report relatively lower HRQoLs in patients before ICU admission and after ICU treatment than the general population (Cuthbertson et al., 2005; Hofhuis et al., 2009; Nisula et al., 2013). Therefore, we can infer from these findings that the use of utility values for ICU patients with complications other than VAP is a reasonable proxy to use. Nisula et al., (2013) reported that the HRQoL of patients with acute kidney injury
did not change significantly during their stay in ICU. In patients with acute kidney injury, the mean increases in the EQ-5D index during the six-month follow-up was 0.024 with the baseline utility value of 0.676 at six months (Nisula et al., 2013). It is possible that the HRQoL may decrease with VAP. The same health utility was used for MV and VAP states in the Markov model.

2.2.22 QALY Estimates

We estimated lifetime QALYs by multiplying the distribution from cohort simulation based on the Markov model by utility values derived from EQ-5D for patients in all health states other than ‘dead’ state. For QALY per cycle, health utility specific to each health state (Table 6) were multiplied by the number of patients in each state. Under the conventional assumption of a Markov model where each health state is considered independent of time and preceding conditions, it is assumed that the time within a state is eliminated from the utility process as well. The sum of QALYs for all cycles was found, and then divided by the number of patients initially entered into the model to calculate the total QALYs per patient. After this, QALYs per year were calculated by dividing total QALYs per patient by 365 days.

2.2.23 One-way sensitivity analysis

One-way sensitivity analyses were performed to test the effects on outcome when varying one of the following parameters (Table 8): mortality rate associated with CHX, discount rate, effectiveness of CHX, life horizons, CHX costs, average length of ICU stay, prolonged length of
ICU stay and VAP attributable mortality rate. For both CHX mortality rate and effectiveness of CHX, upper and lower confidence interval from meta-analysis in Sections 2.2.12 and 2.2.14 were chosen. Similarly, assumptions for prolonged ICU days and attributable mortality rate associated with VAP were derived from its confidence interval (Heyland et al., 1999). Parameters for discounting, time horizon and costs of CHX were chosen arbitrarily within reasonable limits. Discounting values of 0% and 3% were selected to assess the effect of no discounting and a common discounting value other than the baseline value of 5%. Costs associated with CHX were selected based on the current market price for CHX swabs for ventilated patients and expert opinion. Since, the average length of ICU stay varies depending on the type of ICU and severity of illness in patients, upper and lower parameters were selected based on several studies with different settings. The median total length of ICU stay for elderly patients with average age of 85 was 4 days (Heyland et al., 2015) while it was 6.1 days for intensivist-directed ICU and 9.3 days in ICU with attending physician (SCCM, 2006).
Figure 1. The Markov model for CEA and CUA of VAP cases in ICU. The 5 possible health states associated with VAP are represented by ovals, and the arrows show possible transitions between the states.
Table 3. Transition probabilities for health states associated with VAP

**Control Group - No CHX**

<table>
<thead>
<tr>
<th>Description</th>
<th>Original</th>
<th>Standard Error</th>
<th>Distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of acquiring VAP in intubated patients DAY 1-5</td>
<td>0.033</td>
<td>0.023</td>
<td>Normal</td>
<td>Cook et al., 1998</td>
</tr>
<tr>
<td>DAY 6-14</td>
<td>0.013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of acquiring VAP in intubated patients DAY 15+</td>
<td>0.013</td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Probability of mortality in ventilated ICU patients</td>
<td>0.160</td>
<td>0.0026</td>
<td>Normal</td>
<td>Muscedere et al., 2010</td>
</tr>
<tr>
<td>Daily probability of mortality in ICU patients with VAP</td>
<td>0.028</td>
<td></td>
<td></td>
<td>Heyland et al., 1999;Section 2.2.11</td>
</tr>
<tr>
<td>Probability of ventilated patients with VAP returning to ‘ventilated after VAP’ state</td>
<td>0.180</td>
<td></td>
<td></td>
<td>Section 2.2.15</td>
</tr>
<tr>
<td>Probability of patients in ‘ventilated after VAP’ state acquiring VAP again</td>
<td>0.274</td>
<td>0.0199</td>
<td>Normal</td>
<td>Combes et al., 2007</td>
</tr>
</tbody>
</table>

**Intervention group – with CHX**

<table>
<thead>
<tr>
<th>Description</th>
<th>Original</th>
<th>Standard Error</th>
<th>Distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of acquiring VAP in intubated patients DAY 1-5</td>
<td>0.018</td>
<td>0.013</td>
<td>Normal</td>
<td>Section 2.2.14</td>
</tr>
<tr>
<td>DAY 6-14</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of acquiring VAP in intubated patients DAY 15+</td>
<td>0.008</td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Probability of mortality in ventilated patient</td>
<td>0.166</td>
<td>0.0026</td>
<td>Normal</td>
<td>Section 2.2.12</td>
</tr>
<tr>
<td>Daily probability of mortality in ICU patients with VAP</td>
<td>0.029</td>
<td></td>
<td></td>
<td>Heyland et al., 1999;Section 2.2.11</td>
</tr>
<tr>
<td>Probability of ventilated patients with VAP returning to ‘ventilated after VAP’ state</td>
<td>0.178</td>
<td></td>
<td></td>
<td>Section 2.2.15</td>
</tr>
<tr>
<td>Probability of patients in ‘ventilated after VAP’ state acquiring VAP again</td>
<td>0.169</td>
<td>0.0167</td>
<td>Normal</td>
<td>Section 2.2.14</td>
</tr>
</tbody>
</table>
Figure 2. Forest plot of comparison: 1 Mortality, outcome: 1.1 Mortality associated with CHX.

