QATAR UNIVERSITY

COLLEGE OF PHARMACY

CLINICAL AND ECONOMIC EVALUATION OF SURFACTANT USE IN THE MANAGEMENT OF MECONIUM ASPIRATION SYNDROME IN THE INTENSIVE CARE SETTING IN QATAR

BY

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ABSTRACT

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Title: Clinical and Economic Evaluation of Surfactant Use in the Management of Meconium Aspiration Syndrome in the Intensive Care Setting in Qatar

Supervisor of Thesis: Dr. Daoud Al-Badriyeh, PhD.

Background. Surfactant replacement therapy is widely used in the management of the life-threatening condition of Meconium Aspiration Syndrome (MAS), with no clear guidance on its best use. This thesis constitutes two phases. Phase one was to conduct a systematic overview of literature systematic reviews (SRs) and randomized clinical trials (RCTs) on surfactant therapy in neonatal MAS. Phase two was to evaluate the clinical and economic impact of surfactant use in MAS management in the NICU setting in Qatar, including different surfactant dosing regimens.

Methods. For the SR, we searched EMBASE, PROQUEST and PubMed to summarize the different effects of surfactant lung lavage (SLL) and bolus surfactant (BS) therapies in neonates with MAS. Phase two of the thesis was a retrospective cost-effectiveness analyses to evaluate critically ill neonates with MAS receiving surfactant versus standard care, and those receiving single versus multiple dosing surfactant therapy at NICUs in Hamad Medical Corporation (HMC), Qatar. Available medical records in the duration from 2014 to 2019 were utilized. Decision-analytic models from the hospital perspective were designed to measure all the possible consequences of all comparisons. The base case of the model was analyzed based on a multivariate analysis via Monte Carlo simulation. Primary endpoints were treatment success defined as improvements in oxygenation over baseline 24 h after treatment, evaluated by the reduction of oxygen index (OI) to less than 10, and the overall direct medical cost of therapy. Sample size was calculated to achieve results with 80% power and a significance level of 0.05.

Sensitivity analyses were conducted to enhance the robustness and generalizability of the results.

Results. With a total of 1,377 patients, three SRs and two RCTs were included in our SR analysis. Surfactant effectiveness was concluded by low-quality SRs, with high risk of bias, which was contradicted by high-quality SRs, with low risk of bias. In SRs, the SLL reduced mortality, need for extracorporeal membrane oxygenation, and hospitalization, while the BS did not. In recent high-quality RCTs, however, the two modalities did not significantly differ. For the cost-effectiveness evaluation in phase two of the thesis, the standard care achieved a success of 75% versus 51% with surfactant (odd ratio = 2.84; P = 0.029). The surfactant use was dominated by the standard care in MAS, with cost-saving of QAR 48,653 per patient in favor of the latter. Single dose surfactant dominated the multiple doses regimen, with a cost saving of QAR 12,582 per patient and a 57% treatment success, compared to 33% (odd ratio = 1.2; P = 0.839). Here, the study groups did not achieve the calculated sample size and, hence, the evaluation was piloting in nature. Sensitivity analyses demonstrated the robustness of all study conclusions.

Conclusion. The literature evidence on surfactant effectiveness and its method of administration is sparse and inconsistent. Based on the first cost-effectiveness evaluations of surfactant use in MAS in the literature. Standard care was cost effective and dominant over surfactant therapy in both clinical and economic outcomes. A cost analysis of single dose surfactant therapy versus the multiple dosing approach demonstrated overall cost savings with the single dosing approach. The results support the recent trend by some HMC practitioners of favoring standard care over surfactant in the NICU practices of HMC.

DEDICATION

to the most inspiring ladies in my life; my mother, may Allah grant her Jannatu Al Firdaus, and my wife

ACKNOWLEDGMENTS

It was a tough journey full of stress, falls, joy and achievements. Commitment to a full-time job, being an expat with wife and two kids in a different country, taking care of family, along with studying masters was a huge challenge. There are many people I would like to acknowledge. People who helped me throughout the journey and made it feasible.

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CHAPTER 1: INTRODUCTION

1.1 Meconium Aspiration Syndrome

Meconium is a dark green fecal material produced in the intestines of a fetus before birth. It is normally retained in the intestine until delivery, and the newborn will pass it for the first few days of life. Meconium is viscous in nature and usually contains a lot of ingredients such as bile acids, cholesterol, gastrointestinal secretions, lanugo, amniotic fluid, blood, bile, mucus, pancreatic secretions, vernix caseosa and solid particles like cellular debris and proteins. The main factor that differentiates meconium from stool is that it is sterile and does not contain bacteria. Intrauterine distress, such a lack of oxygen, can cause passage of meconium into the amniotic fluid for fetuses to gasp reflexively and, thus, aspirating amniotic fluid containing meconium into their lungs (1,2).

Meconium aspiration syndrome (MAS) as a medical condition refers to a spectrum of disorders affecting newborns as a result of aspiration of meconium-stained amniotic fluid (MSAF), which can occur before, during, or immediately after birth. Notably, this occurs during the transition from a fluid-filled organ to an air-filled organ (3). These neonates are born in amniotic fluid stained with meconium and, in essence, meconium is found within their lungs. In other words, MAS can be described as respiratory distress affecting newborns, with no congenital respiratory disorders or any other underlying pathology, which is mainly caused by inhalation of MSAF into their tracheobronchial tree (4). It is associated with harmonious radiological conclusions, which are difficult to explain (4). The existence of the MAS has been for quite a long time and continues to present problems to healthcare workers taking care of neonates throughout the world. Mainly, it is of grave concern to perinatologists and neonatologists alike.

1.2 Pathophysiology

Literature defined three main mechanisms through which MAS causes respiratory distress in newborns:

- Airways obstruction
- Bronchial cells injury and inflammation
- Surfactant release inhibition and surfactant inactivation

MAS pathophysiology is a series of complex events that contain different mechanical, chemical and inflammatory effects. Complete airway obstruction can occur upon meconium aspiration and results in complete lung collapse known as atelectasis. When the obstruction is partial, the air is trapped in the distal air spaces and would cause distension of the same effect known as a ball and valve effect (3). Trapped air may rupture into the pleural cavity causing pneumothorax, or into the pericardial cavity causing pneumopericardium, or alternatively may rupture into the mediastinum causing pneumomediastinum (3).

It was argued that the presence of meconium within the respiratory tree causes the pressure within the pulmonary circulation to rise considerably and can be attributed to two factors (3). Firstly, the thickening of the vessel wall causes a reduction in the lumen and, hence, the high pressure due to the same amount of blood being forced through the now changed vessel. Second, the presence of meconium within the respiratory tree causes irritation that results in inflammation (3). Despite the meconium being sterile, it predisposes the infant to pulmonary infections that are often life-threatening. Analyses have shown meconium in the terminal airways of fetuses that were dead on birth. Nonetheless, the correlation amid intrauterine transmission of meconium advancement of fetal suffering and the pathophysiology of asphyxia in fetuses is not clearly established (4).

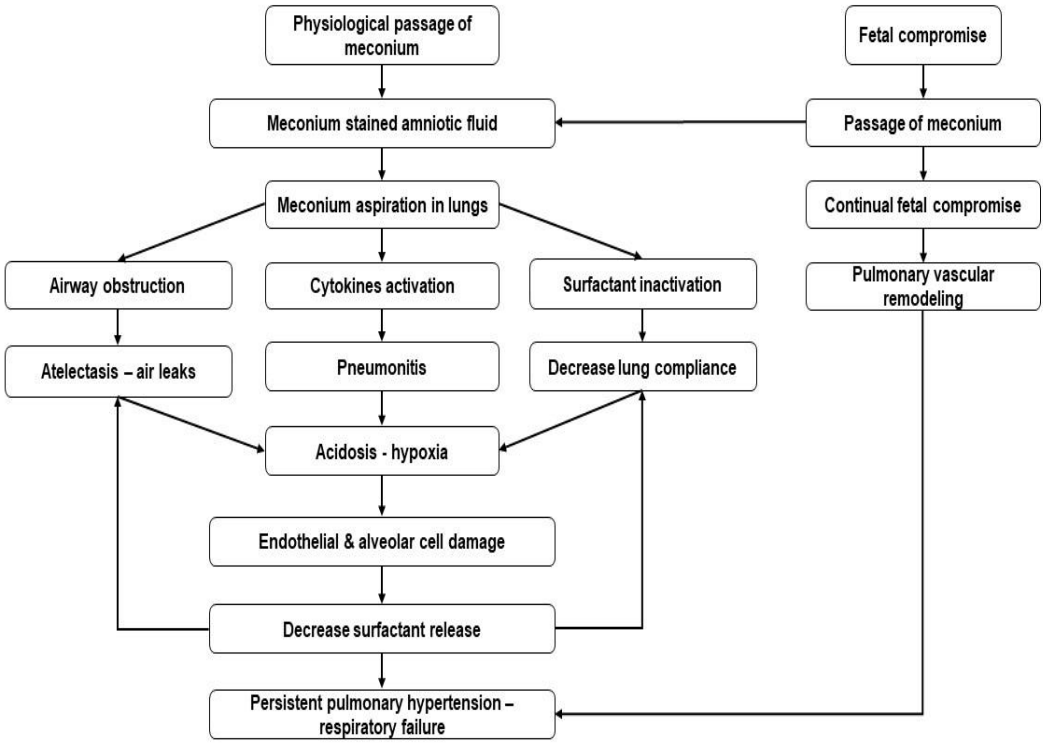

Figure 1. Diagrammatic illustration of MAS pathophysiology

Meconium can trigger inflammation in different ways. Meconium is partially unexposed to the immune system as it is normally retained inside intestines, and when it is aspirated, the immune system recognizes it as a foreign substance and initiates a vigorous immune response (5). Meconium is a potent inflammatory mediators activator including prostaglandins, reactive oxygen species, and cytokines (5). It is a source of pro-inflammatory cytokines, such as interleukins (IL-1, IL-6, IL-8), tumor necrosis factor (TNF), as well as mediators produced by macrophages, epithelial cells, and neutrophils that may injure the lung tissue. Additionally, activated cytokines and leukocytes generate reactive oxygen and nitrogen species which have cytotoxic effects (5). Oxidative stress results in bronchoconstriction, vasoconstriction, accelerated cellular apoptosis, and platelet aggregation (6). Activation of toll-like receptor (TLRs)

has been deemed to be one of the pathways that trigger the inflammatory response in MAS recently (5,7). Phospholipase A2 (PLA2), which is found in meconium with high amounts and is considered a potent proinflammatory enzyme, may lead to necrosis and destruction of lung epithelium, surfactant dysfunction and high rates of cell apoptosis which contribute significantly to meconium-induced lung damage. This is induced, directly or indirectly, through arachidonic acid stimulation (6,7). Coagulation cascade and vasoactive substances, such as platelet-activating factor (PAF), can also be activated by meconium and may lead to the destruction of capillary endothelium and basement membranes. Alveolocapillary membrane injury results in leakage of cells, plasma proteins, and liquid into the alveolar spaces and interstitium (6).

Another important contributing factor in MAS pathophysiology is surfactant inactivation and inhibition of surfactant release (7). Surfactant is a normal substance synthesized by alveolar cells (type II) and is made of a complex of proteins, phospholipids, and saccharides. It performs the most important functions of lowering surface tension in order to allow lung expansion during inspiration, preventing lung collapse after expiration by stabilizing alveoli, as well as prevents its edema. Surfactant also contributes to lung defense and protection as it is also an anti-inflammatory agent. Surfactant enhances the removal of senescent cells and inhaled particles away from the alveolar structure (8). Surfactant release inhibition and deactivation has been intensively observed in MAS patients. The extent of surfactant inhibition depends on the concentration of both meconium and surfactant. When the surfactant concentration is low, even highly-diluted meconium results in surfactant dysfunction, whereas the meconium effects are considerably limited with high surfactant concentrations. Meconium may affect surfactant mechanisms by preventing its spreading over the alveolar surface, decreasing the concentration of surfactant proteins (surfactant protein

A, SP-A and surfactant protein B, SP-B mainly), and by changing the structure and viscosity of surfactant (9). Several morphological alterations occur after exposure to meconium, most notably is the airway epithelium detachment from the stroma, and epithelial cells shedding into the airway. These indicate a direct detrimental effect on lung alveolar cells because of the introduction of meconium into the lungs (7).

All of these eventually lead to a most serious condition called persistent pulmonary hypertension (PPHN). PPHN is not a condition associated with MAS only, it may be associated with various respiratory diseases like pneumonia and sepsis. It has been estimated that nearly 15-20% of MAS-diagnosed infants develop PPHN. A combination of vasoconstriction, hypoxia, and perfusion/ventilation mismatch can trigger PPHN, depending on the meconium concentration within the respiratory tract (1,10). PPHN in newborns is the leading cause of death in MAS (5).

Many infants suffering from MAS do have a full recovery of the functions of pulmonary (11). However, MAS newborns can have slightly higher chances of respiratory infections in their initial years of life since their lungs are still recovering (11). Common disease complications include severe parenchymal pulmonary illness, air block syndrome, pulmonary hypertension, pneumothorax, pneumopericardium and pulmonary interstitial emphysema (3). Severely affected newborns have higher risks of developing Reactive Airway Disease (RAD) in the initial six months after birth. MAS children can develop chronic lung disease from the strong pulmonary complication (11). Due to poor respiration, higher rates of neurodevelopmental defects are associated with those infants who developed MAS (12).

1.3 Diagnosis

The diagnosis for MAS is done based on its severity (13,14). The symptoms can

indicate if the disease is mild, moderate or severe. There is a need to note the respiratory pain in newborns with MSAF, as well as the other features that may be present, such as hypercapnia and tachypnea (3). Physical examination findings include yellow-green staining of fingernails, umbilical cord, skin or under the vocal cords. MAS typical clinical presentation is cyanosis, ended expiratory grunting, alar flaring, and barrel chest as a result of air trapping and tachypnea, which can be considered as a compensatory mechanism by the body for signs of cerebral irritation, mainly seizures or jitteriness, resulting from cerebral edema and hypoxia may appear later (1,15).

Different laboratory and diagnostic examinations should be performed to ensure the physical findings and confirm the diagnosis. Laboratory investigations include continuous blood gas analysis, full blood count, serum electrolytes and acid-base status monitoring, which benefit in detecting hypoxia, acidosis, and infections that are usually associated with MAS.

As for diagnostics, chest x-ray, echocardiography, and brain imaging are the most commonly used tools. The chest x-ray is very useful in confirming MAS diagnosis, to see the extent of intra-thoracic pathology, to identify atelectasis as well as to ensure appropriate positioning of the endotracheal tube and umbilical catheters. Echocardiography ensures normal cardiac structure, assesses cardiac function, and determines the severity of pulmonary hypertension and right-to-left shunting. Brain imaging may be used later in the disease course in case an infant's neurologic examination is abnormal.

MAS calls for a thorough diagnosis and test since it can easily be mistaken for pneumonia (13) and other conditions such as transient tachypnea and hyaline membrane disease (16). Differential diagnosis should be considered. For transient tachypnea found in the newborns, the differentiating signs and symptoms are that it occurs to children

within the gestational period, and there is often the presence of a history of maternal diabetes. For most children born of diabetic mothers, they appear to be macrosomic. Tachypnea is depicted as the primary feature without cyanosis or hypoxia. Differential tests for transient tachypnea include chest X-ray whose findings may comprise perihilar markings and occurrence of fluids within the transverse fissure on the right-hand side (16). Deficiency of surfactant protein B causes severe respiratory distress in both preterm as well as term newborns, resulting in the typical clinical presentation of hyaline membrane illness. Molecular testing is used for the demonstration of the absence of a surfactant protein B shortage. Also, arterial blood gases determination indicates the presence of severe acidosis as well as hypoxemia. Other conditions include lung hypoplasia, cyanotic congenital heart illness, and persistent pulmonary hypertension (17).

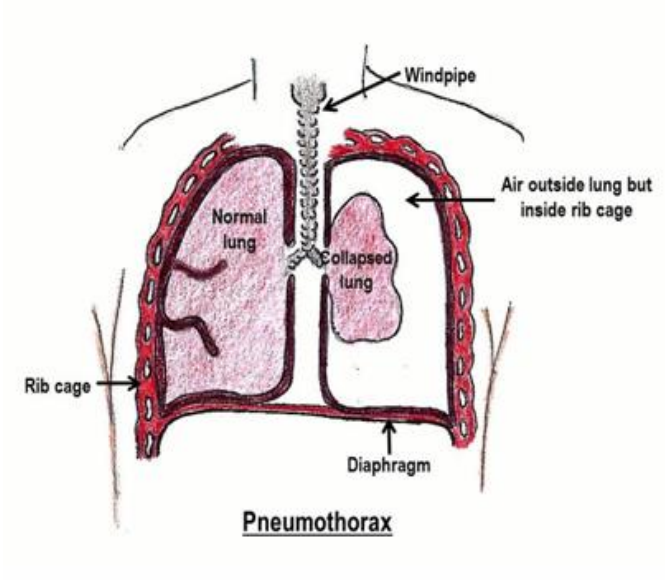

Figure 2. Diagrammatic illustration of pneumothorax

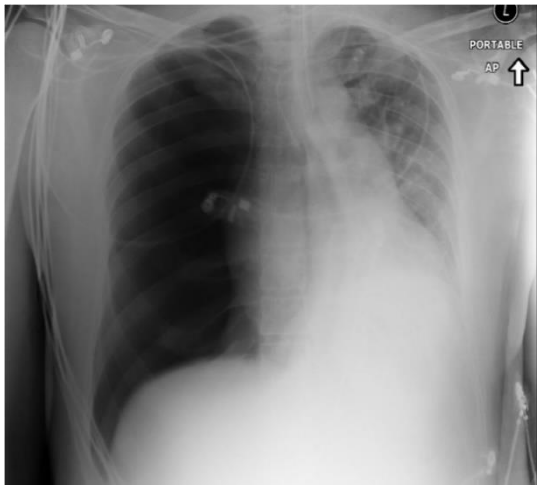

Figure 3. X-ray imagining of pneumothorax

1.4 Epidemiology

Variability between different studies has been noticed. Data on the epidemiology of MAS is vast with many researchers carrying out their own research with different aims, characteristics, and measures. The reported incidence of MAS development, from infants born with MSAF, has varied from 3% to 14% (18,19). According to Greenough et al, one in every seven pregnancies in the United States of America (USA) develops a meconium staining of amniotic fluid (20). Another study was done in the USA to show that 1.5% of admitted neonates to the neonatal intensive care unit (NICU) develop MAS (21). A study done by Thornton et al reported that the number of weighted hospital discharges with diagnosed MAS with respiratory symptoms in the USA for the year 2012 reached 9295 (22). A study conducted in an urban Pakistanis estimated neonatal mortality of about 27.3% in newborns, with the history or evidence of meconium passage during delivery (23). A study conducted in China found that, among all neonates, MAS becomes a source for 10% of cases of respiratory failure and is associated with up to 39% of morbidity and high mortality (24). In this study, no epidemiological data about the condition was reported.

1.5 MAS Management

Moderate and severe MAS are life-threatening conditions that should be handled in a NICU setting (25). Management starts at delivery time and different measures should be taken to ensure patient stability. As per United Kingdom National Institute for Health and Care Excellence (NICE)'s clinical guidelines for intrapartum care for healthy women and babies published in 2014 (26), meconium suction, neonatal resuscitation, and respiratory support should be considered at the earliest. Other treatment options include oxygen therapy, an empirical antibiotic to rule out sepsis, electrolytes, and nutrients in addition to inhaled nitric oxide and inotropes in specific cases. Different studies reported surfactant replacement therapy as a useful and effective treatment in MAS management (9,25,27,28).

1.5.1 Neonatal intensive care unit

The NICU is specialized in the care of newborn infants who are sick or born prematurely (13,29,30). Furthermore, when a child is born, a lot of changes take place in order for the infant to fully function independently. The kidney, heart, liver, and lungs are the major organs that undergo major changes to facilitate the neonates' well-being outside the uterus (29,30). Sometimes some of these organs, notably the heart and lung, fail to undergo the necessary changes in their physiological function and, hence, the neonate has to be admitted to an NICU to support life.

NICU combines technology and trained health care to better help the neonates (29,30). Most of the babies admitted to the unit are born prematurely; meaning that they are born before the 37 weeks of gestation are completed and, thus, their organs are immature and cannot sustain the patient outside the uterus (29,30). Apart from premature infants, NICU sees the admission of neonates born with congenital defects and certain congenital infections like rubella and toxoplasmosis, which are passed to

the neonate from the mother who gets infected with the same in the second and third trimesters (29,30).

Additionally, there are many factors in and around the delivery process that increase the neonates' risk of being cared for in an NICU. These factors include a breech presentation at birth, delivery through the cesarean section and delivery using forceps that is most notably cited to be a major cause of birth asphyxiation (29,30). Factors affecting the fetus are also involved and include; a gestation period that is either too long or too short (should be from 37-42 weeks), therapeutic interventions that may harm the neonate such as the use of a drug that crosses the blood-placenta barrier, neonates who require special procedures as the ones who suffer from hemolytic disease of the newborn and, finally, those born with the various congenital disorders (29,30).

1.5.2 Neonatal resuscitation

Neonatal resuscitation is a combination of interventions applied in support of newborns' airway circulation and breathing. The essential key factor in neonatal resuscitation is effective ventilation. The international agreement statements and guidelines from numerous bodies advise on the best ways to resuscitate newborn babies as ensuring that there is effective ventilation (31). They also recommend providing Positive Pressure Ventilation (PPV) with ventilation devices utilizing face masks, which, whether automatically shaped or round, should have a cushioned rim (31).

When chest compression is being done on a neonate, force is to be applied to the lower 3rd of the sternum, avoiding putting pressure on the xiphoid (32). The lower 3rd of the sternum is just above the xiphisternum. It is very important to ventilate amid chest compressions (32). In every 3rd chest compression, there should be a ventilation breath. In every minute, ninety chest compressions and thirty breaths should be administered (32).

1.5.3 Mechanical ventilation

Generally, mechanical ventilation (MV) refers to the process by which the natural act of spontaneous breathing is replaced by artificial means (20). This could either be by means of a ventilator or it could be done manually by a trained medical practitioner; most commonly by a respiratory therapist or an anesthetic specialist who would compress a bag and valve mask devices (20). There are two types of MVs. The invasive form that had been used for a long time and the non-invasive form whose popularity is continuously growing (20). According to Yoshioka et al, MV failures have the potential to expose the patients to risks that are unacceptable (33). Therefore, Yoshioka et al maintain the need for enhancing safety measures as an important consideration (33).

1.5.3.1 Invasive form

A procedure is called or termed as invasive if any device is in the trachea. This could either be through an endotracheal tube or tracheostomy (20). The two major types of ventilation are a positive pressure ventilation and a negative pressure ventilation. A positive pressure system works by causing an increase in pressure in the airways, causing air entry into the lungs and, hence, the name positive pressure (20). The negative pressure system works by creating a negative pressure system around the chest of the patient and the end result is that air is sucked into the lungs (20). This method is less commonly used today. Windisch et al state that invasive forms can be interventions that assist in saving a life for patients faced with both breathing and respiratory challenges (34). They further suggest that invasive forms of ventilation could be applicable at the time of acute respiratory failure, weaning as well as a chronic respiratory failure when it is difficult to manage non-invasive ventilation (34). Moreover, invasive forms of ventilation can be used for patients while surgical procedures are underway (35). An example of invasive MV is the high-frequency

oscillatory ventilation (HFOV), an MV that utilizes a constantly distending pressure; a high rate of airway pressure of about 900 cycles per 60 seconds. As a result, small tidal volumes are developed, which often are small compared to the dead space (33). HFOV is currently a rescue therapy, whose use is only at the time when conventional ventilation fails because an infant experiences PPHN or when the infant develops MAS. Additionally, HFOV is used in conditions of air trickle syndromes like pneumothorax as well as pulmonary interstitial emphysema. Extracorporeal membrane oxygenation (ECMO) is another kind of invasive MV where special tubes, referred to as cannulas, are fitted into the child's blood vessels heading to his/her heart as well as bloodstream (36). The use of ECMO is based on age, weight, size as well as the reason for the utilization of the ECMO. Cannulas help transfer the child's blood via tubes to a machine where the blood is supplied with oxygen and the carbon dioxide is removed (36).

1.5.3.2 Non-invasive form

In the non-invasive form of MV, a face mask has been designed for use. The researchers agree that this comes at an advantage as it eliminates the complications associated with the invasive procedure and it can be used for the long term by patients who have chronic conditions (20). Indications for its use include acute respiratory distress due to a number of medical conditions, most commonly chronic obstructive pulmonary disease (20). Other medical conditions include exacerbation of heart failure.

The long-term use of the procedure is seen in severe chronic obstructive pulmonary disease and in patients with neuromuscular disease of any kind that limits their ability to breathe independently (20). As earlier alluded, the use of non-invasive MV is slowly gaining momentum. According to Mehta et al, pressure-limited ventilators are common in the ICU for intubated patients (37). Sinuff et al provide that pressure-limited ventilators are used to assist in easing pressure in spontaneous breathing. They provide

adjustable inspiratory as well as expiratory rations at a rate that is controlled (38). An example of non-invasive MV includes continuous positive airway pressure (CPAP). CPAP is a positive form of a ventilator that permits mild air pressure on a continuous basis enabling the airways to remain open in individuals with breathing difficulties.

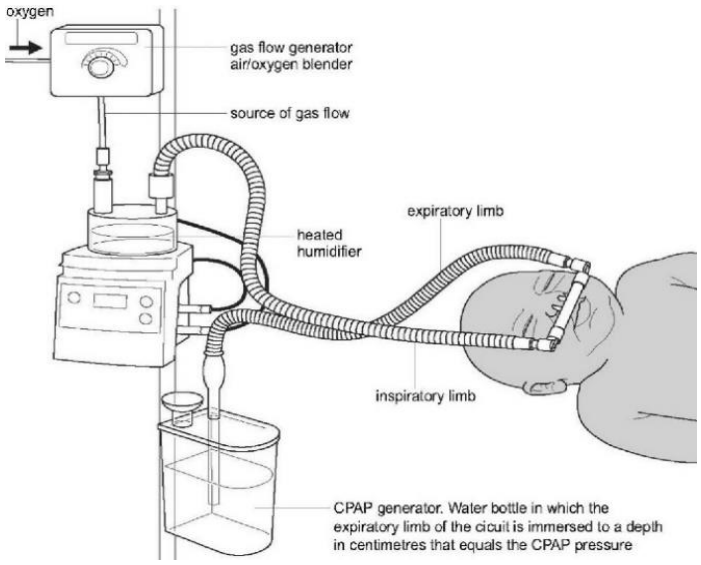

Figure 4. Continuous positive airway pressure (CPAP)

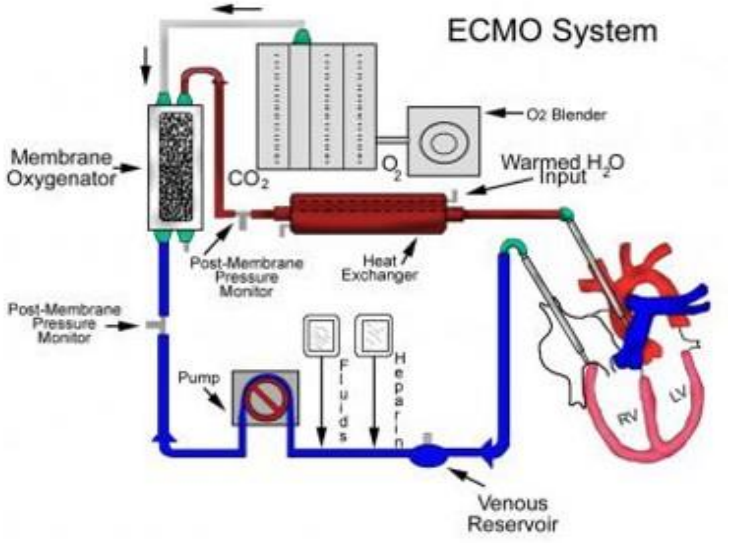

Figure 5. Extracorporeal membrane oxygenation (ECMO)

1.5.4 Surfactant replacement therapy

One of the roles of the pulmonary surfactant includes the reduction of surface tension (39). Lopez-Rodriguez et al argue that the surfactant also contributes to the stabilizing of the alveoli and, therefore, preventing the collapsing tendency of lungs (39). Additionally, once the baby has been born, the surfactant plays an important role as it causes the inflation of the lungs (39). Before then, the lung is solid and not expanded, but hypercapnia and hypoxia drive respiration. The other function of the surfactant is the defense against infections in the respiratory system (39). Lopez-Rodriguez et al aver that the pulmonary surfactant is secreted by two types of cells, the Type 3 alveolar epithelial and the Clara. Type 3 cells are also called the pneumocytes and their characteristic feature is the presence of microvilli on the alveolar surface (39). The Clara cells are located in the bronchioles and are also called bronchial exocrine cells. Surfactant is a lipoprotein molecule formed by lipids, proteins (surfactant protein (SP)-A, SP-B, SP-C, and SP-D), and ions (39). A surfactant replacement therapy is performed in infants with surfactant deficiency, which is considered to be the critical cause of mortality and, particularly, morbidity.

In the preterm babies, especially those diagnosed by respiratory distress syndrome (RDS), surfactant therapy is believed to reduce respiratory morbidity as well as mortality amongst preterm infants. In surfactant trials, comprised of newborns between 23 and 34 weeks, and with a birth weight of about 500 and 2,000 g (4), surfactant replacement therapy showed remarkable effects in minimizing instances of pneumothorax and pulmonary interstitial emphysema (PIE). Different exogenous preparations of the surfactant as medication are available; synthetic and animal-derived. Both have been suggested to be beneficial in terms of reducing mortality and pneumothorax. The three available animal-derived types; beractant, calfactant, and

poractant alpha, are the most commonly used, with no significant difference in effectiveness seen among them (40). Aerosolized surfactant, as a new method of surfactant delivery, has been tested in one small RCT with RDS infants and the authors reported that no clear benefits have been obtained and the method still needs to be optimized (40).

Table 1. Different exogenous surfactant preparations

	Generic name (Trade name)	Origin	Surfactant protein (SP) types
	Animal-derived surfactant		
1	Calfactant (Infasurf®)	Calf lung lavage	SP-B/SP-C
	Calfactant (BLES®)	Cow lung lavage	SP-B/SP-C
2	Beractant (Survanta®)	Minced bovine lung extract	SP-C/low SP-B content
3	Poractant (Curosurf®)	Minced porcine lung extract	SP-B/SP-C
	Synthetic surfactant with no peptides		
4	Colfosceril palmitate (Exosurf®)	Synthetic	---
	Synthetic surfactant with peptides		
5	Lucinactant (Surfaxin®)	Synthetic	Sinapultide

It has been observed that the exogenous surfactant clinical effect passes by three different stages after administration (41); the first one appears shortly within minutes after administration, and the only clinical response in this stage will be based on the physical properties of surfactant. The efficacy of surfactant preparation in rapid distribution to different lung areas is the rate-limiting step in this stage, with faster response associated with SP-B higher content surfactants. The next stage comes within hours post-administration and is a result of the sustained effect from the first dose. It includes lung mechanisms improvements with better gas exchange functions. The last stage comes as a continued clinical response from either one dose or multiple doses of

surfactant administration within multiple days. Endogenous surfactant restoration is observed in this stage (41).

Surfactant administration in MAS has shown to have benefits in terms of oxygenation improvement. In addition, shorter duration of MV and lower number of infants requiring ECMO have been reported in the literature. However, a firm conclusion about the value of surfactant use in MAS has not been confirmed (41).

1.6 Pharmacoeconomics

Pharmacoeconomics provides a tool for decision makers to measure, compare and analyze both the costs and consequences from different perspectives, so better considerations can be taken into decisions about available therapeutic options and resources (42). This includes the ability to predict long-term comparative effects of different interventions, involving clinical, economic and humanistic outcomes, which is commonly referred to in the literature as the Echo model (42,43). Pharmacoeconomics is the field that assesses the use of pharmaceutical products and services in relation to welfare (43), with the aim of the efficient use of resources.

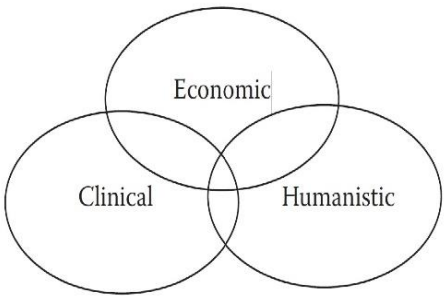

Figure 6. The Echo Model

1.6.1 Types of Pharmacoeconomic Evaluations

There are four types of pharmacoeconomics studies, namely cost-minimization analysis

(CMA), cost-effectiveness analysis (CEA), cost-benefit analysis (CBA) and, finally, cost-utility analysis (CUA) (44). The cost component is identical among the different pharmacoeconomics types in the way costs are defined, calculated and handled. The difference between the different types of evaluations is in relation to the outcome component of the evaluations.

1.6.1.1 Cost-minimization analysis (CMA)

It is the simplest of the pharmacoeconomics evaluations. It is also the least common of evaluations in practices as it is concerned with determining the least expensive option when equivalency between outcomes is evident. Comparing generic products is the clearest example of this type of evaluation, in which drugs are bio-equivalent, but costs can easily vary (42).

1.6.1.2 Cost-effectiveness analysis (CEA)

CEA uses the natural units in measuring outcomes e.g. low-density lipoprotein (LDL) and blood glucose levels. The ease of the natural unit availability in patients' records at routine practices and the familiarity of practitioners with them constitute an advantage for the CEA over other types of evaluations, and it is because of which the CEA is the most common type of pharmacoeconomics evaluations performed in practices and the literature. (42). In CEA, different alternatives can only be compared when they are evaluated against the same type of outcome measure, which is a major disadvantage.

When a dominance status is not identified among alternatives (i.e. a comparator that is better in cost and effect, Table 2), the result of the CEA is presented as an incremental cost-effectiveness ratio (ICER) which, as per the equation illustrated in Figure 7, is the additional cost associated with an additional unit of outcome provided by the more expensive alternative among two comparators. Another disadvantage of CEA is that it does not take the humanistic outcomes into consideration.

Table 2. Simple cost-effectiveness grid

	High effect	Low effect
High cost	ICER	Dominated
Low cost	Dominant	ICER

$$ICER = \frac{Cost\ A - Cost\ B}{Effect\ A - Effect\ B}$$

Figure 7. Incremental cost-effectiveness ratio (ICER) calculation

1.6.1.3 Cost-benefit analysis (CBA)

In this approach, both clinical and economic outcomes are measured in monetary units. This overcomes the major disadvantage of CEA and allows decision makers to compare different unrelated interventions such as the introduction of teleservice for medication adherence follow up versus implementation of a new antidiabetic clinic, whereby comparators do not have to have similar types of outcome measures (42). It additionally is used to know if the benefits of an intervention outweigh its costs. Outcomes of CBA are presented as net benefit values or benefit-cost ratio values. It is worthy to mention that this type of analysis is not widely used as the presentation of clinical outcomes in monetary values is very challenging. It is argued that there is no consensus on the best method to convert clinical outcomes to monetary values (42,43).

1.6.1.4 Cost-utility analysis (CUA)

CUA is similar to CBA in that it allows evaluating different options when the types of their outcome measures differ. The approach of performing a CUA is identical to that with a CEA, except that the CUA uses the Quality-Adjusted Life Years (QALY) as the unit of effectiveness measurement. QALY is calculated based on life years as well as

the patient utility in the years, with the utility being an evaluation of the quality of life (QoL) aspect of health, which is represented via a score that ranges between ‘0‘, in case of death, to ‘1‘ for perfect health. The CUA, therefore, has the advantage of collapsing humanistic considerations as well as aspects of social preference into the comparative outcome measurement (42,43). The main disadvantage of CUA is the subjectivity in measuring patient preferences and lack of consensus about accurate measurement tools for utility (42).

Table 3. Summary of pharmacoeconomics studies types

Type	Description	Units	Applications
CMA	Concerned with determining the least expensive option	Monetary units only	Comparing the costs of two or more alternatives that have a demonstrated equivalence in therapeutic outcomes
CEA	Concerned with comparing and analyzing the costs and consequences of different competing treatment options or interventions to determine the most cost-effective or dominant option	*Costs*: monetary units *Outcomes*: natural units	Calculating the additional cost for producing one additional unit of outcome with one option over another, when the same unit of outcome measurement is used
CBA	Evaluation of different options with presenting both costs and outcomes in monetary units	*Costs*: monetary units *Outcomes*: monetary units	Comparing different programs or interventions with entirely different outcomes, based on the return to investment
CUA	Comparing the costs of different treatment options in terms of quality of life (utility). The most cost-effective or dominant option is determined	*Costs*: monetary units *Outcomes*: Quality-adjusted life years (QALY)	This calculates the additional cost of an option over another for producing one additional QALY.

1.6.2 Decision analysis

Decision analysis is a systematic approach used to model the available options in pharmacoeconomic evaluations. The analytic model allows decision makers to better compare different decision options by following the outcome consequences and the resource utilization associated with them, to eventually calculate clinical and economic values of interest that are needed to compare the options (42). The model is best graphically represented via a decision-analytic tree, which represents such a model as a sequence of process components, allowing one to choose from a set of choices by visualizing how these and their consequences compare. Building and analyzing decision-analytic models is relatively direct, especially with the availability of computer software that simplifies calculations. Examples of software include Palisade‘s @Risk® (www.palisade.com) and Treeage® software (www.treeage.com).

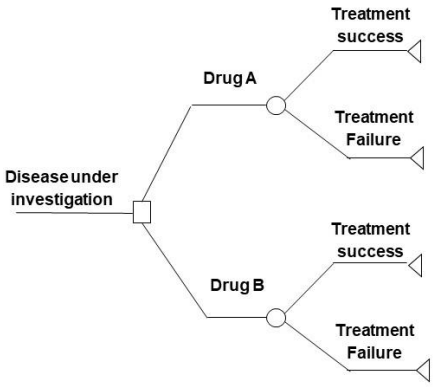

Figure 8. Simple example design of decision tree

Structuring the decision-analytic model requires following certain steps (42,43):

- To specify and frame the research question
- To determine different available alternatives and study assumptions

- To construct the decision model that relates comparative alternatives to their outcomes of interest within a time horizon that is relevant and of interest
- To populate the decision model with outcome probabilities
- To populate the decision model with the cost of utilized resources in patient management
- To analyze the overall model's costs and effectiveness results
- To conduct sensitivity and uncertainty analysis

1.6.3 Perspective

It refers to the point of view from which the pharmacoeconomics problem is being answered. In other words, it is about identifying for whose interest the evaluation is being conducted (42,45). Only after this is determined, the appropriate outcomes and costs to be taken into consideration in the economic evaluation can be defined. The main perspectives of studies include:

- *Payer perspective*: This indicates that the cost of obtaining services by payers is included in the analysis. An example of this is insurance companies.
- *Hospital perspective*: This indicates that analyses include the cost that generally relates to the hospital or healthcare systems, such as the costs of medications, laboratory tests, and hospital stay.
- *Society perspective*: The broadest of the perspectives that comprehensively evaluates all costs and consequences at the level of society.

1.6.4 Types of the cost

Cost refers to the sum total of the resources put in place in the production and delivery of a particular therapeutic option (44). Different types of costs include direct medical

costs, direct non-medical costs, indirect costs, and intangible costs (42). The medical cost is further divided into fixed and variable costs (44). Fixed cost refers to capital within the healthcare sector such as a genetic testing device. It is fixed as it does not change with the number of patients performing genetic testing. A variable cost, on the other hand, varies with the number of patients; a great example would be the cost of drugs or the cost of syringes (44). The non-medical cost is the cost of non-medical resources that would be incurred by the patient, for example, the cost of transportation to the hospital. The indirect cost would be the cost of lost productivity. When a patient is a hospital inpatient, there is work productivity that is lost because the patient, for example, lies in bed most of the time. The value of this is measured, as an example, via the salary value of the productivity time lost. The intangible cost would be the cost of pain, suffering, and depression for which the patient and the family have to mostly pay (44). Other types of costs that are not widely used include productivity cost which is analog to the indirect cost, and opportunity cost which is the value of a forgone benefit because the resources available were not utilized in the best decision pathway possible. The value is not necessarily monetary in nature (44)

In relation to the calculation of cost, it is important to also note that the value of any monetary unit varies throughout time, whereby the purchasing power of money decreases as time goes by. This is because of the earning capacity of money and, as a consequence, inflation. It is, therefore, very important to adjust the cost value of resources if this is based on a financial year that is different from that at the time of decision making (43). Adjustments are conducted based on two important principals: inflation and discounting. Inflation is the adjustment of past monetary values to their current values. The Consumer Price Index (CPI) is used as the inflation rate indicator. CPI measures variations in the price level of a weighted average market basket of

consumer goods and services purchased by households (42,43). The other principle, discounting, is used to bring future cost values to their past values (43).