Figure 3. Forest plot of comparison: 2 Effectiveness of CHX, outcome: 2.1 VAP Incidence.
### Table 4. Daily mortality rate specific to age in Canadian population (Statistics Canada, 2015c)

<table>
<thead>
<tr>
<th>Age</th>
<th>Mortality rate in male</th>
<th>Mortality rate in female</th>
<th>Average mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>0.01682</td>
<td>0.01051</td>
<td>3.771E-05</td>
</tr>
<tr>
<td>69</td>
<td>0.01852</td>
<td>0.01161</td>
<td>4.160E-05</td>
</tr>
<tr>
<td>70</td>
<td>0.02040</td>
<td>0.01284</td>
<td>4.594E-05</td>
</tr>
<tr>
<td>71</td>
<td>0.02247</td>
<td>0.01420</td>
<td>5.072E-05</td>
</tr>
<tr>
<td>72</td>
<td>0.02475</td>
<td>0.01573</td>
<td>5.605E-05</td>
</tr>
<tr>
<td>73</td>
<td>0.02726</td>
<td>0.01743</td>
<td>6.195E-05</td>
</tr>
<tr>
<td>74</td>
<td>0.03004</td>
<td>0.01934</td>
<td>6.853E-05</td>
</tr>
<tr>
<td>75</td>
<td>0.03310</td>
<td>0.02146</td>
<td>7.582E-05</td>
</tr>
<tr>
<td>76</td>
<td>0.03647</td>
<td>0.02384</td>
<td>8.394E-05</td>
</tr>
<tr>
<td>77</td>
<td>0.04019</td>
<td>0.02649</td>
<td>9.296E-05</td>
</tr>
<tr>
<td>78</td>
<td>0.04430</td>
<td>0.02947</td>
<td>1.030E-04</td>
</tr>
<tr>
<td>79</td>
<td>0.04883</td>
<td>0.03280</td>
<td>1.143E-04</td>
</tr>
<tr>
<td>80</td>
<td>0.05383</td>
<td>0.03654</td>
<td>1.268E-04</td>
</tr>
<tr>
<td>81</td>
<td>0.05935</td>
<td>0.04074</td>
<td>1.408E-04</td>
</tr>
<tr>
<td>82</td>
<td>0.06543</td>
<td>0.04545</td>
<td>1.564E-04</td>
</tr>
<tr>
<td>83</td>
<td>0.07215</td>
<td>0.05074</td>
<td>1.739E-04</td>
</tr>
<tr>
<td>84</td>
<td>0.07957</td>
<td>0.05669</td>
<td>1.935E-04</td>
</tr>
<tr>
<td>85</td>
<td>0.08776</td>
<td>0.06338</td>
<td>2.155E-04</td>
</tr>
<tr>
<td>86</td>
<td>0.09680</td>
<td>0.07091</td>
<td>2.402E-04</td>
</tr>
<tr>
<td>87</td>
<td>0.10678</td>
<td>0.07940</td>
<td>2.680E-04</td>
</tr>
<tr>
<td>88</td>
<td>0.11780</td>
<td>0.08897</td>
<td>2.993E-04</td>
</tr>
<tr>
<td>89</td>
<td>0.12997</td>
<td>0.09977</td>
<td>3.346E-04</td>
</tr>
<tr>
<td>90</td>
<td>0.14341</td>
<td>0.11196</td>
<td>3.746E-04</td>
</tr>
<tr>
<td>91</td>
<td>0.15794</td>
<td>0.12542</td>
<td>4.190E-04</td>
</tr>
<tr>
<td>92</td>
<td>0.17326</td>
<td>0.13991</td>
<td>4.670E-04</td>
</tr>
<tr>
<td>93</td>
<td>0.18931</td>
<td>0.15541</td>
<td>5.187E-04</td>
</tr>
<tr>
<td>94</td>
<td>0.20604</td>
<td>0.17190</td>
<td>5.743E-04</td>
</tr>
<tr>
<td>95</td>
<td>0.21839</td>
<td>0.18849</td>
<td>6.234E-04</td>
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<td>96</td>
<td>0.23536</td>
<td>0.20653</td>
<td>6.843E-04</td>
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<tr>
<td>97</td>
<td>0.25290</td>
<td>0.22549</td>
<td>7.491E-04</td>
</tr>
<tr>
<td>98</td>
<td>0.27092</td>
<td>0.24526</td>
<td>8.180E-04</td>
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<td>99</td>
<td>0.28933</td>
<td>0.26571</td>
<td>8.906E-04</td>
</tr>
<tr>
<td>100</td>
<td>0.30802</td>
<td>0.28671</td>
<td>9.667E-04</td>
</tr>
</tbody>
</table>

### Table 5. Consumer price index health component in 2006 and 2015 (Statistics Canada, 2015a)

<table>
<thead>
<tr>
<th>Year</th>
<th>CPI Health Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>105.9</td>
</tr>
<tr>
<td>2015</td>
<td>119.8</td>
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</tbody>
</table>
Table 6. Daily costs related to VAP with and without CHX intervention in 2015 Canadian dollars

<table>
<thead>
<tr>
<th>Costs</th>
<th>Control</th>
<th>Intervention</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV DAY1</td>
<td>$ 3081.46</td>
<td>$ 3084.46</td>
<td>Cost of ICU stay on day 1</td>
<td></td>
</tr>
<tr>
<td>MV DAY2-30</td>
<td>$ 2941.24</td>
<td>$ 2944.24</td>
<td>Cost of ICU stay on days 2-30</td>
<td></td>
</tr>
<tr>
<td>MV DAY31+</td>
<td>$ 2816.26</td>
<td>$ 2819.26</td>
<td>Cost of ICU stay with ventilator on days more than 31</td>
<td>Ontario fee guide for Physician charge 2015;</td>
</tr>
<tr>
<td>VAP DAY1</td>
<td>$ 3137.80</td>
<td>$ 3137.80</td>
<td>Cost of VAP on day 1</td>
<td></td>
</tr>
<tr>
<td>VAP DAY2-30</td>
<td>$ 2997.58</td>
<td>$ 2997.58</td>
<td>Cost of VAP on days 2-30</td>
<td></td>
</tr>
<tr>
<td>VAP DAY31+</td>
<td>$ 2872.60</td>
<td>$ 2872.60</td>
<td>Cost of VAP on days more than 31</td>
<td></td>
</tr>
<tr>
<td>CHX</td>
<td>$ 3.00</td>
<td></td>
<td>Cost of CHX</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Table 7. Health utility for MV, VAP, discharge and dead states

<table>
<thead>
<tr>
<th>Utilities</th>
<th>EQ-5D</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>uMV</td>
<td>0.652</td>
<td>Quality of life at admission to ICU</td>
<td>Nisula et al., 2013</td>
</tr>
<tr>
<td>uVAP</td>
<td>0.652</td>
<td>Quality of life with VAP (Proxy)</td>
<td>Proxy</td>
</tr>
<tr>
<td>uDischarge</td>
<td>0.676</td>
<td>Quality of life after ICU discharge</td>
<td>Nisula et al., 2013</td>
</tr>
<tr>
<td>uDead</td>
<td>0</td>
<td>Quality of life at death</td>
<td>Proxy</td>
</tr>
</tbody>
</table>
Table 8. Assumptions used in one-way sensitivity analysis