1.6.5 Sensitivity analysis

Sensitivity analysis, also known as uncertainty analysis, is one way of predicting the outcome of given sets of variables. It is performed by assigning uncertain input ranges to the baseline values of the inputs and changing the values of variables (inputs), to then look at the effect this has on the overall system (42). According to VanderWeele et al, sensitivity analysis is critical for the determination of the manner in which different values representing the independent variable influence a certain dependent variable within a particular cluster of assumptions (46). Sensitivity analysis, which can be either probabilistic or deterministic based on the types of variables, is performed as part of pharmacoeconomics evaluations to investigate the robustness and increase the generalizability of findings, enabling a better interpretation of final conclusions by decision makers.

There are different types of the sensitivity analysis (43,47):

- *One-way sensitivity analysis*: In this type, the researcher tends to see the effect of changes in one specific model input while keeping values of all other variables the same without modification. This type is the most widely used and the easiest to interpret.
- *Multi-variate sensitivity analysis*: This is about applying modifications on two or more variables at the same time, while keeping the remaining variables constant as per their baseline inputs. It is more tedious than a one-way sensitivity analysis in terms of processing and even the interpretation of results. It, however, offers the advantage of better reflecting the real-life

status of uncertainty, whereby there is an overlapping uncertainty that exists among several variables at any point in time.

- *The scenario sensitivity analysis:* It represents the change in one or multiple underlying methodological approaches and assessing their impact on the model as a whole.
- *Threshold analysis*: It is a type of analysis that helps identify the exact value of a variable/input of interest at which the model's conclusion changes. It is commonly done as part of the one-way and multi-variate sensitivity analyses.

Just as with the decision analysis, software such as Palisade‘s @Risk® (www.palisade.com) and Treeage® software (www.treeage.com) greatly enable simplified sensitivity analyses of pharmacoeconomics models, whereby values of uncertain variables can be systematically varied based on pre-defined uncertainty ranges associated with the variables. This can be automatically performed for 1000s of times for any targeted variable in the model.

1.7 Qatar country profile

Qatar is located on the southern coast of the gulf in the peninsula. The country had an estimated population of 2,687,871 persons in December 2019 (48).

In 2017, the total gross domestic product (GDP) was approximately USD 170.8 billion, accounting for a quarter of the global economy (49). In 2019, the average annual GDP per capita based on the purchasing power parity remained above USD 134,000 (50); the world highest. In 2014, the total public health expenditure was 35% of GDP per capita (50), with an anticipated increase in healthcare spending to USD 6.6 billion in 2022 (51).

The life expectancy in Qatar is 78- 81 years of age. The probability of dying under five years old is 7.3 per 1000 live births. The mortality rate within infants is 5.8 per 1000 live births (50).

Medical services are delivered in Qatar by two main governmental healthcare institutions; the Primary Healthcare Corporation (PHCC), which represents the primary healthcare provider with approximately 27 centers around the country, and Hamad Medical Corporation (HMC), which is the major and most important healthcare provider including more than 10 secondary and tertiary hospitals. Different private healthcare institutions are available, and they also deliver high-quality services. Part of HMC is Women's Wellness and Research Center, which is the major maternity hospital with the largest tertiary NICU in the country. The NICU of Al-Wakra Hospital is a smaller NICU at HMC, followed by that of Al-Khor hospital of HMC (52).

CHAPTER 2: LITERATURE REVIEW

The medical literature includes numerous research studies that summarize the research conducted on the use of surfactant in MAS in the NICU setting. Studies are different in treatment regimens, doses, outcome measures and results, and/or the methodological aspects.

Randomized controlled trials (RCT) as well as non-randomized studies (NRSs) reported surfactant administration by two different methods; bolus surfactant administration (BS) endotracheally and surfactant lung lavage (SLL) with the diluted solution of surfactant. These two methods were tested against different comparators. Table 4 and 5 summarizes the main characteristics, reported outcomes and results for RCTs and NRSs.

2.1 Comparison between bolus surfactant administration and standard care

BS was tested against standard care including ventilation, adequate fluids, and other medicines in three RCTs; one in China by Bo Sun et al (2005) (53), and two studies in the USA by Findlay et al (1996) (54) and Lotze et al (1998) (55), as well as in two NRSs done in China by Dong-Mei Chen et al (2015) (56) and HUANG et al (2016) (57).

There were different reported doses of BS in different studies; 100 mg/Kg, 150 mg/Kg, and 200 mg/Kg with different number of administered doses. Lotze et al (55), in a study used need for ECMO as the primary outcome, reported using the dose of 100 mg/Kg four times; the first dose of surfactant was given within 30 minutes after entry into the study and was followed by three additional doses at 6-hour intervals before ECMO. After ECMO was implemented, four additional doses were given six-hourly. The use

of a dose of 150 mg/kg was reported by Findlay et al (54), which was repeated every 6 hours for a maximum of 4 doses. Additionally, the study done by Bo Sun et al (53) used a combination of 100 mg/kg and 200 mg/kg. The dose of 200 mg/kg was first administered and repeated at 6 to 12-hour intervals and, then, the dose of 100 mg/kg was administered to a maximum of a total of four doses; the dose was repeated if one or more of the following occurred. First, deterioration of oxygenation index (OI) by 2 from baseline. Second, aspiration of meconium-stained liquid from the airways with no improvement of OI from baseline. Thirdly, inter-current complications such as air leaks that were not related to surfactant administration.

As for the NRSs, the study done by HUANG et al, which was a comparison of a combination of HFOV plus BS against HFOV alone, reported using 2 doses; the first was 100 – 200 mg/kg, while the second was 100 mg/kg (57). The other study done by Dong-Mei Chen et al included three groups to investigate the effect of each of conventional mechanical ventilation (CMV) and HFOV against BS with doses ranged between 100 and 200 mg/kg (56).

Duration of respiratory support, respiratory functions, and complications were the main reported outcomes, with different results in the different studies. While respiratory support needed was significantly lower with the use of BS in the studies done by Findlay et al (54) and Dong-Mei Chen et al (56), Lotze et al study (55) and the larger RCT done by Bo Sun et al (53) reported no significant difference between groups. In this study, oxygen index (OI) was used as indicator to represent the respiratory functions improvement over time. Rapid improvements in respiratory parameters and oxygenation was observed earlier in surfactant group, and there was significant difference in the treatment success rate as defined based on OI values, in comparison to control group. However, collection of data to 7, 14 and 28 days was completed in

few cases and no significant difference was observed between groups. The same was observed in the cohort studies done by Dong-Mei Chen et al (56) and HUANG et al (57) where oxygenation indicators were significantly lower in BS groups; as represented by fraction of inspired oxygen (FiO2) and mean airway pressure (MAP) in Dong-Mei Chen et al study, and P/F value (partial pressure of oxygen and fraction of inspired oxygen) and OI in HUANG et al study.

Findlay et al investigated the incidence of PPHN in both study groups, and reported that PPHN was resolved in all infants received BS between 18 and 24 hours versus none of the infants in the control group ($p<0.001$) (54). This was contradicted by the results of Lotze et al in which no differences between the two groups were noticed in regard to the overall incidence of severe complications, pulmonary, neuroimaging and cardiac complications (55).

2.2 Comparison between surfactant lung lavage and standard care

In relation to SLL, this was tested against standard care including total respiratory support, ventilation by means of conventional mechanical ventilation, HFOV or ECMO, use of medicines such as alkalosis, paralysis, vasopressors, or sedation in three RCTs; Bandiya et al (2019) in Turkey (58), Dargaville et al (2011) in Australia (59) and Wiswell et al (2002) in the USA (36), as well as in one case series study done by Dargaville et al (2007) in Australia (60). Diluted surfactant solution of 5 mg/ml with a volume up to 15 ml/kg was used in all studies except the one done by Wiswell et al (36) in which the volume of 8 mL/kg (2.5 mg/mL) was used over approximately 20 seconds and the procedure was repeated twice. In this study, no significant difference was noticed between groups in the treatment failure rates, defined as increase in OI value

>25 or more than 50% above baseline (whichever came first), as ascertained on at least 2 arterial blood gas readings within a 3-hour period.

In addition, Dargaville et al found that there was no significant difference in total duration of respiratory support, defined as the cumulative duration of all periods of intubation and nasal CPAP, between groups (59,60). The same was reported in the study done by Bandiya et al where SLL was found to be well tolerated in MAS patients but there was no change in overall duration of respiratory support between groups (58).

2.3 Comparison between surfactant administration and corticosteroids

The use of corticosteroids and surfactant in MAS patients was reported in two studies; Salvia-Roige´s et al (2004) study in Spain (61), which was retrospective in the control groups and prospective in the test groups, and the RCT done by TAN Xiu-Zhen et al (2016) in China (62).

The study done by Salvia-Roige´s et al (2004) included three groups, comparing the standard therapy alone, against standard therapy plus SLL (four aliquots of surfactant solution 15mg/ml), and against a combination of standard therapy, SLL (four aliquots of surfactant solution 15 mg/ml) and a single dose of intravenous dexamethasone (0.5 mg/kg) within the first 5 hours of life (61). The standard therapy in this study included MV, bicarbonate, inotropic drugs, volume expanders (crystalloids), antibiotics, analgesia with fentanyl, sedation with midazolam, vecuronium for muscle paralysis when synchronization with the ventilator was not achieved, as well as adjunctive iNO. Need for MV and oxygen therapy was decreased with SLL groups, but statistical significance was not reported. No secondary respiratory infections, air leaks or deaths were reported in SLL groups as well (61).

BS with dose of 100 mg/kg tested against the combination of BS plus budesonide 0.25 mg/kg in the study done by TAN Xiu-Zhen et al (2016) in China (62). The number of administered doses were not reported. In this study the authors used different respiratory parameters of mean P/F value, percutaneous oxygen saturation degree (TcSaO2), PaO2 and arterial blood Carbon dioxide partial pressure (PaCO2) to investigate the effect of corticosteroids, and significant result at 6 hours and up to 24 hours was observed in favor of combination of budesonide and surfactant over surfactant alone (62).

2.4 Direct comparison between bolus surfactant administration and surfactant lung lavage

Gadzinowski et al (2008) in the study done in Poland on both term and pre-term infants (gestational age < 37 weeks) tested the use of the combination of SLL (5 mg/ml with a volume of 15 ml/kg as four parts), BS as two doses each of 100 mg/Kg, and inhaled nitric oxide (iNO) against single BS dose of 100 mg/Kg plus iNO only. PPHN and sepsis were reported as comorbidities in the study. All respiratory parameters showed significant improvement in the first group at different time points (63).

Another study done by LIN Xin-Zhu et al (2014) in China directly compared BS versus SLL, both when combined with HFOV (64). They reported using the BS dose of 200 mg/kg twice daily and re-medication up to 3 times was applied if needed, but without determining the conditions in which re-medication should be applied (59). As for SLL, surfactant solution of 12 mg/ml concentration, with a volume of 3-5 ml every 10 – 15 seconds was used. Respiratory parameters, in terms of OI and P/F value, showed significant difference after 12 hours in favor of SLL group (64).

These results were contradicted by the result of recent RCT done by Arayici et al (2019) in India (65), that tested 30 ml/kg of diluted porcine surfactant as SLL against BS with dose of 100 mg/Kg. No significant difference is found between both therapies for the overall duration of respiratory support. In addition, the surfactant re-administration and pneumothorax incidence decreased non-significantly in SLL group (65).

Table 4. Main reported primary outcomes

	Primary outcome	Article/Country	Definition	Comparators	Results (significance)
Main reported primary outcomes in RCTs					
1	Respiratory support and measures related to respiratory functions (n=8)	Bandiya et al (2019) – Turkey (58)	Duration of respiratory support and tolerability	SLL (bovine surfactant) Vs. No lung lavage	SLL is well tolerated but there was no change in overall duration of respiratory support
		Arayici et al (2019) – India (65)	Duration of respiratory support (MV and CPAP)	30 ml/kg of diluted porcine SLL Vs. BS porcine surfactant (100 mg/kg)	No significant difference is found between both therapies for the duration of respiratory support. However, the surfactant re-administration and pneumothorax incidence decreased non-significantly in SLLgroup
		Dargaville et al (2011) - Australia (66)	Duration of respiratory support which was defined as the cumulative duration of all periods of intubation and nasal CPAP	SLL + Standard care Vs. Standard care only (Standard care includes HFOV, and, where available, ECMO)	No significant difference between both groups ($p = 0.79$)
		Findlay et al (1996) – USA (54)	The duration of MV and oxygen therapy	BS Vs. Placebo	The duration of MV and oxygen therapy was significantly longer in the control group ($p < 0.05$)
		Lotze et al (1998) – USA (55)	Need for ECMO, ventilator and oxygen requirements	BS Vs. Placebo	The overall need for ECMO was significantly less in the surfactant group ($p = 0.038$), most notably in infants with sepsis (40% decrease) and MAS (29% decrease) versus a 7% decrease in the PPHN group. In addition, no increase was observed in the MV duration, hospital overall stay duration, as well as hours on the bypass.
		Gadzinowski et al (2008) – Poland (63)	OI, PaO_2, $AaDO_2$ and FiO_2	SLL + BS followed by iNO Vs. BS followed by iNO	<u>OI:</u> Statistically significant drop took place in intervention group between 0 and 1 hour (p=0.0003), 0 and 4 hours (p=0.0398) and 0 and 48 hours of treatment (p=0.0001) as well as the comparator group after 48 hours (p= 0.0011) Difference between both groups was statistically significant (for the favor of intervention group) after 1 hour, 4 hours, and up to 24 hours while at 48 hours the results were similar

			$\underline{AaDO_2}$: The drop in $AaDO_2$ in the intervention group was statistically significant between 0 and 24 hours (p=0.0024) and between 0 and 48 hours of treatment (p=0.0021), regarding the comparator group The drop in $AaDO_2$ was statistically significant between 0 and the 48 hours of treatment (p=0.0017) Difference between the drop in both groups was statistically significant (for the favor of intervention group) after 1 hour and 4 hours; while the difference after 24 hour and 48 hour was not significant $\underline{PaO_2}$: A statistically significant increase of PaO_2 in the intervention group was observed between 0 and 4 hours of treatment (P=0.0311), while the increase of PaO_2 in the comparator group, during the 48-hour treatment was not statistically significant (p>0.05) The difference was only significant at 1 hour (for the favor of intervention group) $\underline{FiO_2}$: A statistically significant drop of FiO_2 in the intervention group was observed between 0 and the 1 hour of treatment (p=0.0323), while After 48 hours of treatment, the drop in FiO2 that was observed was not statistically significant (p>0.05). The difference was only significant at 2 hour and 4 hours (for the favor of intervention group)
TAN Xiu-Zhen et al (2016) – China (62)	Mean PaO_2/FiO_2, percutaneous oxygen saturation degree ($TcSaO_2$), an arterial oxygen pressure (PaO_2), arterial blood Carbon dioxide partial pressure ($PaCO_2$)	BS + budesonide Vs. BS	Significant result at 6 hours and up to 24 hours and the difference between groups was significant.

		LIN Xin-Zhu et al (2014) – China (64)	Oxygen index (OI) and P/F value (PaO_2/FiO_2 ratio)	SLL + HFOV Vs. BS + HFOV	Significant difference was observed after 12 hours (in favor of SLL group) in all parameters
2	Treatment success/failure (n=2)	Wiswell, et al (2002) – USA (36)	Treatment failure was defined as when the infant achieved either an OI>25 or an increase in OI to >50% above baseline (whichever came first), as ascertained on at least 2 arterial blood gas readings within a 3-hour period	SLL Vs. Standard care	No significant difference
		Bo Sun (2005) – China (53)	Treatment success defined as improvements in oxygenation and ventilation over baseline 24 hour after surfactant treatment measured as reduction of OI to less than 10	BS Vs. Control therapy	Treatment success rate reached 74% in the surfactant group, while it was around 51% in the other group. Rapid improvements in respiratory parameters and oxygenation was observed earlier in surfactant group. However, this cannot be sustained from 6 hours. Collection of data to 7, 14 and 28 days was completed in only a few cases and there were no significant difference was observed between groups in terms of respiratory parameters and oxygenation. The overall duration of MV was 105+81 and 80+40 hours in the surfactant and control group, respectively. No differences were found.
3	Complications (n=2)	Findlay et al (1996) – USA (54)	The presence of PPHN	BS Vs. Placebo	Between 18 and 24 hours of age, PPHN resolved in all but one of the infants in the study groups versus none of the infants in the control group (p<0.001).
		Lotze et al (1998) – USA (55)	Overall complications, pulmonary, neuroimaging, and cardiac complications	BS Vs. Placebo	No differences between the two groups were noticed in regard to the overall incidence of severe complications, pulmonary, neuroimaging and cardiac complications.
Main reported primary outcomes in cohort studies					
1	Complications (n=3)	Salvia-Roige´s et al (2004) – Spain (61)	Not well defined, include infections and pneumothorax	Standard therapy Vs. SLL Vs.	No secondary respiratory infections, air leaks or deaths were observed in the groups treated with lavage.

				SLL + single early dexamethasone dose	
		Dong-Mei Chen et al (2015) – China (56)	NA	Conventional MV Vs. HFOV Vs. HFOV + BS	There was no significant statistical difference in cranial hemorrhage in three groups (p >0.05)
		Hung et al (2006) – Taiwan (67)	PPHN, seizures and air leak	Small volume SLL Vs. Large volume SLL	Adverse effects were lower in the test group (statistical significance was not reported)
2	Blood gas analysis (n=2)	HUANG et al (2016) – China (57)	PaO2 / PaCO2 OI was defined as (FiO2 × MAP × 100 / PaO2) P/F value	BS + HFOV Vs. HFOV	At 6, 12, 24, and 48 hours post treatment, the test group showed significant inhancement in terms of PaO2, OI, and P/F value over control group (p<0.05)
		Dong-Mei Chen et al (2015) – China (56)	Pulmonary oxygenation indicators, FiO2, MAP	Conventional MV Vs. HFOV Vs. HFOV + BS	The difference in oxygenation indicators was statistically significant (p<0.05). Lower FiO2 and MAP values was observed with group 3 patients, in which BS was used, at different time points, and the difference was found to be statistically significant (p<0.05)
3	MV (n=3)	Salvia-Roige´s et al (2004) – Spain (61)	Need for MV	Standard therapy Vs. SLL vs. SLL + single early dexamethasone dose	The decrease in the need for MV was noted (statistical significance was not reported)
		Dong-Mei Chen et al (2015) – China (56)	NA	Conventional MV Vs. HFOV Vs. HFOV + BS	A significant difference between groups was reported (p< 0.05)
		Hung H.-Y., et al (2006) – China (67)	Duration of MV	Small volume SLL Vs. Large volume SLL	No significant difference between groups

4	Length of hospital stay (n=2)	Dong-Mei Chen et al (2015) – China (56)		Conventional MV Vs. HFOV Vs. HFOV + BS	The duration was decreased significantly (p<0.05)
		Hung et al (2006) – Taiwan (67)	The total duration of hospital stay	Small volume SLL Vs. Large volume SLL	No significant difference between groups
5	Physiological state (n=1)	Dargaville et al (2007) – Australia (60)	Correction of hypotension and acidosis, optimization of ventilatory care, and desaturation	SLL Vs. HFOV	For none of the physiological indices (pH, PaCO2, base excess, AaDo2) was there a clinically significant deterioration noted. No significant difference regarding ventilation
6	Need for oxygen therapy (n=1)	Salvia-Roige´s et al (2004) – Spain (61)	NA	Standard therapy Vs. SLL Vs. SLL + single early dexamethasone dose	The decrease in the need for oxygen therapy was noted (statistical significance was not reported)

SLL: Surfactant lung lavage, BS: Bolus surfactant, HFOV: High frequency oscillatory ventilation, MV: Mechanical ventilation, OI: oxygen index, ECMO: Extracorporeal membrane oxygenation, CPAP: Continuous positive airway pressure, PPHN: Persistent pulmonary hypertension, iNO: Inhaled nitric oxide, PaO2: Partial pressure of oxygen, AaDO2: Alveolar-arterial oxygen gradient, FiO2: Fraction of inspired oxygen, PaCO2: Partial pressure of carbon dioxide, MAP: Mean airway pressure

2.5 Study rationale and research significance

In the NICUs of the WWRC and Al-Wakra Hospital, the main NICUs at HMC - the only tertiary service provider in the country, while for the majority of practitioners the surfactant replacement therapy has been the universal first-line option used in the management of MAS for years, for some other practitioners it is not, where the standard care only is preferable. All this is based on personal opinions and patient experiences; whereby, no local clinical evidence on the use of surfactant therapy in Qatar was ever generated at any level. As discussed above, there are several studies that evaluated surfactant use in the management of MAS. These, however, were not deemed sufficient for the local guidance of decisions in HMC in support of making recommendations on how the surfactant should ideally and consistently be utilized for MAS, primarily for the following reasons:

- RCTs were limited in sample size, with the largest of which including 136 patients (64). The value of studies that reflect real-life local practices cannot be underestimated. Among all the medical records-based studies in literature, however, none was based on a powered sample size.
- There are conflicting results among published studies of surfactant in MAS, with studies reporting varied results for varied outcome measures. The reduction in OI is the ideal primary outcome measure for the evaluation of the surfactant effectiveness (68–70). In the literature, nevertheless, only RCTs targeted the reduction in OI as an outcome. Retrospective studies evaluated surfactants based on secondary outcomes only, such as ECMO use, rate of complications, and MV duration. The reason behind this is important, which is that the reduction in the OI, as measured in RCTs, is very difficult to measure in retrospective studies that are medical records based. OI is a reliable indicator for respiratory functions as it

combines different respiratory parameters in one equation (OI = mean airway pressure [MAP] × fraction of inspired oxygen [FiO2] × 100 ÷ Partial pressure of oxygen in arterial blood [PaO2]) (70). The main issue with obtaining OI in clinical practice is that it requires arterial punctures or an indwelling arterial line to obtain PaO2. This is practically challenging as indwelling arterial line catheterization is not routinely performed in NICUs, including in Qatar, due to its associated risks (70). An innovative approach for measuring OI reduction based on retrospective medical records data, based on real-life clinical practices, is most needed for the purpose of enabling enhanced future studies in the international local setting.