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Baseline</th>
<th>Scenario A</th>
<th>Scenario B</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHX mortality rate</td>
<td>OR = 1.05</td>
<td>1.70</td>
<td>0.65</td>
</tr>
<tr>
<td>Discounting</td>
<td>5%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Effectiveness of CHX</td>
<td>OR = 0.54</td>
<td>0.76</td>
<td>0.38</td>
</tr>
<tr>
<td>Time horizon</td>
<td>35 years</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Costs of CHX</td>
<td>$3.00</td>
<td>$10.00</td>
<td>$1.00</td>
</tr>
<tr>
<td>Average length of ICU stay</td>
<td>6.5 days</td>
<td>4</td>
<td>9.3</td>
</tr>
<tr>
<td>Prolonged ICU days</td>
<td>4.3 days</td>
<td>1.5</td>
<td>7</td>
</tr>
<tr>
<td>VAP attributable morality rate</td>
<td>5.8%</td>
<td>-2.4%</td>
<td>14.0%</td>
</tr>
</tbody>
</table>

*Adjusted to 2015 Canadian dollars
Chapter 3 Paper

3 Paper

Cost-Utility Analysis of Oral Antiseptic Chlorhexidine in decreasing Ventilator-Associated Pneumonia in Intensive Care Units

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3.1 Introduction

Pneumonia is an infection caused by the invasion and overgrowth of microorganisms in pulmonary parenchyma that induces inflammation provoking intra-alveolar exudates (Alcón et al, 2008; Mandell & Wunderink, 2011). It is associated with a sharp shooting pain aggravated by inspiration or coughing (Longo et al., 2011). Ventilator-associated pneumonia (VAP) is a type of pneumonia found in patients who were mechanically ventilated for at least 48 hours (ATS, 2005). An average of 10-20% of patients on mechanical ventilators in the intensive care unit (ICU) develop VAP (Chlebicki & Safdar, 2007), but its incidence can be as high as 78% (Rello et al., 2002). This is problematic because VAP is associated with adverse outcomes such as increased morbidity, higher mortality, and increased economic burdens. One large Canadian study reported a median of seven days from ICU admission to the onset of VAP (Heyland et al., 1999). On average, patients with VAP are subject to an additional 4-9 days in hospital and 4.3 days in ICU (Muscedere et al., 2014).
VAP is more pronounced in resource limited countries with significant differences in VAP incidence rates among industrialized and resource limited countries. Recent publications report one to four VAP cases per 1000 ventilator days in North America and around 15 cases per 1000 ventilator days in resource limited countries (Rosenthal et al., 2012).

Pneumonia in general is triggered by microbial proliferation and the host’s defensive response to those pathogens once microbial pathogens reach the alveoli (Alcón et al, 2008; Longo et al., 2011). Patients with decreased levels of consciousness are at a higher risk of aspiration, particularly during their sleep (Longo et al., 2011). The host defense system is usually sufficient for preventing lung infections and pneumonia in healthy adults and the type of pathogens encountered are less virulent (Alcón et al., 2008); however, patients admitted to hospital have significantly impaired host defense systems for a number of reasons.

Increasing evidence in the literature suggests a strong link between colonization of dental plaque, respiratory pathogens and VAP (Munro et al., 2006). Anti-septic chlorhexidine (CHX) is one preventive strategy that targets oral pathogens. CHX application applied topically, as a part of oral hygiene care, is known to reduce the odds of VAP in adults by 40%, i.e. for every 15 mechanically ventilated patients in ICU, daily CHX application will prevent one patient from developing VAP (Shi et al., 2013). Concordance with clinical practice guidelines, with the use of daily CHX, is important in decreasing VAP rates. However, possibility of mortality associated with CHX is of a rising concern. Therefore, this conflicting evidence on CHX justifies the need for further research on its clinical and economical aspects, hence its degree of cost-effectiveness and cost-utility. The main objective of this study is to evaluate the cost-utility of CHX solution in preventing VAP in mechanically ventilated ICU patients compared to placebo or standard care that does not include CHX.
3.2 Methods

The fundamental concept of economics lies on scarcity of resources and choice. Health economics has different methods to evaluate how resources are distributed in health care system and how they can be allocated (Haddix et al., 2003; Elliott et al., 2005). Economic evaluation is one example, which consists of cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis. Each measures the difference in resource consumed and effectiveness generated between different intervention strategies (Haddix et al., 2003; Elliott et al., 2005). The CUA incorporates the effects of treatments in means of both extension of life but also its effect on the patient’s quality of life (QoL), expressed in quality-adjust life-years (QALYs) for example (Petitti, 1999). An overall economic outcome of CEA and CUA is the incremental cost-effectiveness ratio (ICER) or cost-utility ratio (ICUR) respectively, which can be estimated either directly from patient data or through decision modeling such as Markov model.

\[ ICUR = \frac{Cost_A - Cost_B}{Effectiveness_A - Effectiveness_B} \]  

A Markov model is an analytical structure that synthesizes input parameters such as costs and QoL specific to health states and their transition probabilities to determine life-years, and QALYs (Drummond et al., 2005). In this study, it consisted of 5 health states: 1) ventilated without VAP, 2) ventilated with VAP, 3) ventilated after VAP, 4) discharged from ICU without ventilation and VAP, and 5) dead. The transition between states is described in Figure 1. The number of cohorts moving from states to another was determined by the transition probability associated with each state. It is assumed that the all patients enter the model through the
‘ventilated without VAP’ state, which refers to the state where the patient is under ventilation upon entry to the ICU and is free of VAP. This is a non-absorbing state because patients can move out of this state and transfer to the state of either ‘ventilated with VAP’, ‘ventilated after VAP’, ‘discharge from ICU after discontinuation of ventilation and without VAP’, or ‘dead’. Other non-absorbing states of ‘ventilated with VAP’ occurs when a patient acquires VAP in the ICU and ‘ventilated after VAP’ is where patients are recovered from VAP yet remaining in the ICU with ventilation. The state of ‘discharged from ICU after discontinuation of ventilation and without VAP’ consists of patients being discharged from the ICU and therefore in absence of ventilation and VAP. The remaining state of dead was modeled as a final absorbing health state that all cohorts would eventually reach in the end, allowing a termination of the whole Markov process upon absorption of the entire cohort.