- Important is that, in the NICUs in Qatar, while most clinicians follow the single-dose approach of surfactant administration, it seems that several choose instead to administer pre-determined multiple subsequent doses of the surfactant, assuming an enhanced efficacy. In the literature, there are no reports of an evaluation of how the single versus the multiple dosing approaches compare in terms of effectiveness.
- Internationally, including in Qatar, there are no comparative cost-effectiveness evaluations of the use of the surfactant in the management of MAS. For better understanding the trade-off between costs and consequences, comparative economic evaluations of the surfactant, including against standard care, need to be conducted to guide decisions about the best utilization of limited resources.
- There is no data on the economics of MAS management, in Qatar and internationally, including the use of surfactant, and including via both single and multiple dosing. This includes any information about the utilization of resources with surfactants and MAS in general. Assessing the impact of surfactant on resource consumption is most important for better understanding its impact on NICU budgets for decision makers and practitioners to consider, beyond the acquisition costs only.

This relates to appreciating the economic impact of the clinicians' handling practices of side effects, or their handling strategies of failures. This information can be useful for decision makers and clinicians alike when considering and revising their protocols and practices in Qatar.

Our literature review suggested that there are numerous studies published over the years of more than 15 RCTs and observational studies. For settings where practices do not have quality local initiatives to guide and contribute to evidence for local decision making, published meta-analyses systematic reviews (SRs) provide the only top source of evidence for most. Indeed, there seem to be several SRs published in the past decade, citing RCTs and observational studies. However, the variability in the quality, focus, and structure of SRs potentially leads to limitations to easy access and interpretation of evidence and, therefore, these reviews often fail to efficiently support decision making in healthcare. Within the context of guiding the decision making on the use of surfactants for MAS, there is a need to systematically bring together, assess, and summarize the top meta-analyses evidence out there, added to most recent studies that are not included in SRs, especially as a robust evidence to support the effective surfactant modality is still not proved. The systematic overview of SRs is a relatively recent study type for the purpose of addressing the growing problem of information overload, enabling an approach to filter evidence so as to enhance access to targeted information of interest, including quality (71).

2.6 Study objectives

The core aim of the current thesis is to generate information to facilitate the delivery of effective, efficient, and cost-effective use of surfactant in MAS management in the Qatari NICU, which is via local comparative clinical and economic evaluations of the

surfactant in MAS.

The overall research in the current thesis is divided into two phases, which are described below:

Phase 1: Surfactant therapy for MAS in neonates: A systematic overview of SRs

To put outcomes of local surfactant evaluations in an international context of evidence, and to generate an overall condensation of the top evidence so far for the international audience, the objective of this phase was to perform a systematic overview to summarize the characteristics, outcomes, and quality of SRs, and the RCTs that were not part of the SRs, in the literature.

- This systematic review has already been accepted for publication:
    - Abdelaal M, Abushanab D, Al-Badriyeh D. *Surfactant therapy in Meconium Aspiration Syndrome in neonates: A systematic overview of systematic reviews*. Journal of Comparative Effectiveness Research 2020. Accepted.

Phase 2: Pharmacoeconomics evaluations of surfactant use for MAS in NICUs in Qatar

The objective of this phase was to conduct comprehensive assessments of the relative utilization cost of surfactant against its outcomes as first-line therapy in MAS in Qatar. This was performed through the following two evaluations from the hospital perspective of HMC.

- Evaluation 1: CEA of surfactant versus non-surfactant regimens of therapy.
- Evaluation 2: CEA of single versus multiple dosing regimens of the surfactant therapy.

CHAPTER 3: MATERIALS AND METHODS

3.1 Phase 1: Surfactant therapy for MAS in neonates: A systematic overview of SRs

(This section of the thesis has been extracted from the following publication:

Abdelaal M, Abushanab D, Al-Badriyeh D. *Surfactant therapy in Meconium Aspiration Syndrome in neonates: A systematic overview of systematic reviews*. Journal of Comparative Effectiveness Research 2020. Accepted)

This is a systematic overview that follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist recommendations for reporting (Appendix 1).

3.1.1 Identification and selection of SRs

We searched EMBASE, PROQUEST and PubMed databases with variations of the key terms “meconium”, “meconium aspiration syndrome” and “surfactant” since inception to week 1 of January 2020 for identifications of literature on this topic. Search strategies can be seen in Appendix 2. No restrictions were imposed on the search. In addition, to identify potentially missed relevant literature, we have searched Google Scholar and references of relevant reviews (grey literature).

Studies that were SRs or comparative clinical trials on neonates with MAS that were treated with surfactants and assessed for mortality and morbidity were considered for inclusion.

Any included SR, identified as SR or meta-analysis, was one that:

(i) systematically identified the evidence about using the surfactants

(ii) summarized the different outcomes from different sources

(iii) synthesized summative evidence about each of the different outcomes.

Included RCTs are the ones that were not included in any of the included SRs in the current study.

We have excluded studies such as expert opinions, previous SRs of current/updated ones, narrative reviews, conference abstracts and editorials.

3.1.2 Selection of studies

Two reviewers independently screened title/abstracts for inclusion and exclusion, and then the eligible studies were subjected to the full-text screening based on the aforementioned definition of an SR. The same two reviewers conducted full-text screening, and any discrepancies were resolved by consulting the senior author.

3.1.3 Data abstraction and scoring

Two authors independently extracted the data of interest from each included SR. The extracted data related to the study characteristics, literature search strategies, patient characteristics, intervention, comparator, outcome measures, duration of follow-up, effect estimates, surfactant type, formulation, and the number of doses. In addition, we also extracted the relevant data from recently published RCTs that are not included in the most recent SR.

3.1.4 Quality assessment of RCTs

The CASP (Critical Appraisal Skills Programme) tool was used to assess the quality of included RCTs. Two reviewers independently did the scoring on each item of CASP RCT tool. Any disagreements were resolved by consensus. If consensus was unable to be reached regarding any item, a third reviewer was involved for adjudication.

CASP consists of 11 questions, of which the first three questions are screening questions and can be answered quickly. If the answers are “yes”, it is worth proceeding with the remaining questions. With some degree of overlap between the questions,

researchers are asked to record a “yes”, “no” or “can’t tell” to most of the questions. A number of italicized prompts are given after each question

3.1.5 Quality assessment of SRs

AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) is a 16-item instrument used to determine the methodological quality of SRs. This tool requires assessors to answer “yes,”, “no,”, “partial yes”, or “not applicable”; and AMSTAR-2 has a good agreement, reliability, construct validity, and feasibility to assess the quality of SRs. The overall methodological quality of each SR was rated as, high, moderate, low and critically low according to the guidance document. We used the online AMSTAR-2 checklist for the purpose of this study (https://amstar.ca/Amstar_Checklist.php).

3.1.6 Assessment of risk of bias in SRs

Two reviewers independently performed the risk of bias assessment using the ROBIS (Risk of Bias in Systematic Reviews) tool for all included SRs. Any disagreements between the reviewers were resolved by discussion. Reviewers were asked to read the ROBIS guidance document and understand the assessment procedure prior to employing this tool. This tool was completed in 3 phases: (1) assess relevance (which is optional), (2) identify concerns with the review process and (3) judge risk of bias in the review. Phase 2 involves assessment of the risk of bias in four domains, through 21 signaling questions (SQs), from which bias is likely to be introduced: study eligibility criteria; selection and identification of studies; collection of data and study appraisal; and findings and synthesis. In phase 3, the overall quality of each SR was rated as “high risk of bias”, “unclear risk of bias”, or “low risk of bias” depending upon the rating given for each signaling question in phase 2.

3.1.7 Data analysis

Data were reported descriptively and graphically using Microsoft Excel 2016. Ethical approval for this work was not required because the sample included published SRs, not humans or animals. Since there were less than 10 SRs included in this study, we did not assess the association between publication year, impact factor and quality of the SR.

3.2 Phase 2: Pharmacoeconomics evaluations of surfactant use for MAS in NICUs in Qatar

In accordance with the study objectives, two different evaluations have been conducted.

- Evaluation 1: CEA of surfactant versus non-surfactant regimens of therapy.
- Evaluation 2: CEA of single versus multiple dosing regimens of the surfactant therapy.

The research is a comparative economic decision-analytic model, in which a population of interest is followed up throughout time to examine the development of specific outcome measures of interest; clinical and economic. In this study, the use of surfactant replacement therapy and the standard care regimen were comparatively evaluated as available treatment options for MAS cases in the primary NICU settings at HMC.

3.2.1 Decision-analytic model structure

The pharmacoeconomics analysis was conducted based on a decision-analytic model to describe the infant management flow in the NICU, where possible consequences of interest were considered as shown in the model trees in Figures 9 and 10. All patients were followed till NICU discharge. In Evaluation 1, mechanically ventilated neonates with MAS were initially assigned to one of the two arms; surfactant plus standard care or standard care only with no surfactant therapy. As for Evaluation 2, mechanically

ventilated neonates who received surfactant as a treatment for MAS plus standard care were assigned to one of the two arms; multiple or single dosing regimens, based on the pre-determined number of administered surfactant doses. In any tree, for each treatment arm, the model included three possible treatment pathways depending on whether the initial treatment was successful, and on the consequences of failures. Patients were followed until therapy was considered successful or a failure; where the patient either continued on standard care only or as a result of mortality.

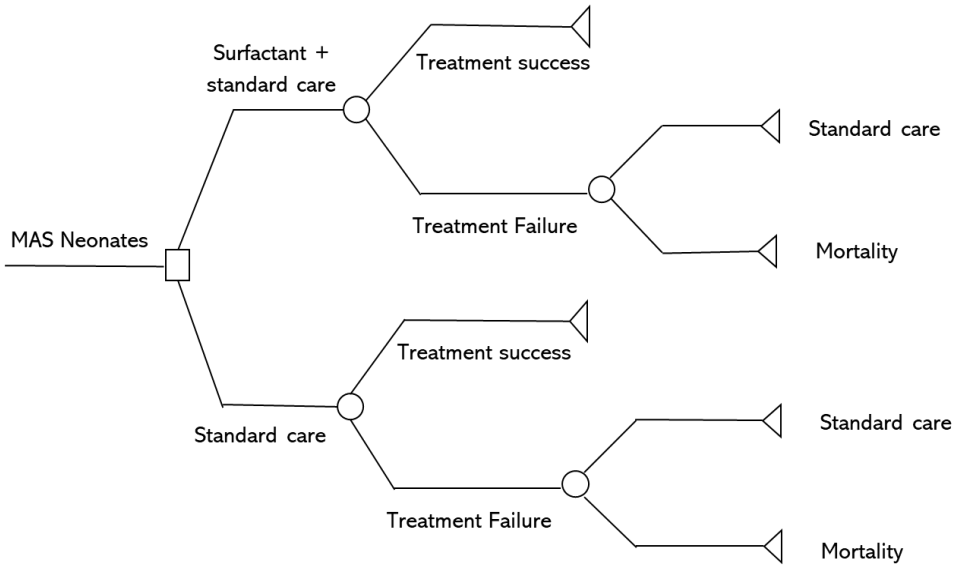

Figure 9. Evaluation 1 decision tree

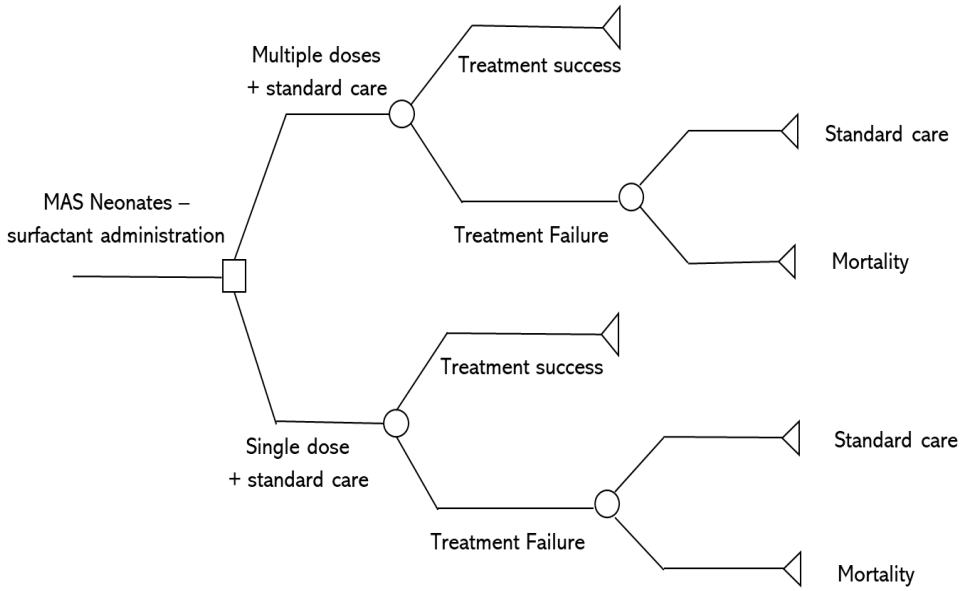

Figure 10. Evaluation 2 decision tree

3.2.2 Model clinical inputs

Data inputs in relation to clinical outcomes and their probabilities were extracted from Cerner medical records as relevant patients in HMC.

3.2.2.1 Population and settings

The main governmental non-profit medical institution in Qatar is HMC, with 12 hospitals under its management as well as the national ambulance service and the home and residential care services. The WWRC and Al-Wakra hospital are among those hospitals with high-capacity, premium quality, and well-developed NICU services. HMC medical records data of mechanically ventilated neonate patients, who are in the NICU because of MAS during the 2014-2019 period, has been extracted for the purpose of two evaluations. In Evaluation 1, the use of surfactant therapy in addition to standard care for MAS was evaluated against the no-surfactant approach of therapy (standard care alone). In Evaluation 2, as an addition to standard care for MAS, a single dose administration of surfactant was compared to the administration of pre-planned multiple doses of surfactant as an alternative approach.

3.2.2.2 Inclusion criteria

All mechanically ventilated neonates who were admitted to NICU between 1st January 2014 and 1st September 2019 and diagnosed with MAS, either received standard care only (mechanical ventilation, adequate fluids, antibiotics, and other medicines) or received standard care plus surfactant. As per guidelines (26,41), the surfactant is administered endotracheally as BS administration with an average dose of 100 mg/kg. The bovine originated surfactant type; beractant solution 25 mg/ml (trade name Survanta), is the only surfactant type used in HMC and is available at the formulary.

3.2.2.3 Exclusion criteria

- Neonates with any congenital anomalies, congenital heart disease, and birth defects
- Neonates with any non-MAS respiratory conditions.
- Non-ventilated neonates

3.2.2.4 Outcome measures

3.2.2.4.1. Primary outcome measures

- The groups were compared according to the rate of successful treatment, defined as an improvement in oxygenation and ventilation over baseline after 24 hours of treatment start, with a targeted reduction of OI to less than 10 [OI=MAP (in cmH2O) x FiO2 x 100/PaO2 (in mmHg)] (53)
- Resource utilization, including an economic decision-analytic model of surfactant use in MAS in the NICU setting

3.2.2.4.2 Secondary outcome measures

- Duration of respiratory support
- Length of NICU stay
- Mortality (within the first 28 days of age)

3.2.2.4.3 Definition of surfactant success rate

Oxygen index (OI) is one of the most reliable indicators to evaluate respiratory functions in different NICU conditions related to respiratory distress, lung injury and respiratory failure e.g. PPHN, RDS. It is calculated using the equation of OI = MAP × FIO2 × 100 / PaO2, where MAP indicates 'mean airway pressure', FIO2 indicates 'fraction of inspired oxygen' and PaO2 indicates 'partial pressure of oxygen' in arterial blood (70). OI has been used as an indicator to initiate some treatment options like iNO and to evaluate the response to surfactant therapy (68–70,72).

Although OI is a very reliable indicator, limitations associated with its use have been addressed. OI is considered an invasive measure as it requires an indwelling arterial line to measure PaO2, which is mostly not part of routine handing of cases (70).

The oxygen saturation index (OSI) is a recently introduced another measure of respiratory functions (70,72). Replacing PaO2 with oxygen saturation (SpO2) in how OI is calculated, the OSI is calculated to equal MAP × FIO2 × 100 / SpO2. The use of OSI, in assessing the severity of the disease as well as tracking the treatment progress, provides the great advantage of relying on the non-invasive pulse oximetry vital measure to measure SpO2 values instead of the invasive methods to measure the PaO2 with the OI. The non-invasive pulse oximetry is a routine measure in NICUs. OSI has been validated in pediatric and neonates intensive care unit patients as a reliable index for assessing the severity of the respiratory failure and lung injury (70,72,73).

Very recently, Muniraman et al (2019) and Rawat et al (2015) have proofed the strong linear association between OI and OSI, with a very good agreement (70,72). Further, Rawat et al (2015) tested the ability to predict OI values from OSI using the equation OI = 2 × OSI. For various mean OI values, the corresponding mean OSI values showed good sensitivity and specificity and a high negative predictive value. In addition,

Muniraman et al (2019) concluded that the regression equation (OI = OSI x 1.783 +0.0745) showed a strong linear association of OSI and OI.

In the Qatari NICU, and as discussed above, it is not feasible to measure the PaO2 and, hence, the OI based on routinely collected retrospective medical records data, which is why, as also discussed earlier, no observational studies in the literature have included a primary outcome measure of a surfactant such as the OI measure. In the current study, we use the innovative approach of determining the success rate of surfactant therapy via utilizing the available OSI values to calculate the OI values in neonates. As indicated above (section 3.2.3.1), the rate of surfactant success is based on the vital measures as reported after 24 hours of the start of treatment.

3.2.2.5 Ethics approval

Required ethics approvals were granted through Medical Research Center (MRC) of HMC; MRC-01-17-047 (Appendix 3) and MRC-01-19-427 (Appendix 4). Informed consent is not required in this study.

3.2.2.6 Data Collection

Cerner electronic medical records system was used to identify the subjects that can be included in our study. We included subjects admitted to HMC during the period of 2014-2019. The Cerner system was not implemented before that time. For inclusion and exclusion of patients, the needed number of medical records was ordered from the information technology department of HMC, to be based on the descending order of the HMC healthcare number (HC number), which is an identification number for each subject in HMC. Whenever a patient was excluded, a replacement patient was ordered based on the sequential HC number order.

The HC number, which is a unique number identifying each subject, was used to gaining the required data. Access to Cerner was achieved through the special credentials

provided by the information technology department at HMC. The provided list of medical records only included de-identified patient information, based on the safe harbor method, whereby all records were kept anonymous by assigning a unique code to each subject's HC number. Extracted data from medical records included clinical improvement, oxygenation, respiratory functions, medications, and NICU stay, in addition to resource utilization data. All patients have been followed and related data have been collected from admission till NICU discharge. The data collection form can be seen in Appendix 5.

3.2.2.7 Sample size

The population sample size used for clinical data extraction was calculated utilizing ClinCalc.com, which is a tool used for evidence-based clinical decision support (74).