The population of the study consisted of ventilated ICU patients free of pneumonia upon admission with an average age of 65. Children were excluded. Intervention for this study was the standard ICU care with CHX application of multiple concentrations at 0.12-2.0% as a preventive therapy for VAP. The control group consisted of either placebo or standard ICU care without CHX application.

Relative mortality associated with CHX use (Berry 2011; DeRiso 1996; Fourrier 2000; Fourrier 2005; Munro 2009; Scannapieco 2009) and effectiveness of CHX (Bellissimo-Rodrigues 2009; Berry 2011; Cabov 2010; DeRiso 1996; Fourrier 2000; Fourrier 2005; Munro 2009; Ozcaka 2012; Panchabhai 2009; Scannapieco 2009; Tantipong 2008) were estimated through a meta-analysis of the relevant studies included in the recent systematic reviews. Dichotomous data,
which included events and the total number of participants in CHX and control groups, from the selected studies was analyzed using the Mantel-Haenszel statistical method with random effect to measure pooled odds ratio. The results show that compared to the control group, the CHX intervention group had 1.05 times (95% CI 0.65-1.70) higher odds of mortality (Figure 2) and 0.54 times (95% CI 0.38-0.76) lower odds of incidence of VAP (Figure 3).

The rest of the input parameters including transition probabilities, costs, and health utilities were derived from published literature. Daily cycles and a lifetime horizon were assumed while both costs and benefits were discounted by 5% (Bonneux and Birnie, 2000). Costs were inflated to 2015 Canadian dollars and a third party payer perspective was adopted. One-way sensitivity analyses were conducted to incorporate uncertainties in the CUA estimates (Table 8).
3.3 Results

The mean cost of VAP for patients who received CHX was $8,776.03 per patient while the mean cost of VAP for patients who did not receive was CHX $9,580.56. The total incremental cost difference between groups was $-804.53, favoring CHX therapy.

The strategies were similar in terms of life-years and QALYs. The total incremental difference in life-years was 0.008 life-years gained with CHX. The mean life-years for CHX group were 2.782 life-years per patient, which was only marginally more than the mean life-years for patients who did not receive CHX (2.774 life-years per patient). In addition, the total incremental difference in QALY was 0.005 QALYs in CHX group. The mean QALY for CHX group was 1.880 QALY per patient, which was only marginally more than the mean QALYs for patients who did not receive CHX 1.875 QALYs per patient. On this note, ICER and ICUR indicated that CHX therapy is less costly with comparable health outcome compared to the control.

3.3.1 One-way sensitivity analysis

One-way sensitivity analyses were conducted for parameters as listed in Table 9. Variation of most parameters yielded similar results. Assumptions of, 5- and 10-year time horizon, increase in the costs of CHX therapy ranging between $1-10, discounting factors of 0-3%, variations in attributable morality rate of VAP resulted in similar results to the base model. However, with increased mortality risk associated with CHX, reduced effectiveness of CHX in terms of increased VAP incidence and reduced prolonged ICU days with VAP and average length of ICU
stay resulted in reduced life-years lived and QALYs. In summary, CHX therapy for ICU patients was less costly with comparable health outcomes than the control without CHX.

3.4 Discussion

It is important to prevent VAP due to its associated reduced survival, QoL, and increased resource utilization. Although topical CHX has been shown to reduce VAP as a part of a preventive strategy, its associated adverse events are a rising concern (Shi et al., 2013; Price et al., 2014). Therefore, it is not only important to understand the effectiveness of CHX but also its cost-effectiveness because it helps to identify opportunities for resource allocation and allow informed decision. While survival alone is not a sufficient endpoint in assessing resource allocation, HRQoL is considered as an equally important an outcome measure (Oeyen et al., 2010; Stricker et al., 2005). For this reason, CUA was selected for our study because it provides information on both quantity and quality of life. The aim of this study was to evaluate the cost-utility of using CHX compared with placebo/usual care in preventing VAP among ventilated ICU patients.

We relied on several assumptions for our study to eliminate uncertainties where possible and strengthen our model. The first assumption is that the patients are free of pneumonia at baseline when admitted to ICU. This ensures that we capture the preventive effect of CHX. It is not possible to separate probabilities between placebo and standard care in some systematic reviews and meta-analysis. Therefore, the assumption made here is that both placebo and standard care are controls.
Some of the weakness is associated with the following assumptions of our model. Although health may deteriorate after discharge, it is not captured in our model. Being discharged in our model implied improved health state and the probability of developing VAP was zero once discharged. No distinctions were made between timing of weaning and VAP incidence. Although VAP can occur in patients with noninvasive mechanically ventilation, it was assumed that all ventilation is invasive in this study. Lastly, no other complications from VAP or ventilation were included in this model because the focus of this study is on the CHX treatment in preventing VAP. These assumptions may the limit the generalizability of CHX effect where complication may occur however they were inevitable to control for confounding factors.

The most important input parameters of our model, probability of CHX associated death and effectiveness of CHX, were estimated by conducting meta-analysis. Our results indicated 1.05 times higher odds (95% CI 0.65-1.70) of mortality that is not statistically significant (Figure 2); and 0.54 times lower odds (95% CI 0.38-0.76) of developing VAP with CHX (Figure 3). This indicated that there may be some increase in mortality with CHX yet there is still a very important effect from CHX to consider.

The primary outcome from our study was that when compared with standard care, CHX intervention produced additional 0.008 life-years and 0.005 QALYs with cost savings of $804.53. Therefore, the result indicates that VAP preventive care including CHX is similar to the care without CHX. Further, the analysis suggests that the small gain in life-years lived and QALYs are from prolonged stay in ICU associated with VAP and overall mortality effect from CHX.

To our knowledge, this is the first study to evaluate the cost-utility of CHX in preventing VAP and therefore no direct comparison can be done. However, this finding is in accordance with a
cost-benefit analysis on varying VAP preventive strategies where oral care with CHX was found to exceed usual cost-to-effectiveness (Branch-Elliman et al., 2015).

One-way sensitivity analyses yielded similar results to our baseline in Table 9 for most scenarios, while increased mortality risk associated with CHX, reduced effectiveness of CHX in terms of increased VAP incidence and reduced prolonged ICU days with VAP resulted in reduced life-years lived and QALYs. Of these, CHX associated mortality rate had the greatest impact on the results. This highlights the importance of conducting further research and obtaining more evidence on the magnitude of attributable mortality to CHX.

A merit of this study is that this is the first study to evaluate the cost-utility of CHX application in mechanically ventilated patients in the ICU using primary data from Canadian literature. The results provide a platform for a systematic, rather than intuitive, allocation of healthcare resources in Ontario in particular. Further, this study highlights the connection between oral and general health and importance of collaboration between health care providers of different fields and health economists.

However, there are several limitations with this study. First is the availability of data. Due to the limited availability of primary data, for example, data on the incidences of VAP and the rates of mechanical ventilation specific to Ontario, Canada transitional probabilities and costs were extracted from the literature. VAP incidences were obtained from several sources including the literature and self-reported VAP incidences at several institutions across Canada. Second, certain information was missing in the dataset. For example, comorbidities, frailty before ICU admission and severity of VAP are usually not reported and are assumed relatively equal in all ICU patients. Third, data are subject to variability between and within institutions due to individual and centre practice pattern variations. Variation may be found in the type of treatments, the
duration of the intervention, the accuracy of the data, and the regimen of preventive CHX therapy. Therefore, average values were estimated. In addition, having a single intervention in this analysis limits the understanding of VAP prevention strategies as a whole. Interdependence of CHX effect in conjunction with other preventive strategies is unclear. Therefore broadening the scope of CUA and including other possible interventions for example prophylactic antibiotic treatment will reflect real world events better. Generalizability of the results may be limited in terms of costs because health care costs fluctuate with varying provinces. Another limitation is that there is a limited generalizability due to inclusive bias of selected group of the target population. Therefore results may not be applied directly to other settings out of hospital due to the differences in the nature of the population, and the setting.

Deterministic analysis performed in this study uses single point estimates of variables and most likely case is evaluated. In doing so, uncertainties around variables were not considered in the base model but they have been dealt in one-way sensitivity analysis. However, this type of sensitivity analysis may underestimates additive and multiplicative effects of variables. Therefore if often does not explain overall uncertainty of a modeled result. To overcome these limitations, multi-way sensitivity analysis and/or probabilistic sensitivity analysis with Markov chain Monte Carlo simulation is recommended.

This study provides valuable information for policymakers in health care as it will contribute to a more informed debate on resource allocation priorities with respect to budget planning and policy implementation of VAP prevention protocol. With this information, hospitals will be able to plan and allocate their budgets more efficiently. For healthcare providers, this information will be useful in determining what to practice in clinic as to whether CHX should be provided in the
protocol for day-to-day care. Furthermore, our findings may have a global impact particularly in countries where incidence of VAP is high and resources are limited.

Implications for research include further investigation on mortality associated with CHX, obtaining QoL associated with VAP from ICU patients. Further research on different demographics such as in pediatric population and in different settings other than ICU will also be beneficial. For example in long-term care facilities where risk of aspirational pneumonia is high could also be considered as CHX is often not part of a standard care. It is also important to understand mechanism of CHX and its effect when used in conjunction with other preventive treatments. Therefore, CUA on other preventive strategies such as antibiotics will permit further informed comparison with CHX. Lastly as new information and further methodologically robust data becomes available re-do of analysis will be valuable.
3.5 Conclusion

The results from our CUA suggest CHX oral antiseptic in ICU for preventing VAP as compared to the care without CHX resulted in comparable health outcome, yet it was cost saving. Possible concerns have recently emerged regarding the associated trend towards an increased mortality risk with CHX use, and as further methodologically robust data becomes available this analysis should be updated. The decision for an ICU patient to use CHX for prevention of VAP should consider trade-offs between the benefit and risks, and integrate the patient’s values and preferences. Based on the results of our study and understanding its limitations, it is suggested that the use of CHX, as a component of an overall preventive protocol for mechanically ventilated high-risk ICU patients in hospitals, may be revised. Prevention is not only important to minimize unnecessary adverse health effects on patients, but also to relieve the burden on healthcare systems. Finally, it is important to remember that VAP prevention is not solely about using CHX or not, rather it is about adherence to evidence-based protocol bundles to achieve maximal effectiveness at a minimal cost.
Figure 2. Forest plot of comparison: 1 Mortality, outcome: 1.1 Mortality associated with CHX

Figure 3. Forest plot of comparison: 2 Effectiveness of CHX, outcome: 2.1 VAP Incidence.
### Table 9. Cost, effectiveness, ICER and ICUR of VAP prevention with CHX and control

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost ($)</th>
<th>Effectiveness (life-years)</th>
<th>Effectiveness (QALYs)</th>
<th>Incremental cost ($)</th>
<th>Incremental effectiveness (life-years)</th>
<th>Incremental effectiveness (QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9,580.56</td>
<td>2.774</td>
<td>1.875</td>
<td>-804.53</td>
<td>0.0084</td>
<td>0.0057</td>
</tr>
<tr>
<td>CHX</td>
<td>8,776.03</td>
<td>2.782</td>
<td>1.880</td>
<td></td>
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</table>

### Table 10. Cost, effectiveness, ICER and ICUR of VAP prevention with CHX and control from one-way sensitivity analysis

<table>
<thead>
<tr>
<th>Variables tested</th>
<th>Cost ($)</th>
<th>Effectiveness (life-years)</th>
<th>Effectiveness (QALYs)</th>
<th>ICER ($/life-years)</th>
<th>ICUR ($/QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>- 804.53</td>
<td>0.0084</td>
<td>0.0057</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mortality rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>from CHX use</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>OR = 1.70</td>
<td>- 1,441.95</td>
<td>- 0.1435</td>
<td>- 0.0970</td>
<td>10,050.10</td>
<td>14,871.91</td>
</tr>
<tr>
<td>OR = 0.65</td>
<td>- 329.77</td>
<td>0.1215</td>
<td>0.0821</td>
<td></td>
<td></td>
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<tr>
<td>Discounting</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3%</td>
<td>- 805.08</td>
<td>0.0089</td>
<td>0.0061</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0%</td>
<td>- 805.89</td>
<td>0.0099</td>
<td>0.0067</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Effectiveness of</td>
<td></td>
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<tr>
<td>CHX (incidence</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>of VAP)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>OR = 0.76</td>
<td>- 446.78</td>
<td>- 0.0023</td>
<td>- 0.0015</td>
<td>193,857.20</td>
<td>288,620.96</td>
</tr>
<tr>
<td>OR = 0.38</td>
<td>- 1,062.41</td>
<td>0.0160</td>
<td>0.0109</td>
<td></td>
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</tr>
<tr>
<td>Time horizon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td>- 804.53</td>
<td>0.0133</td>
<td>0.0091</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 years</td>
<td>- 804.53</td>
<td>0.0066</td>
<td>0.0045</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cost of CHX</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$10.00</td>
<td>- 786.17</td>
<td>0.0084</td>
<td>0.0057</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$1.00</td>
<td>- 809.78</td>
<td>0.0084</td>
<td>0.0057</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 10. Cost, effectiveness, ICER and ICUR of VAP prevention with CHX and control from one-way sensitivity analysis (Cont’d)