3.2.2.7.1 Evaluation 1: CEA of surfactant versus non-surfactant regimens of therapy

In the RCT performed by Bo Sun et al (2005) to evaluate the safety and efficacy of exogenous surfactant replacement therapy for severe MAS, subjects were randomly assigned either to the surfactant group or control group. This RCT enrolled neonates from 19 NICUs across China and directly compared surfactant versus standard care therapy with regard to different aspects of respiratory functions, duration of MV, complications and survival rates in both groups. Important, is that this is the only relevant literature study to, just like our study, include in the assessment of the respiratory function the OI clinical cutoff value of 10 as a main indicator for the determination of treatment success/failure (the primary endpoint) and for the need for repeated dosing via a second, third or fourth dose. The measures were repeated over time; 1 hour, 3 hours, 6 hours, 24 hours, 2 days and up to 14 days, giving a comprehensive picture of oxygenation improvement with the test treatment. In this RCT, the incidence of treatment success in the surfactant group was 74% after 24 hours

of administration, while it was 50% in the control group (53). Based on this anticipated difference in success rate, and reported results with 0.05 alpha and 80% power, 63 neonates were deemed needed to be included in each of the surfactant and non-surfactant groups (total= 126).

3.2.2.7.2 Evaluation 2: CEA of single versus multiple dosing regimens of the surfactant therapy.

To the best of our knowledge, there are no studies in literature that evaluated the multiple doses regimen of surfactant in any way. Based on the expert opinion of specialists at the NICU of HMC, the multiple doses regimen of surfactant was anticipated to enhance the success rate in MAS by 25% relative to the single-dose surfactant administration. This calculated a population sample size of 62 subjects in each study group (total = 124), to generate results with 0.05 alpha and 80% power.

3.2.2.8 Statistical analysis

Patient baseline demographics were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Categorical baseline variable data were analyzed using Chi-square and Fisher's exact tests to test for the similarity between any of the two study groups in the two evaluations. The p-value of the Chi-square test was used if no more than 20% of cells had expected counts of less than five. However, if more than 20% of the expected counts were less than five, the p-value of Fisher's exact test was used. All data were calculated using an alpha of 0.05. Numerical and percentage measures were used to describe the categorical variables. As for the continuous data, the normality test was done, and the Student's t-test was used if data were found to be normally distributed. If variable data were not normally distributed, the Mann-Whitney test was performed. A multivariate regression analysis of baseline patient characteristics and relevant outcomes will be performed if differences between

the study groups were measured in relation to the baseline characteristics.

3.2.3 Running base case decision analysis in model

To account for inherent uncertainties in retrospective clinical input data, the base case of the model was based on a multivariate sensitivity analysis of the input clinical data based on the retrospective data collected from the medical records, and that in relation to outcome probabilities with determined uncertainty of ±10%, and in relation to the NICU and MV durations with an assigned uncertainty of ±20%, using Monte Carlo simulation with 10,000 iterations and a triangular type of random input distribution from uncertainty. Monte Carlo is a systematic technique that allows multiple model runs, to enables a simulated cohort of patients, where, in each re-run of the model, the baseline value of the uncertain model input is randomly replaced by a new value of the input that is selected from within a pre-defined uncertainty range. The Monte Carlo simulation was conducted via @Risk-7.5® (Palisade Corporation, NY, US).

3.2.4 Model perspective

A hospital perspective was adopted in the economic modeling. Only the costs of direct medical resources for managing MAS in mechanically ventilated neonates were assessed. Medical costs related to other underlying diseases (e.g. cost of medications to treat other medical disorders) and indirect hospital costs (e.g. staff salary) were not included. Intangible costs were also excluded from this study due to the retrospective nature of the observational cohort research. The direct medical resources of interest included:

- Surfactant medications
- MV and oxygen therapy
- Diagnostics, laboratory, and monitoring tests
- Length of NICU stay

3.2.5 Model cost inputs and calculations

Costs were calculated in the Qatari Riyal (QAR) for the year 2019/2020, with no cost discounting performed given the short timeframe of the analysis. The cost of surfactant therapy was the cost associated with exogenous surfactant doses used until success or failure. The overall cost of each therapy outcome pathway included both, the primary costs of initial treatment and their secondary costs as associated with patient management, including that of failure. Medication costs involved in this study were based on drug wholesale prices, as paid by HMC. All resource costs included in the analysis were derived from the Accounting and Finance Department at HMC.

The trade-off between the comparative cost and effectiveness outcomes of study interventions in this model was presented via the ICER (and ICUR). When dominance (higher effect and lower cost) is reported in favor of an intervention over another, the relative cost savings were reported. The willingness-to-pay threshold (i.e. cost-effectiveness threshold), against which the ICER is interpreted for whether an intervention is considered cost effective, is not formally available in Qatar. There is no officially approved cost-effectiveness ratio based on which interventions in the Qatari practice is deemed cost-effective. The WHO's suggestion of using 1-3 times the GDP per capita as the value of the threshold in a country is arbitrary and not based on any methodological justification (75). In this thesis, an estimated value of QAR 550,00 per outcome was used as a threshold. This is adapted from the threshold value of USD 150,000 per QALY, an increasingly accepted higher threshold value in the USA (76), which is also within the range suggested by WHO for Qatar.

3.2.6 Sensitivity analysis

One-way and multivariate uncertainty analyses were performed to indicate the robustness of the evaluation conclusion against potential variations in the model inputs.

All uncertainty analyses were run via the Monte Carlo technique with an iteration and a type of sampling distribution as was described previously in section 3.2.7.

3.2.6.1 One-way sensitivity analyses:

Variations in the surfactant cost, NICU stay cost, ventilation duration and the NICU stay duration as collected retrospectively from the medical records were investigated for their effect on the study outcomes. Uncertainty of ±50% was used with surfactant and NICU stay costs. Also, a one-way sensitivity analysis was to exclude the laboratory and diagnostic tests from the relevant patient management resources considerations.

3.2.6.2 Multivariate sensitivity analyses:

Uncertainty of ±5% was used with all model costs by means of Monte Carlo simulation, including the cost of NICU stay, laboratory tests, diagnostics, iNO cost, and surfactant acquisition cost.

CHAPTER 4: RESULTS

4.1 Phase 1: Surfactant therapy for MAS in neonates: A systematic overview of SRs

(This section of the thesis has been extracted from the following publication:
Abdelaal M, Abushanab D, Al-Badriyeh D. *Surfactant therapy in Meconium Aspiration Syndrome in neonates: A systematic overview of systematic reviews*. Journal of Comparative Effectiveness Research 2020. Accepted)

Our literature search yielded 1797 studies from all databases. After the removal of duplicates (n=591), we screened the titles and abstracts and removed the irrelevant articles (Figure 11). The relevant articles were subjected to full-text screening and, finally, we identified three SRs (77–79) and two RCTs (58,65).

The main characteristics of the included SRs are presented in Table 5 and the recent RCTs are presented in Table 6. All three SRs included randomized trials that used accepted methods of randomization. However, the SR conducted by Choi et al also included eight non-randomized studies (NRSs) (78). Studies in one SR (78) used surfactant lung lavage (SLL) and were not blinded, whereas three of the studies that were included in the Cochrane SR (77), which used bolus surfactant (BS), were blinded, except one RCT (53). Three of the RCTs in the third SR (79), by Natarajan et al, were on antibiotic use in MAS (80–82). The remaining studies in this SR, which studied the surfactant use, used both SLL and BS.

The identified SRs included 13 unique RCTs (1106 patients), and the eight NRSs (60,61,83–88) (178 patients). All these studies reported hospital admission outcomes.

Of the 10 RCTs on surfactant for MAS, four used SLL and the remaining studies tested

BS (36,53–55,58,59,65,89–91). Among the four RCTs that tested SLL, one tested a synthetic surfactant (Surfaxin), while the other studied bovine surfactant for lavage. In contrast, all BS studies evaluated only natural or animal surfactants that were made from either bovine or porcine.

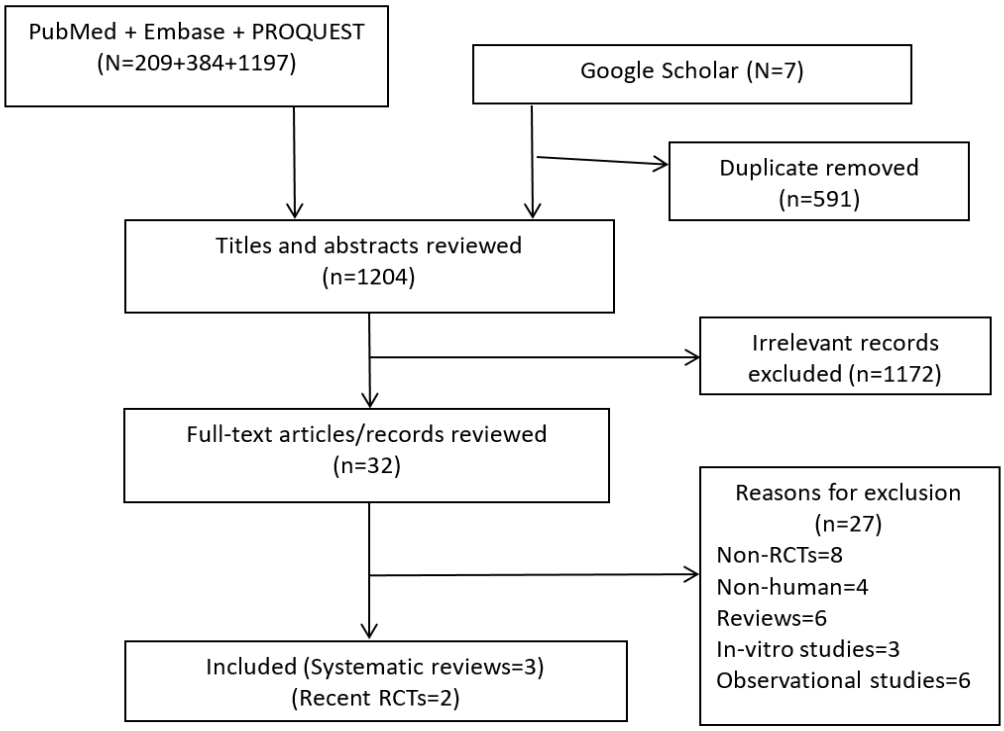

Figure 11. Flow diagram of literature search results

4.1.2 Summary of outcomes of included SRs

The SR conducted in 2012 by Choi et al (78) included both RCTs and NRSs studies that assessed the effects of SLL therapy for MAS. This review included studies that were clinically heterogeneous in terms of the severity of the disease, method of surfactant administration, initial intervention time, and combined treatment modalities. A meta-analysis of two RCTs indicated that the SLL significantly decreased death or the need for ECMO (risk ratio [RR] 0.34, 95% confidence interval [CI] 0.11 - 0.99)

with no heterogeneity, however, no statistically significant difference was found for the pneumothorax outcome (RR 0.39, 95% CI 0.08 - 1.95).

This review also included eight NRSs, and the meta-analysis of studies with available data indicated that SLL had a significant effect on air leaks (RR 0.52, 95% CI 0.28 to 0.96; 6 studies), pneumothorax (RR 0.45, 95% CI 0.23 to 0.89; 5 studies), and death or the need for ECMO (RR 0.35, 95% CI 0.13 to 0.94; 6 studies). These results are inconsistent with those from RCTs. However, the allocation methods in these studies with concurrent control may prone to selection bias.

A Cochrane review (77) was conducted to determine the efficacy of surfactant administration in the treatment of late preterm and term infants with MAS in RCTs. The meta-analysis of four trials (326 infants) showed no statistically significant effect on mortality (RR 0.98, 95% CI 0.41 to 2.39; typical risk difference [RD] -0.00, 95% CI -0.05 to 0.05) with no heterogeneity. There were no statistically significant reductions in the secondary outcomes of the duration of assisted ventilation, supplemental oxygen, pneumothorax, air leaks, chronic lung disease, and need for oxygen at discharge, but not for the hospital stay (median duration -8 days, 95% CI -14 to -3) and need for ECMO (RR 0.64, 95% CI 0.46 to 0.91; typical RD -0.17, 95% CI -0.30 to -0.04; 2 RCTs).

A recent SR conducted by Natarajan et al (79) studied surfactant therapy and antibiotics in neonates with MAS. Of the 11 RCTs, eight studies assessed the effects of the surfactant use and the other three were on the use of antibiotics. Both SLL and BS methods did not reduce the risk of mortality (RR 0.38, 95% CI 0.09 to 1.57, 2 studies; and RR 0.80, 95% CI 0.39 to 1.66, 5 studies, respectively), however, both methods decreased the hospital stay duration (mean difference −2.0, 95% CI −3.66 to −0.34, 1 study; and RR −4.68, 95% CI −7.11 to −2.24 days, 4 studies), and mechanical

ventilation duration (mean difference −1.31, 95% CI −1.91 to −0.72, 2 studies; and mean difference -5.4, 95% CI −9.76 to −1.03 days, 5 studies). There was no significant reduction with the use of antibiotics for MAS in the risk of mortality (RR 1.72, 95% CI 0.22 to 13.31, 3 studies), sepsis (RR 1.31, 95% CI 0.34 to 5.07, 3 studies), and duration of hospital stay and duration of oxygen therapy.

Among the studies included in these SRs, only the Chinese Study Group 2005 (92) and Lotze et al (1998) (55) studied the incidence of complications, which indicated no significant difference between the studied groups. The complications monitored were technical, neurologic, pulmonary, hemorrhagic, cardiac complications and proven sepsis.

4.1.3 Review of recent RCTs

An RCT (65) conducted in Turkey compared the use of SLL against BS in newborns with MAS diagnosed according to the criteria of: evidence of meconium passage at or before delivery, presence of respiratory distress after <2 h birth, chest radiography typically suggesting aspiration of meconium. Patients in SLL group (n=17) received 30 ml/kg of diluted porcine surfactant and BS group (n=16) received porcine surfactant (100 mg/kg) in repetitive dose endotracheally. SLL did not show any advantage over BS therapy on the duration of respiratory support, HFOV or iNO requirement. A total of three deaths occurred (2 in SLL group and 1 in BS group). The quality score of this RCT based on the CASP checklist was 9/11.

Another RCT (58) conducted in India included term infants with MAS who had moderate to severe respiratory distress (Downes score >4) and were randomized to SLL with bovine surfactant (Survanta®), diluted using normal saline to a phospholipid concentration of 20 ml/kg (n=31), or to no lung lavage (NLL) (n=29). The median duration of respiratory support was 34 hour in SLL group and 44 hour in NLL group.

The duration of oxygen therapy post-respiratory support decreased by 78% in SLL as compared with NLL group. There was no significant difference between both groups for the duration of hospital stay and oxygen therapy, death, ECMO, the incidence of clinical sepsis, pneumothorax, persistent pulmonary hypertension, discharge, and death. The quality score of this RCT based on the CASP checklist was 9/11.

4.1.4 Methodological quality of SRs

The three SRs were found to be of high, low and critically low quality (Table 6). Of the seven critical items, only item 10 was satisfied by all three SRs, and protocol registration before the commencement of SR and the reporting of a list of excluded studies with justification were not satisfied by two SRs. The majority of the SRs satisfied the remaining non-critical domains, which were; items 1, 3, 6, 8 and 16 (n=3), items 5, 12 and 15 (n=2), and none of the SR satisfied the item 10 (funding for the included studies).

4.1.4 ROBIS

SRs were found to be of high (79), unclear (78) and low (77) risk of bias on the assessment of ROBIS. The sequence of domains that contributed to high risk of bias in the Natarajan et al SR were: domain 3 and domain 4. For unclear risk of bias in the Choi et al SR, the contributing domain was number 2. The major SQs that were contributing to the rating of the high risk of bias were in domain 3 (3.4 and 3.5) and domain 4 (4.5 and 4.6). The major SQs that were contributing to rating the unclear risk of bias were in domain 2 (2.3, 2.5) (Figure 12).

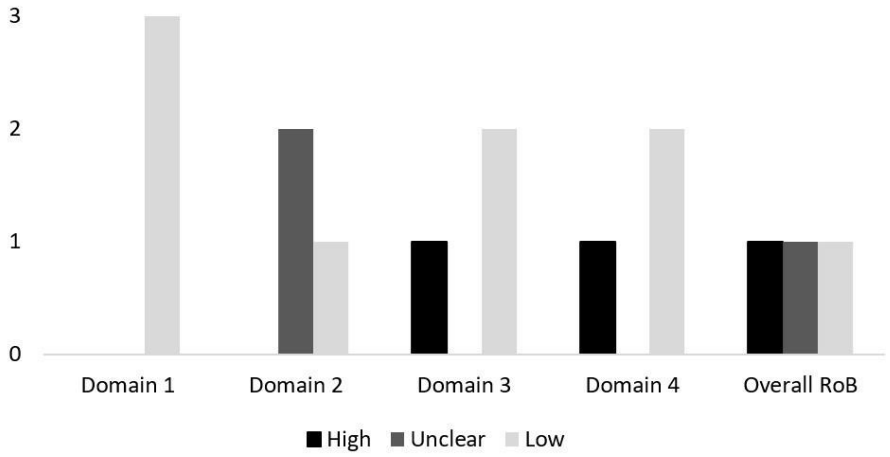

Figure 12. ROBIS risk of bias (RoB) assessment in included SRs

Table 5. Summary of included SRs

SR	Population	Interventions	Comparators	Outcomes	Follow-up	Conclusions	AMSTAR-2	ROBIS
El Shahed et al (77) (2014) 4 RCTs	Late preterm and term infants diagnosed with MAS	Surfactant therapy (BS) four doses of 100-150 mg (6ml)/kg beractant (Survanta®) and porcine lung-derived surfactant (Curosurf®) at 200 mg/kg, with repeated doses of 200, 100 and 100 mg/kg	Air placebo, control group and standard care	Mortality (RR 0.98, 95% CI 0.41 to 2.39), treatment with extracorporeal membrane oxygenation (RR 0.64, 95% CI 0.46 to 0.91), pneumothorax, Hospital stay (MD -8 days, 95% CI -14 to -3 days)	4-28 days	Surfactants instillation may reduce the severity of respiratory illness and decrease the number of infants with progressive respiratory failure requiring support with ECMO	High quality	Low risk of bias
Choi et al (78) (2012) 2 RCTs 8 NRSs	Infants diagnosed with MAS	Lung lavage with diluted surfactant (Lucinactant) 2.5–10 mg/ml, Beractant 5/10/5.3 mg/ml)	Non-surfactant control	Mortality (RR 0.44, 95% CI 0.13 to 1.50), need for ECMO (RR 0.27, 95% CI 0.04 to 2.08), pneumothorax ((RR 0.39, 95% CI 0.08 to 1.95)	1-28 days	Lung lavage with diluted surfactant found to improve the clinical outcomes	Low quality	Unclear risk of bias
Natarajan et al (79) (2016) 11 RCTs	Term neonates diagnosed with MAS	SLL (Survanta, 15 ml/kg aliquots and 150 mg/kg), Surfaxin (2.5 and10 mg/ml), Bovine surfactant (70 mg/kg), Porcine surfactant (120/mg/kg), Curosurf (100-200 mg/kg)	No lavage, supportive care, air placebo	In-hospital Mortality (SLL; RR 0.38, 95% CI 0.09 to 1.57 vs BS; 0.80, 95% CI 0.39 to 1.66), Duration of hospital stay (MD − 4.68, 95% CI −7.11 to − 2.24), Duration of oxygen Therapy (SLL; MD 0.03, 95% CI −1.36 to 1.42 vs BS; MD− 4.06, 95% CI -10.8 to 2.7)	1-7 days	Surfactant instillation in both routes reduced mechanical ventilation duration and hospital stay duration. In addition, BS reduces the need for ECMO.	Critically low	High risk of bias

Table 6. Summary of included RCTs

RCT	Year	Population	Intervention	Comparator	Outcomes	Duration	Conclusion
Bandiya et al (58)	2019	Infants diagnosed with MAS who had moderate to severe respiratory distress (Downes score >4)	SLL (Bovine surfactant [Survantant®] diluted in normal saline to a phospholipid concentration of 5 mg/ml)	No lung lavage	Duration of respiratory support and tolerability	1-2 days	Lung lavage is well tolerated but there was no change in overall duration of respiratory support.
Arayici et al (65)	2019	Newborns diagnosed with MAS	SLL 30 ml/kg of diluted porcine surfactant	Porcine surfactant (100 mg/kg) as bolus	Duration of respiratory support (mechanical ventilation and nasal continuous positive airway pressure Mortality	3-3.5 days	No significant difference found between both therapies for duration of respiratory support. However, incidence of pneumothorax and surfactant re-administration decreased non-significantly in lavage group.