<table>
<thead>
<tr>
<th>Variables tested</th>
<th>Cost ($)</th>
<th>Effectiveness (life-years)</th>
<th>Effectiveness (QALYs)</th>
<th>ICER ($/life-years)</th>
<th>ICUR ($/QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>- 804.53</td>
<td>0.0084</td>
<td>0.0057</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Average length of ICU stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 days</td>
<td>- 654.97</td>
<td>0.0033</td>
<td>0.0022</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9.3 days</td>
<td>- 946.89</td>
<td>0.0133</td>
<td>0.0090</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prolonged ICU days with VAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 days</td>
<td>- 375.17</td>
<td>- 0.0032</td>
<td>- 0.0022</td>
<td>115,688.88</td>
<td>171,796.14</td>
</tr>
<tr>
<td>7 days</td>
<td>- 1,198.16</td>
<td>0.0190</td>
<td>0.0129</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VAP attributable mortality rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 2.4%</td>
<td>- 813.51</td>
<td>0.0068</td>
<td>0.0046</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14.0%</td>
<td>- 795.63</td>
<td>0.0099</td>
<td>0.0067</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Adjusted to 2015 Canadian dollars
Chapter 4 Discussion

4 Discussion

4.1 Importance of this study

It is important to prevent VAP as it is associated with reduced survival, QoL and increased resource utilization. Although a CHX antibacterial agent has been shown to reduce VAP amongst various preventive methods, associated adverse events with CHX is a rising concern (Shi et al., 2013; Price et al., 2014). In turn, there has been discussions in the direction of downgrading CHX application from a high recommendation to a weak suggest recommendation in the new VAP guideline. Therefore, it is not only important to understand the effectiveness of CHX but also its cost-effectiveness from the economic evaluation, as it will provide an additional dimension in discussion for health care providers and policy makers. While survival alone is not a sufficient endpoint in assessing resource allocation, HRQoL is considered as an equally important an outcome measure (Oeyen et al., 2010; Stricker et al., 2005). For this reason, CUA was selected for our study because it provides information on both quantity and quality of life. The aim of this study was to evaluate the cost-utility of using CHX compared with placebo/usual care in preventing VAP among ventilated ICU patients.

We defined several assumptions for our study to eliminate uncertainties where possible and strengthen our model. The first assumption is that the patients are free of pneumonia at baseline when admitted to ICU. This ensures that we capture the preventive effect of CHX. It is not possible to separate probabilities between placebo and standard care in some systematic reviews and meta-analysis. Therefore, both placebo and standard care are considered as controls.
Some of the weakness is associated with the following assumptions of our model. Although health may deteriorate after discharge, it is not captured in our model. Being discharged in our model implied improved health state and the probability of developing VAP was zero once discharged. Despite a thorough assessment of ventilated patients prior to weaning, patients can fail to extubate and be placed under ventilation again. Krinsley et al. (2012) reported a higher rate of pneumonia and death in these patients than in those patients who were successfully extubated (Krimley et al., 2012). However, our Markov model did not make any distinction between patients with successful weaning and those with unsuccessful weaning, and assumed the same rate of acquiring VAP for all patients. Although VAP can occur in patients with noninvasive mechanical ventilation, it was assumed that all ventilation is invasive in this study. For this reason, our study may be under-estimating the incidence of VAP. Lastly, no other complications from VAP or ventilation were included in this model because the focus of this study is on the CHX treatment in preventing VAP. These assumptions may the limit the generalizability of CHX effect where complication may occur. However they were inevitable to control for confounding factors.

The most important input parameters of our model, effectiveness of CHX and probability of CHX associated death, were estimated by conducting meta-analysis. Although CHX is associated with a reduction in VAP incidence, there is no evidence that shows reduction in mortality from CHX. In fact, its results are open to controversy. Possibility of associated mortality has been reported with the use of CHX in some of the meta-analyses. While Cochrane systematic review by Shi et al. (2013) (OR=1.10, CI 0.87-1.38) reported an insignificant level of mortality associated with CHX, Price et al. (2014) suggested higher mortality level that is significant (OR=1.25, CI 1.05-1.50). Therefore, we conducted a comprehensive search of our own and meta-analysis based on selected relevant studies. The result indicated 1.05 (95% CI
0.65-1.70) times higher odds of mortality that is not statistically significant (Figure 2). The lower and upper band of this confidence interval indicate that although CHX could be preventive of death by 35%, on the other hand it could be increasing by 70%. This infers that there is a trend towards the negative effects of CHX. Future research can shed more light here but at this cross section in time, based on the available information and considering the clinical importance of death, we assumed that there may be some increase in mortality with CHX.

Further, meta-analysis on the effectiveness of CHX was updated focusing on our question and ignoring studies on pediatric patients. It was determined that there is about 46% chance of decreased incidence of VAP in critically ill patients with 95% confidence interval reporting a range of effects that are as high as 62% and as low as 24%. This indicated that there is still a very important effect from CHX to consider.

It should be appreciated that although meta-analysis can be a powerful and informative tool, its results may also be misleading if care is not taken to ensure that the pooled information is reflective of the clinical question at hand (Da Costa et al., 2014). As such, these findings must be interpreted with caution as these results are dependent on the selected studies and extracted number of events, which is at of authors’ discretion. There were a wide range of discrepancies amongst selected studies and also the data that was used in several meta-analyses on CHX mortality. Therefore, we decided to compare and critically appraise the most recent systematic review and meta-analysis as a comparator to the Cochrane systematic review to ensure that the data is valid for our study. Critical appraisal was done using PRISMA and AMSTAR checklists for Price et al., (2014) study (Moher et al., 2009; Shea et al., 2007). We argue that although it satisfied all the criteria from PRISMA checklist except we were unable to locate its registration
information or review protocol for systematic review. According to AMSTAR, we could not conclude whether the research question and inclusion criteria were designed a priori. Further, there was no list of excluded studies nor results on assessment of publication bias, which includes graphical aids and/or statistical test such as Egger regression tests. We concluded the Cochrane review (Shi et al., 2013) serves the purpose of our study on both effectiveness of CHX and mortality associated with CHX. Consequently, we have extracted relevant data from this review. Since our study is based on Canadian health care system, we decided to include studies from Western countries (Bellissimo-Rodrigues 2009; Berry 2011; Cabov 2010; DeRiso 1996; Fourrier 2000; Fourrier 2005; Munro 2009; Ozcaka 2012; Panchabhai 2009; Scannapieco 2009; Tantipong 2008).

On a side note, across varying meta-analyses (Klompas 2014; Li 2013; Pileggi 2011; Synders 2011; Price 2014), Shi et al. (2013) was the only study that did not include a randomized control study by Koeman (2006). Based on the communication with the corresponding author of the Cochrane review, the reason was because the data presented in Koeman (hazard ratio 1.12) was not compatible with the data analysis in their meta-analysis (S. Furness, personal communication, June-July, 2015). We were also unable to extract data on mortality from the information given in this paper. Hazard ratio is the ratio between the probability of event in the exposed and unexposed groups (Hernán, 2010). It provides information on the relative reduction of risk for an event such as death, however only a rough estimate of incidence rate ratio (Hernán, 2010). Hazard ratios includes the effect of censoring on survival whereby a subject is censored if they are lost to follow up, dropped out due to adverse events, or die before the termination of the study if death is not the outcome of interest. Therefore, this ratio of the hazard rates does not reflect accurate number of events. Due to insufficient information obtained despite contacting original authors (Bonten, personal communication, August 2015), we decided to base our model
on a parameter without Koeman (2006).

One observation that we found is that the CHX solution (OR=1.16, CI 0.72-1.88) seemed to be associated with a greater mortality rate than CHX gels (OR=0.89, CI 0.45-1.76) based on the subgroup analysis in the Cochrane systematic review (Shi et al., 2013). It is unclear whether CHX is associated with death and the pathophysiological mechanism by which CHX may increase mortality is not yet understood; therefore, it is difficult to draw any conclusions. However, the difference in the mortality rate between the two types of CHX may be due to the possibility of ingestion of residual CHX solution. Ingested CHX solution may have a prolonged effect and increased risk of absorption. Side effects of CHX should be further be investigated to rule out concerns associated with mortality. Meanwhile, it also raises the importance of complete suctioning of CHX to minimize any possible adverse effects.

The importance of prevention is ever increasing. Assuming 80-90% occupancy of mechanically ventilated beds, there will be 70-93% increased need in Ontario by 2026 than in 2003 (1,096 beds in 2003) (Bell and Robinson, 2005). Successful prevention of VAP will consequently, free up hospital beds and ICU capacity (Amin, 2009). However, this evaluation should be updated once more data is available on mortality risk with CHX.

In addition, with alarming concerns about antimicrobial resistance to common bacteria, prevention is increasingly important (WHO, 2014) as a successful prevention minimizes the need for antibiotic treatment. VAP patients are at high risk for MDR infection and are often overtreated with conventional antibiotic regimens that do not necessarily target responsible pathogens (Kollef, 2000 and 2004). Standard treatment mainly includes regimens for MRSA and Pseudomonas species (Muscedere, 2008). Examples include a combination of vancomycin, ceftazidime, levofloxacin, meropenem and ciprofloxacin (Muscedere, 2008). A study by
Nussenblatt et al., (2014) reports that antibiotics are used as a preventive measure in many patients without VAP for longer than 3 days after a diagnosis of possible VAP (77.4%). This prospective study reported cumulative 1,183 excess days of antibiotics in ICU patients from over-diagnosing and providing treatment for VAP (Nussenblatt et al., 2014). In addition, similar outcomes in patients without VAP regardless of antibiotic treatment suggest that these antimicrobial therapies are clinically unnecessary (Nussenblatt et al., 2014). On this note, antibiotic resistance is putting a burden on health care resources and patient outcomes (Kollef, 2000 and 2004). Administration of antibiotics is often based on clinician preferences and behaviours (Nussenblat et al., 2014). These findings highlight the increasing need for other interventions to reduce the use of prophylactic antibiotic for VAP-suspected patients and consequently reduce antimicrobial resistance. Successful prevention of VAP can prevent patients from undergoing VAP antimicrobial treatment, which would typically lasts for about 7-10 days. In addition, understanding specific types of pathogens that cause VAP will help physicians in selecting the appropriate antimicrobial therapy and in turn, increase the effectiveness of the treatment and reduce the chance of antibiotic resistance (Amin, 2009).

Lastly, the number of geriatric patients, who are at a greater risk of acquiring VAP, is on the rise with the aging population worldwide (Nielsson et al., 2013). This is also true for Canada. There has been about 6.4% increase in the geriatric population between 1971-2011. Another 10% of increase is expected by 2051 resulting in about one in four Canadians to be 65 years or older (Statistics Canada, 2015b). Since advancing age alone is associated with increased morbidity and mortality including incidence of VAP, controlling preventable morbidity and reducing mortality will be key for improved survival and QoL.
4.2 Discussion on results

Compared with standard care, CHX intervention produced additional 0.008 life-years and 0.005 QALYs with cost savings of $804.53 (Table 9). On this note, ICER and ICUR indicated that CHX therapy is less costly with comparable health outcome compared to the control. The analysis suggests that the small gain in life-years lived and QALYs are related to overall mortality effect from CHX and prolonged stay in ICU associated with VAP. To our knowledge, this is the first study to evaluate the cost-utility of CHX in preventing VAP and therefore no direct comparison can be done with other publications. However, this finding is in accordance with a cost-benefit analysis on varying VAP preventive strategies where oral care with CHX was found to exceed usual cost-to-effectiveness (Branch-Elliman et al., 2015). Sinuff et al. (2013) indicated the greatest improvement rate in VAP incidence when CHX is used in concordance with the clinical practice guideline. Together with significant improvements in endotracheal tube design with subglottic secretion drainage and semirecumbent position, VAP rates decreased from 14.2% to 8.8% (p=0.03) over the 24-month study period (Sinuff et al., 2013). Therefore, the application of CHX in high VAP risk patients who are mechanically ventilated may be considered as a component of an overall preventive protocol.