4.2 Phase 2: Pharmacoeconomics evaluations of surfactant use for MAS in NICUs in Qatar

4.2.1 Evaluation 1. CEA of surfactant versus non-surfactant regimens of therapy

4.2.1.1 Demographic characteristics of the study participants

Out of a total 126 neonates included in the study, 63 received surfactant plus standard care and 63 received standard care only. All baseline demographic characteristics were not significantly different (P >0.05) between both groups (Table 7).

Table 7. Evaluation 1 - main baseline patient characteristics

Characteristics	Surfactant group (n=63)	Standard care group (n=63)	P value
Gender			
- Male	29	28	0.525
- Female	34	35	
Delivery type			
- Normal	25	33	0.374
- Cesarean	38	30	
Apgar score at 5 min*	9 (3-10)	7 (0-10)	
Birth weight (gm)¶	3298 ± 464	3221 ±498	0.516
Received iNO	20	15	0.588
Received HFOV	23	17	0.097

iNO = Inhaled nitric oxide, HFOV = High frequency oscillatory ventilation, *reported as median (upper limit – lower limit), ¶ reported as mean ± SD

4.2.1.2 Clinical outcomes

The number of neonates who achieved treatment success as defined in Chapter 3 was significantly higher in the standard care (74.6%) group compared to the surfactant group (50.7%), with a mean difference of 23.9% in favor of standard care, odds ratio (OR) = 2.84. In addition, the non-mortality-based treatment failure rate was lower in the standard care group in comparison to the surfactant group [19.1% versus 46.1%, odds ratio (OR) = 2.77].

Longer durations of MV and NICU stay were reported in the surfactant group compared to the standard care group; 407 hours and 17 days, versus 208 hours and 6 days

respectively. The mortality rate was higher in the standard care group compared to the surfactant group [4 cases (6.4%) versus 2 cases (3.2%)].

Main clinical outcomes of surfactant versus standard care are presented in Table 8 and 9.

Table 8. Evaluation 1 - main clinical outcomes

Outcome	Surfactant group (n=63)	Standard care group (n=63)	P value
Treatment success	50.7% (n=32)	74.6% (n=47)	0.029
Treatment failure - continue on standard care	46.1% (n=29)	19.1% (n=12)	
Treatment failure - mortality	3.2% (n=2)	6.4% (n=4)	
Total NICU stay	407 hours (17 day)	208 hours (9 days)	0.002
Total respiratory support duration	273 hours (11 days)	140 hours (6 days)	0.002

Table 9. Evaluation 1 - summary of clinical outcomes per pathway

Outcome	Average number of surfactant doses	NICU stay (days)	Respiratory duration (days)
Surfactant group (n=63)			
Treatment success	1.3	12	7.5
Treatment failure - standard care	2	22	16
Treatment failure - mortality	3	1	1
Standard care group (n=63)			
Treatment success	0	10	5
Treatment failure - standard care	0	13	8
Treatment failure - mortality	0	2.5	2.5

4.2.1.3 Cost-effectiveness outcome

As discussed in Section 3.2.7.3, the base case of the decision-analytic economic model

was based on a multivariate sensitivity analysis. The economic model input and their uncertainty ranges are summarized in Table 10.

Table 10. Evaluation 1 – input and uncertainty ranges used in the base-case multivariate sensitivity analysis of the model

Model input	Uncertainty range	
	Surfactant (lower end, outcome mean, upper end)	Standard care (lower end, outcome mean, upper end)
Probability of treatment success	0.456,0.507,0.558	0.671,0.746,0.821
Probability of treatment failure	0.444,0.493,0.542	0.229,0.254,0.279
Probability of mortality	0.059,0.065,0.072	0.225,0.25,0.275
Duration of NICU stay with treatment success (days)	9.6,12,14.4	8,10,12
Duration of NICU stay with treatment failure – continue on standard care (days)	17.6,22,26.4	10.4,13,15.6
Duration of NICU stay with treatment failure – Mortality (days)	0.8,1,1.2	2,2.5,3
Duration of ventilation with treatment success (days)	6,7.5,9	4,5,6
Duration of ventilation with treatment failure – continue on standard care (days)	12.8,16,19.2	6.4,8,9.6
Duration of ventilation with treatment failure – Mortality (days)	0.8,1,1.2	2,2.5,3

The unit costs of model resources that were utilized in the patients' management are listed in Table 11.

Table 11. The unit cost of model resources

Item / Name of test	Unit	Cost (QAR)
SURVANTA (surfactant)	4 ml vial (25mg/ml)	764.75
MV	1 machine per patient	429.59

NICU stay	Cost of stay per day	5,862.37
iNO	Cost of cylinder	575
Hematological tests		
CBC	Cost of 1 test during NICU	40
Chemistry tests		
Urea	Cost of 1 test during NICU	50
Creatinine	Cost of 1 test during NICU	50
Sodium	Cost of 1 test during NICU	50
Potassium	Cost of 1 test during NICU	50
Chloride	Cost of 1 test during NICU	50
Bicarbonate	Cost of 1 test during NICU	50
Magnesium	Cost of 1 test during NICU	50
Calcium	Cost of 1 test during NICU	50
Bilirubin	Cost of 1 test during NICU	50
Protein	Cost of 1 test during NICU	50
Albumin	Cost of 1 test during NICU	50
Alkaline Phosphatase	Cost of 1 test during NICU	50
ALT	Cost of 1 test during NICU	50
AST	Cost of 1 test during NICU	50
Glucose	Cost of 1 test during NICU	50
CRP	Cost of 1 test during NICU	60
Microbiology tests		
Blood culture	Cost of 1 test during NICU	70
MRSA screening	Cost of 1 test during NICU	280
Respiratory secretion culture	Cost of 1 test during NICU	370
Urine culture	Cost of 1 test during NICU	390

CSF culture	Cost of 1 test during NICU	810
Blood Gases tests		
PH	Cost of 1 test during NICU	
PO2	Cost of 1 test during NICU	
PCO2	Cost of 1 test during NICU	100
HCO3	Cost of 1 test during NICU	
BE Base excess (Ecf)	Cost of 1 test during NICU	
Diagnostic tests		
X-ray	Cost of 1 test during NICU	60
CT-scan	Cost of 1 test during NICU	460
Ultrasound scan	Cost of 1 test during NICU	210
MRI	Cost of 1 test during NICU	900
Echocardiogram	Cost of 1 test during NICU	380

MV: Mechanical ventilation, iNO: Inhaled Nitric Oxide, CBC: Complete blood count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein

With a higher success rate and lower overall cost with standard care over the surfactant therapy, a negative ICER value was calculated, indicating the dominance of the standard care approach of therapy over the use of surfactant. Main clinical outcomes and mean model probabilities and costs of therapies are summarized in Table 12. The breakdown of cost components for MAS management in each group is presented in Figure 13, with the NICU stay being the most costly and the ventilation and iNO costs being the least (< QAR 1,000)

Table 12. Mean model probabilities and costs of surfactant therapy and standard care

Therapeutic outcome	Surfactant group (n=63)			Standard care group (n=63)		
	Probability	Cost per patient (QAR)	Proportional cost (QAR)	Probability	Cost per patient (QAR)	Proportional cost (QAR)
Treatment success	0.507	86,921	44,069	0.746	67,033	50,007
Treatment failure - continue on standard care	0.461	155,575	71,713	0.191	83,939	15,990
Treatment failure - mortality	0.032	11,766	377	0.064	23,315	1,480
Total mean cost per patient			115,976 (95% CI, 113,948 – 118,004)			67,322 (95% CI, 66,319.95 – 68,324.05)
Incremental cost						48,653
Incremental effectiveness						-0.239
ICER*						-ve value
Mean cost saving*						48,653 (95% CI, 46,388 – 50,918)

* All table data are based on the base case model's multivariate sensitivity analysis

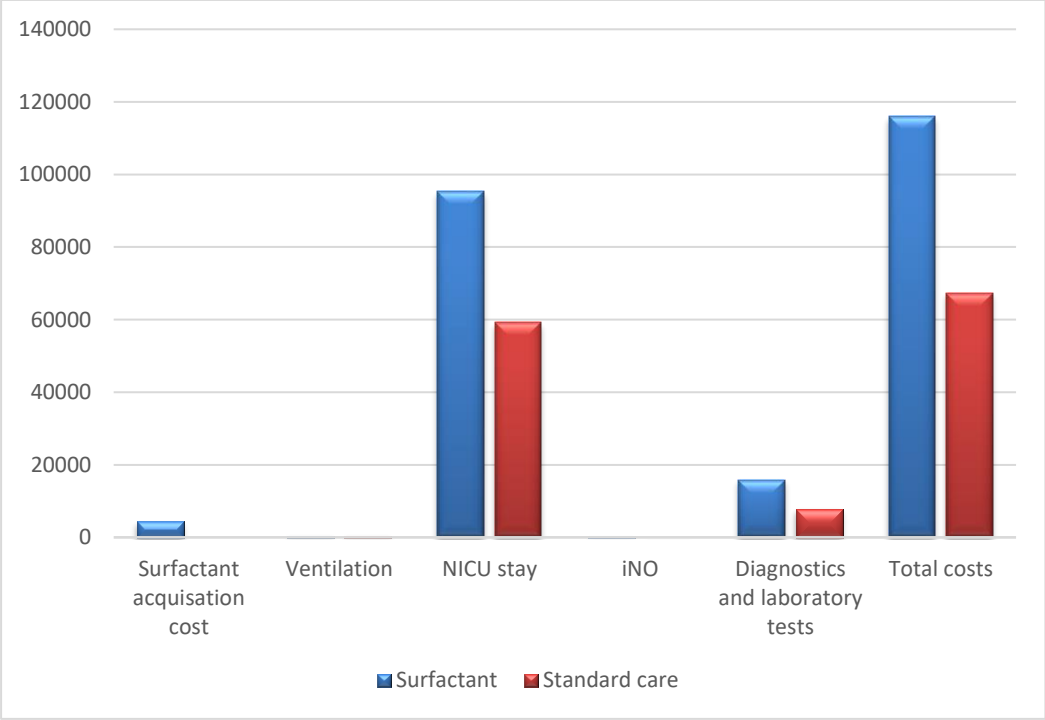

Figure 13. Breakdown of cost components in each group

Based on the multivariate sensitivity analysis at its base case, the dominance of standard care over the surfactant approach of care was maintained in 100% of cases.

Based on the multivariate sensitivity analysis at its base case, the mean effect difference in treatment success was 0.238 (95% CI, 0.226 - 0.249) in favor of standard care over surfactant. The probability curve of relative success is illustrated in Figure 14. In addition, the treatment failure rate, which is not mortality driven, was lower in the standard care group in comparison to the surfactant group, 0.270 (95% CI, 0.269 - 0.271).

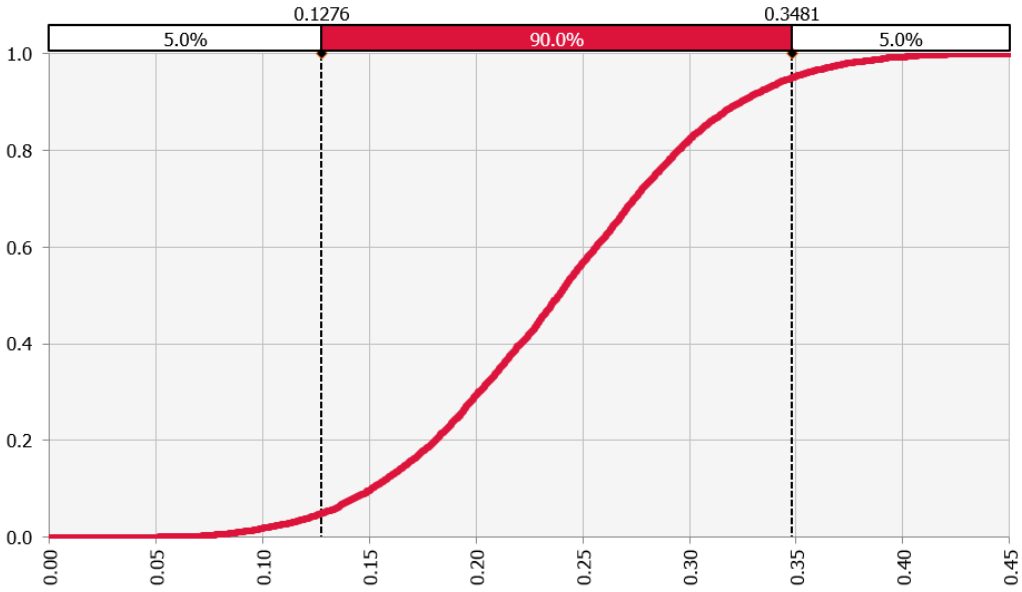

Figure 14. Probability curve of relative success with standard care over surfactant

Based on the multivariate sensitivity analysis at its base case, cost saving in favor of the standard care was QAR 48,653 (95% CI, 46,388, 50,918). Cost saving probability curve is in Figure 15.

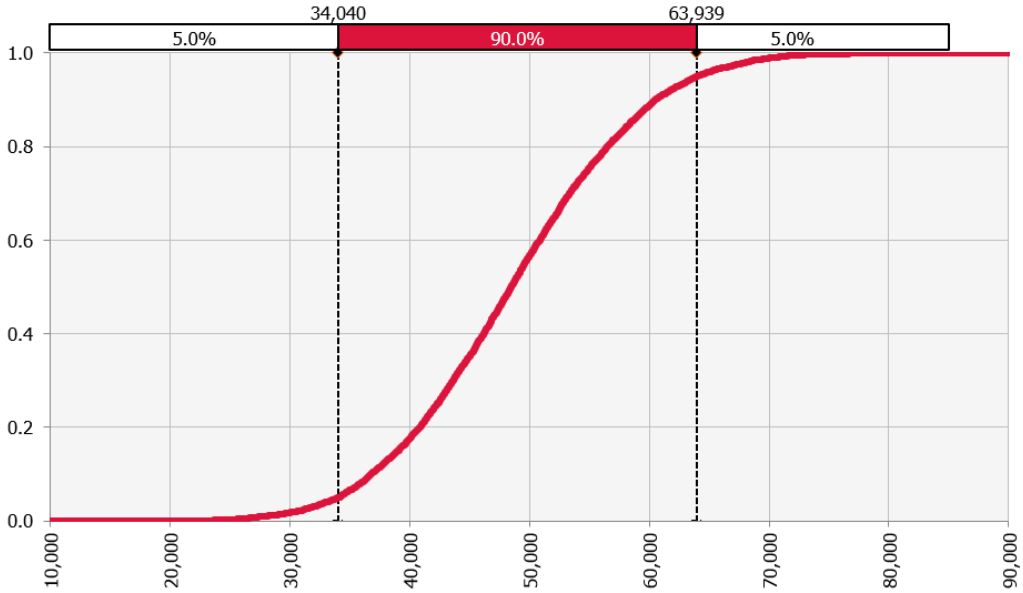

Figure 15. Probability curve of cost savings (QAR) with standard care over surfactant

Based on the multivariate sensitivity analysis at its base case, a tornado analysis of the model inputs as per their impact on the study outcome demonstrated that the most influential inputs are success rate, rate of non-mortality failure, followed by failure rate due to mortality. A tornado analysis that ranks model inputs as per their impact on outcome is presented in Figure 16.

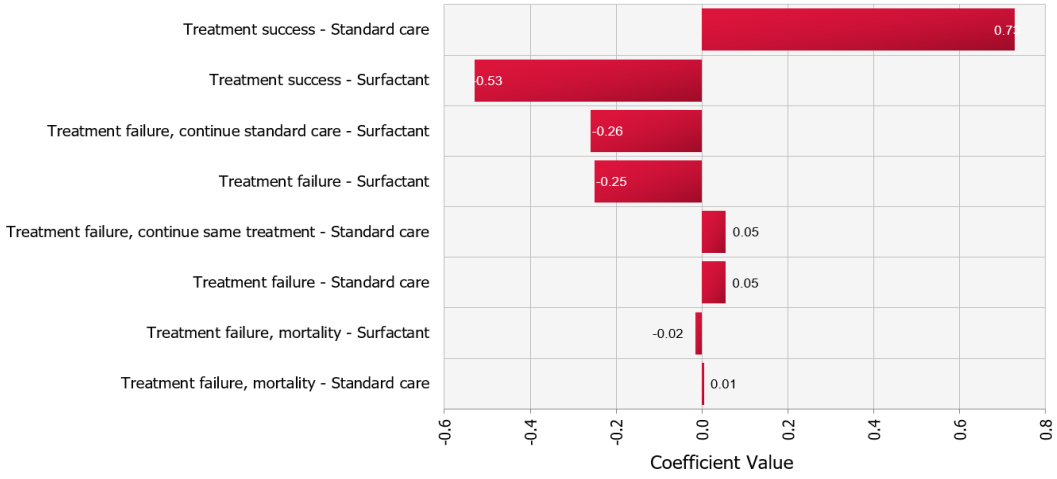

Figure 16. Tornado diagram of Spearman ranking of model input correlation coefficients as per impact on study results

4.2.1.4 Sensitivity analysis

4.2.1.4.1 One-way sensitivity analyses

Key variables and the ranges over which they were varied are presented in Table 13. Importantly, the superiority of any of the interventions was not sensitive to any uncertainty that was associated with the surfactant acquisition NICU stay costs and the exclusion of diagnostic and laboratory tests from consideration.. Therefore, no further analysis to determine threshold input values at which study conclusion changes was conducted.

Table 13. Surfactant and NICU costs and their uncertainty ranges in one-way sensitivity analyses

Model input	Uncertainty range	
	Surfactant (lower end, outcome mean, upper end)	Standard care (lower end, outcome mean, upper end)
Surfactant cost (QAR)	382.38,764.75,1147.13	0,0,0
NICU stay cost (QAR)	2931.1,5862.37,8793.5	2931.1,5862.37,8793.5

4.2.1.4.2 Multivariate sensitivity analyses.

Key variables and the ranges over which they were varied are presented in Table 14. Notably, the study outcomes remained robust against the uncertainty that was associated with all model costs.

Table 14. Key variables and their uncertainty ranges in the multivariate sensitivity analysis

Item / Name of test	Cost (QAR)	Uncertainty range (lower end, outcome mean, upper end)
SURVANTA (surfactant)	764.75	762.5,764.75,802.9
MV	429.59	408.1,429.59,451.1
NICU stay	5862.36	5569.2,5862.36,6155.47
iNO	575	546.25,575,603.75

Hematological tests		
CBC	40	38,40,42
Chemistry tests		
Urea	50	47.5,50,52.5
Creatinine	50	47.5,50,52.5
Sodium	50	47.5,50,52.5
Potassium	50	47.5,50,52.5
Chloride	50	47.5,50,52.5
Bicarbonate	50	47.5,50,52.5
Magnesium	50	47.5,50,52.5
Calcium	50	47.5,50,52.5
Bilirubin	50	47.5,50,52.5
Protein	50	47.5,50,52.5
Albumin	50	47.5,50,52.5
Alkaline Phosphatase	50	47.5,50,52.5
ALT	50	47.5,50,52.5
AST	50	47.5,50,52.5
Glucose	50	47.5,50,52.5
CRP	60	57,60,63
Microbiology tests		
Blood culture	70	66.5,70,73.5
MRSA screening	280	266,280,294
Respiratory secretion culture	370	351.5,370,388.5
Urine culture	390	370.5,390,409.5
CSF culture	810	769.5,810,850.5

Blood Gases tests	100	95,100,105
Diagnostic tests		
X-ray	60	57,60,63
CT-scan	460	437,460,483
Ultrasound scan	210	199.5,210,220.5
MRI	900	855,900,945
Echocardiogram	380	361,380,399

MV: Mechanical ventilation, iNO: Inhaled Nitric Oxide, CBC: Complete blood count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein

4.2.2 Evaluation 2: CEA of single versus multiple dosing regimens of the surfactant therapy

4.2.2.1 Demographic characteristics of the study participants

Out of 126 neonates that should be included in the study according to sample size calculation as discussed in section 3.2.4.2, data of 63 subjects only were found in the involved medical institutions, out of which 21 neonates received multiple surfactant doses and 42 received single dose only. All baseline demographic characteristics were not significantly different (P >0.05) between both groups (Table 15).