The results of this CUA may have been underestimated by assigning the same utilities in all ICU patients regardless of whether they are with and without VAP. If we were to assign different values to patients with VAP, which will be smaller utility than the utility for patients without VAP, we are expected to have greater health outcome.
One-way sensitivity analyses yielded similar results to our base model for most assumptions, while increased mortality risk associated with CHX, reduced effectiveness of CHX in terms of increased VAP incidence, reduced prolonged ICU days with VAP and reduced ICU LOS resulted in reduced life-years lived and QALYs (Table 10). Of these variables, CHX associated mortality rate had the greatest impact on the results. This highlights the importance of conducting further research and obtaining more evidence on attributable mortality to CHX because CHX can easily become harmful intervention if the estimate of its associated mortality is biased.

4.3 Strengths and limitations

There are several strengths and limitations to consider for this study. A merit of this study is that this is the first study to evaluate the cost-utility of CHX application in mechanically ventilated patients in the ICU using primary data from Canadian literature where possible. This provides a platform for a systematic, rather than intuitive, allocation of healthcare resources in Ontario in particular. Further, this study showcases the connection between oral and general health and importance of collaboration between health care providers of different fields and with health economists.

There are several limitations with this study. First is the availability of data. Due to the limited availability of primary data, transitional probabilities and costs were extracted from the literature and synthesis of published studies where available. For example, data on the incidences of VAP specific to Ontario were lacking and therefore the search was expanded beyond Ontario. VAP incidences were obtained from several sources including the literature and self-reported VAP
incidences at several institutions across Canada. Second, certain information was lacking in the dataset. For example, previous medical conditions and the severity of VAP are usually not specified and therefore they were assumed as relatively equal in all ICU patients. Third, data are subject to variability per institution. Variation may be found in the type of treatments, the duration of the intervention, the accuracy of the data, and the regimen of preventive CHX therapy. Therefore, average values were used. In addition, having a single intervention in this analysis limits the understanding of VAP prevention strategies as a whole. Interdependence of CHX effect in conjunction with other preventive strategies is unclear. Therefore broadening the scope of CUA and including other possible interventions for example prophylactic antibiotic treatment will reflect real world events better.

Calculating daily cost for ICU stay is challenging and complex (Wilcox and Rubenfeld, 2015). There are top-down and bottom-up methods for such calculation. Top down is dividing overall cost of ICU by the number of ICU stay where as bottom-up methods takes individual cost data into account (Wilcox and Rubenfeld, 2015). In our study, we used bottom up method in a conservative way. Limitation with this method is that although it is possible to extract individual cost data, for example for CHX, it is unknown how comparable these maybe amongst different hospitals at varying locations (Wilcox and Rubenfeld, 2015). Overall cost associated with ICU stay is expected to be greater than our values when taking other costs such as patient transportation costs into an account.

There are both strength and limitation to our cost data. Strength is that it is Ontario specific. We have consulted Ontario medical fee guide for physician cost for ICU patients with ventilation, referred to current literature to have an estimate of ICU cost from Ontario Case Costing, and consulted with expert for their opinion and current market value for CHX cost. In addition, we considered differing ICU cost at different days in ICU and costs specifically for ventilation.
Sensitivity analysis was performed to compare varying cost of CHX. Having said this, its generalizability may be limited in terms of costs because health care costs fluctuate with varying provinces. Another limitation is that there is a limited generalizability due to inclusive bias of selected group of the target population. Therefore results may not be applied directly to other settings out of hospital due to the differences in the nature of the population, and the setting. CUA captures patient-centered outcomes such as mortality and QoL. Despite Wilcox and Rubenfeld’s (2015) suggestion of the surrogate outcome being reduction in ICU cost in absence of mortality and QoL effects when determining cost-savings in ICU, CUA is still a valuable method in determining cost-utility of an intervention.

Deterministic analysis performed in this study uses single point estimates of variables and most likely case is evaluated. In doing so, uncertainties around variables were not considered in the base model but they have been dealt in one-way sensitivity analysis. However, this type of sensitivity analysis ignores the effects from variations in multiple variables and therefore may underestimates additive and multiplicative effects of variables. Therefore it often does not explain overall uncertainty of a modeled result. To overcome these limitations, multi-way sensitivity analysis and/or probabilistic sensitivity analysis with Markov chain Monte Carlo simulation is recommended.

4.4 Implications for practice

This study provides valuable information for policymakers in health care as it will contribute to a more informed debate on resource allocation priorities with respect to budget planning and policy implementation of VAP prevention protocol. With this information, hospitals will be able
to plan and allocate their budgets more efficiently. For healthcare providers, this information will be useful in determining what to practice in clinic as to whether CHX should be provided in the protocol for day-to-day care. Furthermore, our findings may have a global impact particularly in countries where incidence of VAP is high and resources are limited.

4.5 Implications for research

This study highlights the need for future studies on addressing limitations of our study. Knowing that there is a debatable trend in terms of mortality associated with CHX, more studies on this topic will provide a better directionality. Also, obtaining QoL associated with VAP from ICU patients will be valuable for future analysis. Further research on different demographics such as in pediatric population and in different settings other than ICU will also be beneficial. For example in long-term care facilities where risk of aspirational pneumonia is high could also be considered as CHX is often not part of a standard care. It is also important to understand mechanism of CHX and its effect when used in conjunction with other preventive treatments. Therefore, CUA on other preventive strategies such as antibiotics will permit further informed comparison with CHX. Lastly as new information and further methodologically robust data becomes available re-do of analysis will be valuable.

4.6 Conclusion

The results from our CUA suggest CHX oral antiseptic in ICU for preventing VAP as compared to the care without CHX resulted in comparable health outcome, yet it was cost saving. Possible concerns have recently emerged regarding the associated trend towards
an increased mortality risk with CHX use, and as further methodologically robust data becomes available this analysis should be updated. The decision for an ICU patient to use CHX for prevention of VAP should consider trade-offs between the benefit and risks, and integrate the patient’s values and preferences. Based on the results of our study and understanding its limitations, it is suggested that the use of CHX, as a component of an overall preventive protocol for mechanically ventilated high-risk ICU patients in hospitals, may be revised. Prevention is not only important to minimize unnecessary adverse health effects on patients, but also to relieve the burden on healthcare systems. Finally, it is important to remember that VAP prevention is not solely about using CHX or not, rather it is about adherence to evidence-based protocol bundles to achieve maximal effectiveness at a minimal cost.
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