Table 15. Evaluation 2 - main baseline patient characteristics

Characteristics	Multiple doses group (n=21)	Single dose group (n=42)	P value
Gender			
- Male	10	19	0.625
- Female	11	23	
Delivery type			
- Normal	10	15	0.594
- Cesarean	11	27	
Apgar score at 5 min*	8 (4-9)	8 (3-10)	
Birth weight (gm)¶	3203 ± 353	3345 ±510	0.155
Received iNO	6	14	0.461
Received HFOV	7	16	0.629

iNO = Inhaled nitric oxide, HFOV = High frequency oscillatory ventilation, *reported as median (upper limit – lower limit), ¶ reported as mean ± SD

4.2.2.2 Clinical outcomes

The number of neonates who achieved treatment success as defined in Chapter 3 was non-significantly higher in the single-dose group (57.1%) group compared to the multiple-doses group (52.4%), with a mean difference of 4.7% in favor of single-dose regimen, odd ratio (OR) = 1.2. In addition, the treatment failure rate was lower in the single-dose group in comparison to the multiple-doses group [42.9% versus 47.6%, odd ratio (OR) = 0.83].

The duration of NICU stay in both groups did not change significantly; 16 days in the multiple-doses group versus 17 days in the single-dose group. The same was noticed with MV as it reached 11 days in the multiple-doses group versus 10 days in the single-dose group. The mortality rate was 4.8% (n=2) in the single dose group, where there was no reported mortality in the multiple-doses group.

Main clinical outcomes of single versus multiple doses regimens of surfactant therapy are presented in Table 16 and 17.

Table 16. Evaluation 2 - main clinical outcomes

Outcome	Multiple doses group (n=21)	Single dose group (n=42)	P value
Treatment success	52.4% (n=11)	57.1% (n=24)	0.839
Treatment failure - continue on standard care	47.6% (n=10)	38.1% (n=16)	
Treatment failure - mortality	(n=0)	4.8% (n=2)	
Total NICU stay	397 hours (16 days)	412 hours (17 days)	0.681
Total respiratory support duration	270 hours (11 days)	243 hours (10 days)	0.36

Table 17. Evaluation 2 - summary of clinical outcomes per pathway

Outcome	Average number of surfactant doses	NICU stay (days)	Respiratory duration (days)
Multiple doses group (n=21, 15 patients administered 2 doses – 6 patients administered 3 doses)			
Treatment success	2.25	11	7
Treatment failure - standard care	2.28	23	23
Treatment failure - mortality	0	0	0
Single dose group (n=42)			
Treatment success	1	12	8
Treatment failure - standard care	1	23	13.5
Treatment failure - mortality	1	1	1

4.2.2.3 Cost-effectiveness outcome

As discussed in Section 3.2.7.3, the base case of the decision-analytic economic model was based on a multivariate sensitivity analysis. The economic model input and their uncertainty ranges are summarized in Table 18. The unit costs of model resources that were utilized in the patients' management were already listed in Table 10.

Table 18. Evaluation 2 – input and uncertainty ranges used in the base-case multivariate analysis of the model

Model input	Uncertainty distribution	
	Multiple doses (lower end, outcome mean, upper end)	Single dose (lower end, outcome mean, upper end)
Probability of treatment success	0.472,0.524,0.5764	0.514,0.571,0.628
Probability of treatment failure	0.428,0.476,0.524	0.386,0.429,0.472
Probability of mortality	0,0,0.1	0.099,0.111,0.122
Duration of NICU stay with treatment success (days)	8.8,11,13.2	9.6,12,14.4
Duration of NICU stay with treatment failure – continue on standard care (days)	18.4,23,27.6	18.4,23,27.6

Duration of NICU stay with treatment failure – Mortality (days)	0,0,0.2	0.8,1,1.2
Duration of ventilation with treatment success (days)	5.6,7,8.4	6.4,8,9.6
Duration of ventilation with treatment failure – continue on standard care (days)	18.4,23,27.6	0.8,13.5,16.2
Duration of ventilation with treatment failure – Mortality (days)	0,0,0.2	0.8,1,1.2

With a higher success rate and lower overall cost with single over multiple dosing surfactant therapy, a negative ICER value was calculated, indicating the dominance of the single-dose approach of therapy over the multiple-doses regimen. Main clinical outcomes and mean model probabilities and costs of therapies are summarized in Table 19. The breakdown of cost components for MAS management in each group is presented in Figure 17.

Table 19. Mean model probabilities and costs of single and multiple doses regimen of surfactant therapy therapy and standard care

Therapeutic outcome	Multiple doses group (n=21)			Single dose group (n=42)		
	Probability	Cost per patient (QAR)	Proportional cost (QAR)	Probability	Cost per patient (QAR)	Proportional cost (QAR)
Treatment success	0.524	85,508	44,806	0.571	83,901	47,907
Treatment failure - continue on standard care	0.476	166,943	79,465	0.381	156,246	59,589
Treatment failure - mortality	0.0	0	0	0.048	13,686	651
Total mean cost per patient			120,735 (95% CI, 117,689 – 123,782)			108,152 (95% CI, 105,991 – 110,313)
Incremental cost						12582
Incremental effectiveness						-0.047
ICER*						-ve value
Mean cost saving*						12,582 (95% CI, 9,508 – 15,656)

* All table data are based on the base case model's multivariate sensitivity analysis

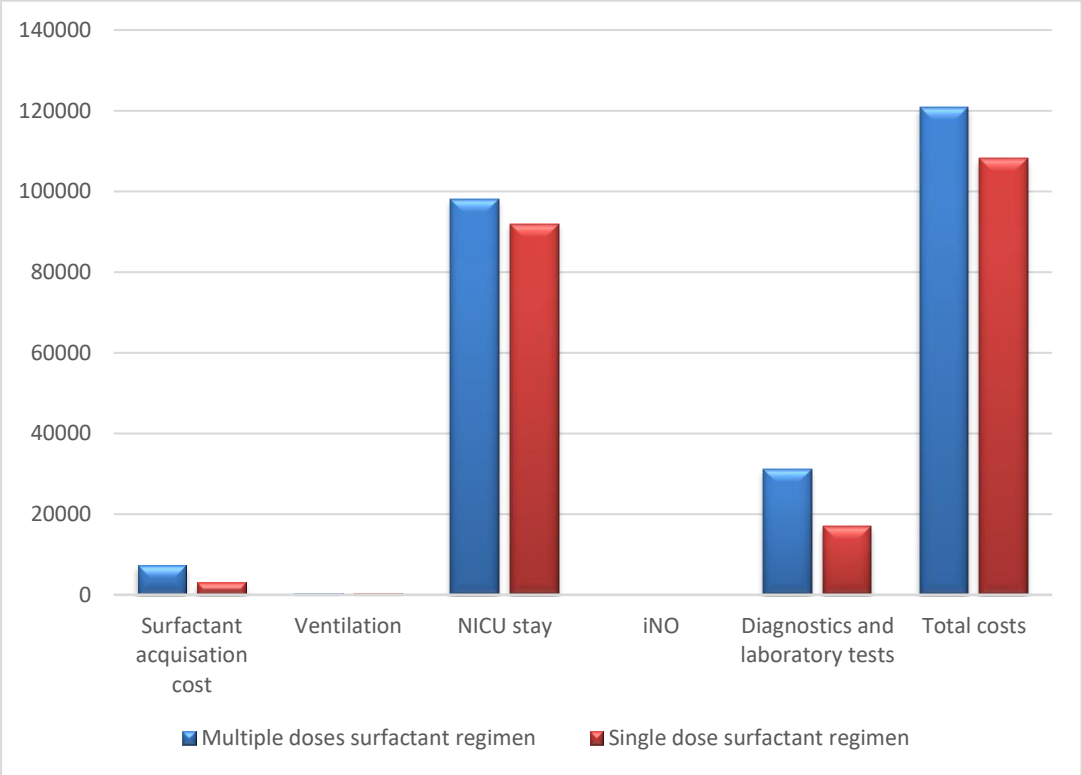

Figure 17. Breakdown of cost components in each group

Compared to multiple dosing, the single dosing was dominant in 66% of cases, and cost effective in 19% of cases. In the remaining 15% of patient cases, the multiple dosing approach was cost effective.

Based on the multivariate sensitivity analysis at its base case, the mean effect difference in treatment success was 0.047 (95% CI, 0.029 - 0.064) in favor of single over multiple doses regimen of surfactant therapy. The probability curve of relative success is illustrated in Figure 18. In addition, the treatment failure rate, which is not mortality driven, was lower in the single dose compared to the multiple doses regimen, 0.073 (95% CI, 0.056 - 0.089).

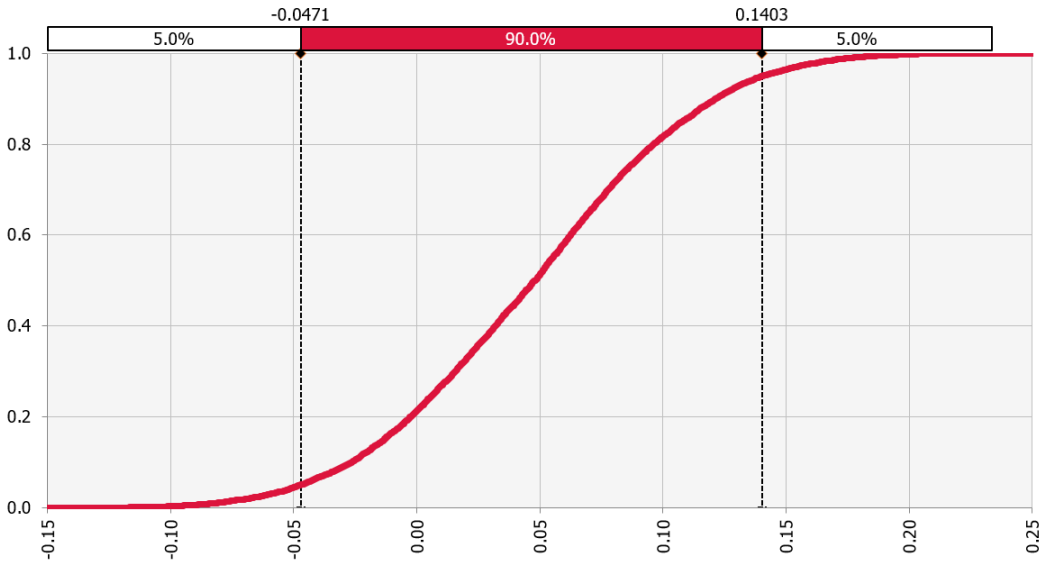

Figure 18. Probability curve of relative success with single over multiple doses surfactant

Based on the multivariate sensitivity analysis at its base case, cost saving in favor of the single-dose therapy was QAR 12,582 (95% CI, 9,508 – 15,656). Cost saving probability curve is in Figure 19.

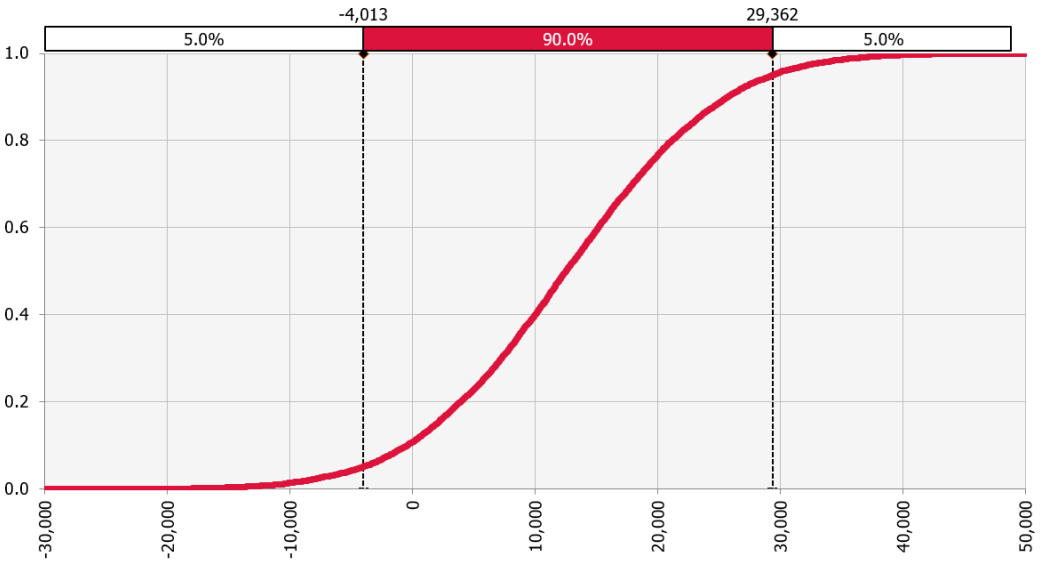

Figure 19. Probability curve of cost savings (QAR) with single over multiple dosing surfactant therapy

Based on the multivariate sensitivity analysis at its base case, a tornado analysis of the

model inputs as per their impact on the study outcome demonstrated that the most influential inputs are treatment overall failure, treatment failure with the continuation of standard care, rate of treatment success, followed by failure rate due to mortality. A tornado analysis that ranks model inputs as per their impact on outcome is presented in Figure 20.

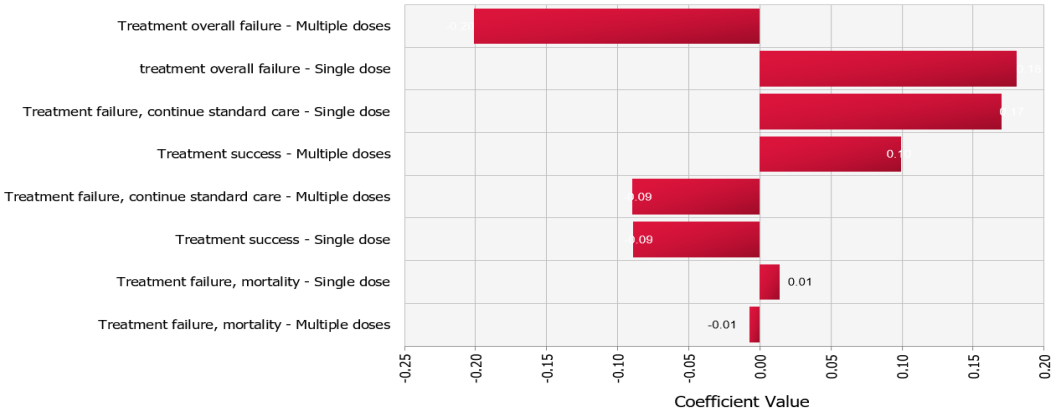

Figure 20. Tornado diagram of Spearman ranking of model input correlation coefficients as per impact on study results

4.2.2.4 Sensitivity analysis

4.2.2.4.1 One-way sensitivity analyses

The model showed no sensitivity against the changes in the surfactant acquisition and NICU stay costs, and the exclusion of the diagnostic and laboratory resource consideration from patient management consideration.

Key variables, the ranges over which they were varied, and their one-way sensitivity analysis outcomes are presented in Table 20.

Table 20. Key variables and their uncertainty ranges in one-way sensitivity analyses

Model input	Uncertainty range: Multiple doses (lower end, outcome mean, upper end)	Uncertainty range: Single dose (lower end, outcome mean, upper end)	Base case outcome distribution	Sensitivity analysis outcome distribution
Surfact cost (QAR)	382.38,764.75, 1147.13	0, 382.38,764.75, 1147.13	SD Dominance – 66% SD Cost effective – 19% MD Cost effective – 15%	SD Dominance – 68% SD Cost effective – 19% MD Cost effective – 13%
NICU stay cost (QAR)	2931.1,5862.37, 8793.5	2931.1,5862.37, 8793.5	SD Dominance – 66% SD Cost effective – 19% MD Cost effective – 15%	SD Dominance – 66% SD Cost effective – 20% MD Cost effective – 14%
Diagnostic and laboratory resource consideration	Excluded		SD Dominance – 66% SD Cost effective – 19% MD Cost effective – 15%	SD Dominance – 64% SD Cost effective – 14% MD Cost effective – 12%

SD = Single dose, MD = Multiple doses

4.2.2.4.2 Multivariate sensitivity analyses

Key variables and the ranges over which they were varied were already presented in Table 13. Notably, the study outcomes remained robust against the uncertainty that was associated with all model costs. The single doing approach was 68% dominant and 19% cost effective against the multiple dosing approach. The latter was cost effective in 13% of patient cases.

CHAPTER 5: DISCUSSION

5.1 Phase 1: Surfactant therapy for MAS in neonates: A systematic overview of SRs

In this overview of systematic reviews, we examined three SRs and two RCTs that were published recently and not included in any SR. All these included SLL and BS methods using natural and synthetic products for MAS treatment.

To add to the comprehensive reporting of the top sources of evidence in the literature that assessed surfactant therapy (bolus and lavage) in MAS, we went beyond the published SRs and included recently published RCTs that are not included in any SRs. Each meta-analysis outcomes in systematic reviews were summarized separately, including in a structured table, which can help readers realize or review interesting outcomes easily.

There is a clear inconsistency in the reported outcomes of SRs, which disable a straightforward interpretation of the usefulness of surfactants for MAS. A meta-analysis of RCTs of SLL in the low-quality SR, by Choi et al (78), concluded surfactant effectiveness against death and ECMO use, but not against the pneumothorax as a result of MAS. In the same SR, a meta-analysis of NRSs concluded effectiveness against all the aforementioned, including the pneumothorax and air leaks outcome. This, however, was all contradicted by a high-quality Cochran meta-analysis (77) on the use of BS, which while suggested decreased progressive respiratory failure requiring ECMO, it concluded no effect against death, pneumothorax, air leaks, and MV duration. With the critically low-quality meta-analysis that looked at both SLL and BS together (79), an effectiveness was not concluded against death, but only against the durations of MV and the hospital stay.

Adding to the inconclusively of surfactant effectiveness, and based on the results of Choi et al and El Shahed et al meta-analyses, one might want to come to the conclusion that SLL are found to be more effective than the BS. This, however, is negated by the two high-quality and most recent RCTs that conclude no difference between SLL and BS in effectiveness (58,65).

An important safety concern is that the installation of a large volume of fluid into a newborn's lung might be a burden, especially in cases of severe MAS, which leads to mortality (93). The El Shahed et al Cochrane review assessed the efficacy of BS and indicated no improvement in morbidity or mortality (77). Nevertheless, while two RCTs (94,95) assessed a surfactant made off porcine administered in small lavage quantity to eight infants and showed improvements in oxygenation, those effects were improved with a large volume of diluted porcine surfactant in a recently published RCT (65).

In vivo studies indicated that there was more release of proinflammatory cytokines occurred in male fetuses when stimulated with lipopolysaccharide stimulation compared to female fetuses (96,97). A recent study (n=95), conducted in Japan, found that male neonates were at a higher risk of developing MAS than female neonates. However, further studies are needed to confirm the role of sex on MAS development (98).

The quality assessment of SRs indicated that none of the SR reported funding source and the two other non-Cochrane reviews did not have prior protocol and did not provide excluded studies list. Hence, based on AMSTAR-2 assessment, the quality of included SRs were rated as high (77), low (78) and critically low quality (79). In addition to that, we have found a similar pattern in risk of bias assessment results based on the ROBIS tool. Among three reviews, only the Cochrane review was found to be of low risk of

bias.

The overview has some limitations. The restriction to English language might have excluded some studies published in other languages. The authors in the current study however do not have the resources to translate the non-English research literature that may generate from a non-restricted search. Furthermore, searching additional index terms to those in the study or additional combinations of them is always possible and may generate additional studies. In addition, the fact that a primary article could have been included in more than an SR may contribute to double counting of data within reported meta-analyses. Not exploration of such overlaps took place in this study.

5.2 Phase 2. Pharmacoeconomics evaluations of surfactant use for MAS in NICUs in Qatar

While the HMC, as the main healthcare provider, is regulated by the Ministry of Public Health in Qatar, the drug formulary selection at the hospitals within HMC is determined by pharmacy and therapeutics (P&T) committees within the corporation. HMC P&T committees traditionally judged medications based on safety and efficacy aspects. In recent years, and due to increased economic burden, they, as well as decision makers in general, have also been increasingly looking at the economic considerations of medications. Indeed, while unrestricted hospital formularies are helpful, they are not economically efficient, including in a rich country like Qatar.

To the best of our knowledge, this study is the first to evaluate the pharmacoeconomics of surfactant use for MAS in NICUs settings worldwide. All patients were followed up until NICU discharge. The study followed all the different patient pathways in the Qatari practice of managing the critically ill neonates who are on MV due to MAS, either they administered standard care only or surfactant beside the standard care. The

study consists of two evaluations, where one is a CEA of surfactant versus non-surfactant regimens of therapy, and second is a CEA of single versus multiple dosing regimens of the surfactant therapy.

The standard care was found superior to surfactant replacement therapy, with higher clinical effectiveness and cost savings of QAR 48,653. Standard care shows significantly higher treatment success rates over surfactant therapy; 75% versus 51% respectively.

In this thesis, the evaluation of multiple surfactant dosing versus single-dose surfactant administration is considered a pilot, seeing that the required sample size was not achieved. Higher treatment success rate, however, was observed in single dose surfactant therapy over multiple doses regimen; 57% versus 52% respectively, with cost savings over QAR 12,000. This corresponds to the dominance of the single dosing over multiple doses of administration. The single dosing approach was between dominant and cost-effective in over 85% of simulated patient cases.

The patient baseline demographic characteristics did not differ between comparators in each of the evaluations. This included all variables that may affect the overall conclusion of the study as suggested in reported in the literature and determined by the clinical experts in HMC. In the NICU setting, standard care is potentially administered prior to taking the decision of surfactant administration by clinicians. This raises the concern that it may affect the treatment clinical outcomes of the surfactant group in a positive way. Nevertheless, adjusting for this, taking into consideration the results of the study and how matched study groups are in both evaluations, including receiving iNO and HFOV, will only add to the advantage of the standard care treatment over surfactant therapy.

For the purpose of the main clinical endpoint in this study, the use of OSI is innovative

and utilized to predict the OI values reflecting the status of the respiratory function of the patients in the Qatari NICU. OI is recommended to be used in clinical practice to determine the severity of different respiratory conditions and to dictate management such as initiation of iNO, need for ECMO or surfactant (72). Although OI is a better indicator to reflect the respiratory functions with different clinical cutoff values, no observational studies used it. OI was reported in RCTs only, and even the most recent RCTs did not tend to use it due to its limitation of being invasive as discussed in Section 3.2.2.4.3. This innovative approach offers the great advantage of utilizing non-invasive, easy and commonly used tools in the clinical practice in a very reliable way that better reflects disease severity and prognosis. However, some limitations have been reported using OSI (70,72) that should be discussed in the context of this study's objectives. First, the SpO2 readings obtained from pulse oximetry may vary based on the pulse oximetry positioning, patient movement, quality of the device itself, and unclean probes. This is unlikely to be an issue in this study as the data indicated were collected from neonates who were admitted to large, highly qualified NICUs within the Joint Commission International (JCI) accredited medical institution of HMC, with well experienced and well-trained staff. Secondly, the non-linear relation between SpO2 and PaO2 at higher values of SpO2 above 95% (72), as illustrated by the sigmoid shape of oxygen-hemoglobin dissociation curve, renders the approach questionable and raises concerns in relation to validity, especially that most of SpO2 values that were included in the study were from 85% to 100%. The study by Rawat et al (2015) (72) included data analysis of measurements from two prospective RCTs databases (total of 225 patients) and proved, by means of repeated-measures analyses via linear mixed-effects models, that OSI can be used in a patient with up to 98% oxygen saturation. This was confirmed in the larger study done by Muniraman et al recently in 2019 which

investigated the correlation between OSI and OI at a wide range of SpO2 values; <85%, 85% - 95% and > 95%. In this study, the Pearson correlation coefficient values were found to be from 0.7 to 0.9 ($p < 0.001$) for all SpO2 values, indicating a strong linear correlation between OSI and OI. Moreover, the accuracy of the derived OI values from OSI at different discriminative clinical cutoff OI points of 5, 10, 15, 20 and 25 were tested and found to be good in terms of specificity, sensitivity, and positive and negative predictive values (70). It is less likely, therefore, for high values of SpO2 to be considered as a concern that hinders the validity of the study approach.

Several studies in literature looked at, just like the current one, comparing the BS to standard care. In the RCT done by Findlay et al (1996) to compare the efficacy of the use of Survanta surfactant and a placebo air ventilation in the management of term infants, forty neonates with MAS were enrolled and equally assigned to the surfactant or air placebo groups (54). The outcomes were different with the two groups as the rate of development of complications in the study group was lower than that in the control group. Furthermore, the patients on Survanta had a shorter stay in the hospital than those on the air placebo. In light of this, the use of exogenous surfactant in the management of MAS proved to be more advantageous than the conventional air placebo.

In their RCT, Gadzinowski et al found out that bolus surfactant could be used alone or as a component in the combination of various modalities in the management of term and preterm neonates with MAS (63).

This was further reiterated in the cohort study performed by Dong-Mei Chen et al who recommended the use of bolus surfactant together with the conventional therapies for MAS to improve the prognosis (56). Dong-Mei Chen et al endeavored to find out the difference between the efficiency of HFOV and BS. They enrolled forty-eight neonates

into their study and divided them into two groups. In the first lot, they investigated the use of HFOV only. In the second group, the authors added the use of BS into the regimen. The paper highlights that the use of combined therapy in the second group shortened hospital stay and reduced the rate of progression to complicated states. Regrettably, this study does not show the results in which the BS was used alone. As such, it is improper to conclude that the use of BS alone is better than the use of HFOV in the management of MAS.

Similar results were highlighted in another cohort study performed by HUANG et al (2016) in which 48 severe MAS children complicated by pulmonary hemorrhage were enrolled in HFOV or BS with HFOV therapies. The authors concluded that the combination of surfactant and HFOV can better enhance respiratory function and shorten the ventilation duration.

The only literature study, however, that evaluated the BS against standard care and used OI as the indicator of respiratory functions was an RCT study by Bo Sun et al. This study reported improved oxygenation and higher treatment success in favor of BS over the control group across 19 Chinese NICUs (53). Although the positive results in oxygenation parameters, no difference was observed in the mean duration of MV, the incidence of major complications and the number of survivors between the two groups. The results of this are different from ours, therefore. Here, in contrast to our study and the majority of studies, where early initiation of treatment is implemented, the initiation of surfactant treatment by Bo Sun et al was late, up to 36 hours after birth. This potentially reduces how success standard care is and reduces generalizability. The authors concluded that further larger and systematic studies of surfactant treatment for MAS, including comparisons between single and multiple dosing of surfactant should be performed in order to develop more precise recommendations in neonates with

MAS.

As reported earlier in our study, neonates who received standard care experienced greater success compared to those on surfactant therapy. Surfactant did not show advantages in terms of achieving better oxygenation and, instead, has shown lower treatment success rates, extended NICU stay and longer MV. As for the comparison between multiple and single dosing regimens, the single dose regimen showed slightly higher treatment success rates with a non-significant difference between both groups in relation to NICU stay and MV duration.

Even if we assume no confirmed differential success outcomes between the single and multiple dosing approaches, the cost analysis on its own has demonstrated that the single dosing approach has certainly been associated with considerable overall cost savings over the multiple dosing approach in the NICU at HMC, including the consideration of the cost of therapies and their consequence. This is an important outcome as, unlike clinical research, economic evaluations are not concerned in terms of hypothesis testing but they are primarily about making cost estimations. Even if an economic evaluation is underpowered, therefore, it still provides important information that may guide decision making (99).

Looking at the factors that contributed the most to the overall result of how surfactant compared to standard care, treatment success, non-mortality treatment failure was the most influential, followed by treatment failure due to mortality. This is anticipated given that success, with relatively high cost per patient, was generally associated with the highest input probability in the model. Treatment failure had a higher cost, but considerably lower contributing probability. Mortality was associated with lower probability and lower cost per patient. When looking at how single dosing compared to multiple dosing, it is treatment failure that generally contributed the most to results,

followed by success, and then mortality. This is explained by that treatment failure had a slightly lesser contributing model probability than success, but at a considerably higher cost per patient.

An important clinical endpoint included in our study was the evaluation of related mortality associated with the study treatments. While mortality rate was higher with standard care over surfactant, and with single dosing than with multiple dosing approaches, it generally had minimal contributing probability to the model results. This means that one cannot argue that it is because of the higher mortality rate with the standard care that this has cost savings over the surfactant use. Compensating for the difference in cost reduction due to high mortality rate with the standard care does not come near to overtaking the difference in the overall cost between the strategies. In any case, it is important to note that mortality in this study, like in the relevant literature studies, is an all-cause mortality that may not, in particular, relate to the use of surfactant versus standard care. This is supported by the fact that, as was concluded by the majority of meta-analyses in the literature (77–79), including the high-quality studies (77), surfactant use has no significant influence on death rate in neonates.

The sensitivity analyses demonstrated the robustness of the cost-effectiveness outcome of both evaluation to all variables. Patients were followed until NICU discharge and the micro-costing approach of unitized resources in patient management was used. The analytic-decision model adopted in this evaluation follows up the important consequences, as consistent with literature studies; Arayici et al (65), Findlay et al (54), Gadzinowski et al (63) and Bo Sun et al (53), until NICU discharge.

Well established methodology and data integrity make RCTS the most reliable source of clinical data for pharmacoeconomics evaluations (100). The controlled nature of RCTs, however, affects its external validity and limits its generalizability to different

settings. This, added to increased cost, time, and effort, gives the observation cohort study design an advantage for the purpose of the pharmacoeconomics evaluations in the current research. To answer current practice questions about the usefulness of surfactant use in HMC, the current cohort study-based economic evaluations provide evidence that is based on actual real-life practices at the setting. Evidence that is based on how therapies have actually performed so far.

Our study is the first that evaluates the surfactant use from the Qatari perspective and, hence, relying on local data that reflects realistic costs of MAS neonates.

Within the context of performing a cohort study, the allocation bias in this study was eliminated via the systematic patient selection, descendingly based on successive hospital admission numbers. This is added to that the inclusion and exclusion of patients were based on a pre-ordered de-identified patients list and not based on direct access to patient histories on the Cerner database. Moreover, because of the sensitive nature of the population, no targeted clinical data were missing in records that could have jeopardized the quality of results.

The effect size used in the sample size calculation for Evaluation 2 was based on an estimation by expert opinion and not on prior results. While this is a valid approach to use in sample size calculations (101–103), it is acknowledged to be a limitation in this study. Another limitation is the lack of assessing long-term disease related neurological outcomes in neonates. Also, no regression analysis was performed in the study to investigate the relationship between variables. However, this was deemed to be unnecessary in the study given the fact that there was no statistical difference between study groups at any of the baseline characteristics. In addition, clinical outcomes that are reported in the literature, such as the need for ECMO and complications as pneumothorax and PPHN, were not reported. However, ECMO, as technique, is not

available in HMC NICUs and, hence, including it in our study was simply not applicable as it is not a management option to include in the model. As for disease complications, and given the retrospective nature of the study and that the extent of data entry for these events was inconsistent among personnel, it was not feasible that for the data to be collected with accuracy. To emphasize, however, this is only about the clinical reporting of the events, and is of no influence on overall management cost of the therapies. This is because the standard practice of handling pneumothorax and PPHN in the HMC NICU is to continue the neonate on standard care, oxygenation and supportive therapy, including ventilation. The current study model already accounts for this fully until NICU discharge.

The results of this study are in contrast to the general HMC practices of surfactant administration. Surfactant administration for MAS in neonates that is not evidence based is not only an issue in Qatar, but it is so in most of the international clinical NICU practices as well, where limited consensus on the best use of surfactant is common, including the dosing regimens (36,53).

With the limited number of available high-quality cost-effectiveness studies of NICU surfactant therapy, the importance of results in the current study extends beyond the local setting of the current study. This is particularly valid given the study's use of an ideal outcome measure, the use of internationally recommended dose regimens, the MAS as a specific indication of interest, and the sensitivity analyses conducted. Providing evidence-based recommendations to decision makers, particularly the HMC stakeholders, enables the opportunity to better allocate the available resources in terms of NICU expenditure. The novel approach of calculating the most reliable OI indicator based commonly used parameters in medical records allows practitioners to better interpret respiratory parameters and, hence, more accurately follow disease severity.

CHAPTER 6: CONCLUSION

Overall, our systematic overview of SRs and recent RCTs considered all the available literature to summarize and critically appraise the evidence using the available tools. While limited evidence of effectiveness against death, ECMO, pneumothorax, air leaks, and MV duration was reported in the literature, this was provided via critically low quality, with a high risk of bias reviews. Higher quality SRs, with low risk of bias, concluded a lack of surfactant effectiveness against primary outcome measures. A similar lack of clarity trend is observed when one tries to draw an overall conclusion about how different surfactant modalities compare. Higher quality studies are needed to determine the effectiveness of BS administration and/or SLL to treat MAS effectively and safely.

From the perspective of practices in HMC, the current research is the first high quality-based cohort CEA in the literature to evaluate the economic and clinical outcomes of surfactant versus standard care, including different surfactant regimens, in mechanically ventilated neonates due to MAS. With a statistically significant lower overall success and higher cost, standard care was dominant and cost effective over surfactant therapy. The single dosing approach of surfactant administration was similarly dominant over the multiple dosing regimen of surfactant. While this cannot be concluded with robustness due to sample size limitation, the comparative cost analysis of the two regimens demonstrated considerable cost savings in favor of the single dosing approach.

Based on the study perspective and its limitations, the results support the recent trend by some HMC practitioners of favoring standard care over surfactant in the NICU practices of HMC.

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APPENDIX 1. PRISMA Checklist

PRISMA-DTA Checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	

PRISMA-DTA Checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	

Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

For more information, visit: www.prisma-statement.org.

APPENDIX 2. Literature search databases in Phase 1 of the thesis

Embase Classic + Embase

Search Strategy:

#	Searches	Results
1	exp meconium/	5603
2	Meconium Aspiration Syndrome.mp. or exp meconium aspiration/	3171
3	Pulmonary Surfactants.mp. or exp lung surfactant/	12647
4	Surface-Active Agents.mp. or exp surfactant/	249496
5	1 or 2	8378
6	3 or 4	260608
7	5 and 6	543
8	limit 7 to (human)	384

PROQUEST

Meconium OR (Meconium Aspiration Syndrome) OR (meconium aspiration) AND (Pulmonary Surfactants) OR (lung surfactant) OR (Surface-Active Agents) with filters: Infant and Newborn filters, and peer reviewed (N=1197)

PubMed

("Meconium"[Mesh] OR "Meconium Aspiration Syndrome"[Mesh]) AND ("Pulmonary Surfactants"[Mesh] OR "Surface-Active Agents"[Mesh])

APPENDIX 3. Ethics approval (MRC-01-17-047) for Phase 2 of the thesis

12/11/2017

مؤسسة حمد الطبية
Hamad Medical Corporation

INSTITUTIONAL APPROVAL LETTER
MEDICAL RESEARCH CENTER
HMC, DOHA-QATAR

Mr. Omar Adnan Ahmad Alsoukhni **Clinical Pharmacist** Department of Pharmacy **AWH**	**Date: 11 December 2017**
Protocol No.	MRC-01-17-047
Study Title	Cost-Effectiveness Analysis Of Surfactant In The Management Of Meconium Aspiration Syndrome In The Neonatal Intensive Care Setting In Qatar
The above titled research study has been approved to be conducted in HMC summarized as below:	
Study type:	Retrospective Data Review
Total no. of medical records:	300
Data collection period:	from 01/01/2014 to 29/08/2017
Hospitals/ facilities approved:	Al Wakra Hospital (AWH),Women's Wellness and Research Center
Team member list:	Dr. Daoud Al Badriyeh, Dr. Rajesh Pattu Valappil, Mr. Mohammed Ahmed Abdelaal Mohammed
IRB approval type:	**'Exempt' under SCH guidelines "*Category 3:* Research involving the collection or study of existing: Data, documents, records and the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects"**

This research study should be conducted in full accordance with all the applicable sections of the rules and regulations of research at HMC and you should notify the Research Center immediately of any proposed changes.

The investigator/ Research team must ensure the study progress is updated in the MRC online system 'ABHATH'.

We wish you all success and await the results in due course.

Prof. Ibrahim A.Janahi
Executive Director of Research
Medical Research Center

Date:11 December 2017

1/2

APPENDIX 4. Ethics approval (MRC-01-19-427) for Phase 2 of the thesis

1/14/2020

مؤسسة حمد الطبية
Hamad Medical Corporation

APPROVAL LETTER
MEDICAL RESEARCH CENTER
HMC, DOHA-QATAR

Dr. Daoud Al-Badriyeh Associate Professor Pharmacy Hamad Medical Corporation	Date: 12th January 2020
Protocol No.	MRC-01-19-427
Study Title	Cost-Effectiveness Analysis Of Surfactant In The Management Of Meconium Aspiration Syndrome In The Neonatal Intensive Care Setting In Qatar
The above titled research study has been approved to be conducted in HMC summarized as below:	
Study type:	Data Review
Data Collection Period:	01 Jan 2014 - 04 Sept 2019
Team Member List:	Dr. Daoud Al-Badriyeh , Dr. Rajesh Pattu Valappil , Mr. Mohammed Ahmed Abdelaal Mohammed , Ms. Alya Salah Babiker Higazy
Review Type :	'Exempt' under MOPH guidelines Category 3: Research involving the collection or study of existing: Data, documents, records and the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects?.
Decision :	Approved
Hospitals/ Facilities Approved:	Al Wakra Hospital (AWH),Women's Wellness and Research Center

This study must be conducted in full compliance with all the relevant sections of the Rules and Regulations for Research at HMC and the Medical Research Center should be notified immediately of any proposed changes to the study protocol that may affect the 'exempt' status of this study. Wherever amendments to the initial protocol are deemed necessary, it is the responsibility of the Principal Investigator to ensure that appropriate reviews and renewed approvals are in place before the study will be allowed to proceed.

Please note that only official, stamped versions of the approved documentation are to be utilized at any stage in the conduct of this study. The research team must ensure that progress on the study is appropriately recorded in ABHATH, the online research system of the Medical Research Center.

1/2

APPENDIX 5. Data collection sheet in Phase 2 of the thesis

Record number: ……..

Date of collection: ……

Active problems: …….

Gender: ☐ Male ☐ Female

Gestational age (weeks): ……

Weight: …… (g)

Type of delivery: ☐ Vaginal Delivery ☐ Cesarean Section

Apgar score at 1 min, 5 min, 10 min and 15 min: …….

Date of admission to NICU: …….

Time of NICU admission: ……..

Duration of stay at NICU: ……..

Data of NICU discharge: ……..

Time of NICU discharge: …….…….

Date of discharge from hospital: ……

Total duration of hospital stay: ……

☐ Surfactant ☐ no surfactant

<u>In case of no surfactant:</u>

Treatment option: ……..

Times of receiving: ……

Route of administration: …….

Duration: …….

<u>In case of surfactant:</u>

Number of administered doses: ….

Surfactant dose: …….

Times of receiving the dose: ……

Received high dose (Yes/No): …….

Route of administration: …….

Duration of administration: …….

Date of administration: …….

Arterial Blood Gas (ABG) before and after surfactant dose

- pH ….…….
- pCO_2 ….……
- pO_2 ….……..
- SpO2 ……...
- HCO_3 ….……..
- Base D/E ….……..
- MAP …….

Methods of mechanical ventilation:

☐ Conventional ☐ HFOV

Duration of Mechanical Ventilator (hours): …….

Date of mechanical ventilation initiation: …….

Time of mechanical ventilation initiation: …….

Date of mechanical ventilation discontinuation: …….

Time of mechanical ventilation discontinuation: …….

Need for high frequency oscillatory ventilation HFOV (Yes/No): …….

Duration (hours): …….

Date of initiation: …….

Time of initiation: …….

Date of discontinuation: …….

Time of discontinuation: …….

Death (Yes/No): ….……. Date of death (if any): ….……...

Time of death (if any): …… ☐ On MV ☐ Off MV

Need for iNO (Yes/No): ……..

Dose: …… Duration: ……..

Vital signs during treatment:

1. Temperature: ……
2. Heart rate: …….
3. Respiratory rate: …….
4. Blood pressure: …….

Adverse drug reactions, times of events, and after how many surfactant doses (if any): (Intracranial hemorrhage - Pulmonary hemorrhage - Blockage of endotracheal tube by mucus secretion – Hyperoxia – Bradycardia - Oxygen desaturation- Allergic reaction Others)

Medications used to resolve drug reactions: ….……

Other medications administered in NICU: ….……

Non- pharmacological interventions while in NICU: …….

Laboratory tests while in NICU

Number of hematology tests: ….……

Number of chemistry tests: ….……

Number of blood gases tests: ….……

Number of metabolic tests: ….……

Number of microbiology tests: ….……

Number of general virology tests: ….……

Number of metabolic tests: ….……

Number of body fluid tests: ….……

Diagnostic tests while in NICU:

X-ray scan: ….…… Number of tests: ….……

CT scan: ….…… Number of tests: ….……

US: ….…… Number of tests: ….……

MRI: ….…… Number of tests: ….……

Other tests: ……. Number of tests: ….……