Incidence, treatment and outcome of critically ill patients with acute respiratory failure

Rita Linko

Academic dissertation

To be presented with the permission of the Medical Faculty of the University of Helsinki, for public examination in the auditorium of Peijas Hospital, Sairaalakatu 1, on May 5th 2012, at 10 am.

Helsinki 2012
Supervisors

Docent Ville Pettölä
Department of Anaesthesiology and Intensive Care Medicine
Helsinki University Central Hospital
Helsinki, Finland

Docent Tero Varpula
Department of Anaesthesiology and Intensive Care Medicine
Helsinki University Central Hospital
Helsinki, Finland

Reviewers

Docent Pirkko Brander
Department of Pulmonary Diseases
Hospital District of Helsinki and Uusimaa,
Hyvinkää Hospital
Hyvinkää, Finland

Docent Ari Uusaro
Department of Intensive Care
Kuopio University Hospital
Kuopio, Finland

Official opponent

Professor Jukka Räsänen
Department of Anesthesiology
Mayo Clinic, Rochester
Rochester, Minnesota, USA
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.


Permission for reprinting was obtained from the publishers of these communications.
In addition some unpublished results are presented.
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABW</td>
<td>Actual body weight</td>
</tr>
<tr>
<td>AECC</td>
<td>American-European Consensus Conference</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>ALI</td>
<td>Acute lung injury</td>
</tr>
<tr>
<td>APACHE</td>
<td>Acute Physiology and Chronic Health Evaluation</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute respiratory failure</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CAP</td>
<td>Community acquired pneumonia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>ECLS</td>
<td>Extracorporeal life support</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>ELSO</td>
<td>Extra-corporeal life support organization</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQOL-5 dimension questionnaire</td>
</tr>
<tr>
<td>FiO₂</td>
<td>Fraction of inspired oxygen</td>
</tr>
<tr>
<td>Fr</td>
<td>Frequency</td>
</tr>
<tr>
<td>Hct</td>
<td>Haematocrit</td>
</tr>
<tr>
<td>HFOV</td>
<td>High frequency oscillatory ventilation</td>
</tr>
<tr>
<td>H1N1</td>
<td>Pandemic influenza A(H1N1) virus infection</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>iNO</td>
<td>Inhaled nitric oxide</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>kPa</td>
<td>Kilopascal (1 kPa=7.5 mmHg)</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
</tbody>
</table>
MODS  Multiple organ dysfunction syndrome
MV   Mechanical ventilation
NIV  Non-invasive ventilation
NMBA Neuromuscular blocking agent
NPPV Non-invasive positive pressure ventilation
OR   Odds ratio
PaO₂ Partial pressure of arterial oxygen
PaCO₂ Partial pressure of arterial carbon dioxide
PF   Partial pressure of arterial oxygen divided by the fraction of inspired oxygen
PBW  Predicted body weight
PCR  Polymerase chain reaction
Pinsp Inspiratory airway pressure
Ppeak Peak airway pressure
PEEP Positive end-expiratory pressure
QALY Quality-adjusted life year
QOL  Quality of life
RCT  Randomized controlled trial
ROC curve Receiver operator characteristic curve
RRT  Renal replacement therapy
SAPS Simplified Acute Physiology Score
SF-36 Short Form 36-questionnaire
SMR  Standardized mortality ratio
SOFA Sequential Organ Failure Assessment
SpO₂ Pulse oximeter saturation
SPSS (PASW) Statistical Package for the Social Sciences (Predictive Analytics SoftWare)
TISS  Therapeutic Interventional Scoring System
Vt   Tidal volume
Vt/ABW Tidal volume per actual body weight
Vt/PBW Tidal volume per predicted body weight
WHO World Health Organization
ABSTRACT

BACKGROUND Acute respiratory failure (ARF) is the most common organ failure in critically ill patients.

The objective of this study was to evaluate the incidence, treatment, and outcome for patients suffering from overall acute respiratory failure, and a subset suffering from pandemic influenza A(H1N1) virus infection, in Finnish intensive care units (ICUs). The predictive value of serum zinc in organ failure and mortality was studied in ARF patients. One-year outcome was assessed. Health related quality of life (HRQOL), quality-adjusted life years (QALYs) for one-year survivors, and cost for one QALY, was estimated.

PATIENTS A total of 958 patients from 25 Finnish ICUs were included in the study of incidence, treatment, and outcome of ARF during an 8-week period. A total of 132 H1N1 patients were assessed for incidence, treatment, and short-term outcome during an outbreak between 11 October and 31 December 2009.

MAIN RESULTS The incidence of ARF, and acute respiratory distress syndrome (ARDS) in the adult population were 149.5/100,000 and 5.0/100,000 per year, respectively. The 90-day mortality of ARF was 31% (95% CI 28-34%), and one-year mortality was 35% (95% CI 32-38%). The incidence of H1N1 was 24.7 per million inhabitants. Hospital mortality of these patients was 8% (95% CI 3-12%). Rescue therapies, except prone positioning, were rarely used. Corticosteroids were used frequently and their use was not associated with mortality in H1N1 patients. The level of serum zinc decreased with increased severity of cardiovascular organ failure, but serum zinc was not associated with 30-day mortality, ventilator support time, or length of ICU stay. HRQOL at one year after ARF was lower than population values of similar age and gender. The mean estimated cost for a hospital survivor was €20,739. The mean (SD) predicted lifetime QALYs were 11.3 (13.0). The mean predicted lifetime cost-utility for all ARF patients was €1,391.

CONCLUSIONS The incidence of ARF was higher, while the incidence of ARDS was lower than reported from other countries. The short- and long-term mortality was low. Serum zinc level did not predict 30-day mortality. The mean gained QALYs were reasonable. Intensive care treatment of ARF patients was cost-effective, regardless of age, disease severity, or type of ventilator support.
1 INTRODUCTION

Treatment of patients needing mechanical ventilation (MV) for acute illness has been centred in intensive care units (ICU) since the 1950s, when the survival of acute respiratory failure (ARF) caused by poliomyelitis dramatically increased with the introduction of artificial ventilation and multidisciplinary teams (Ibsen 1954). Development of and experience in MV enabled treatment of ARF resulting in various pathophysiologic bases (Petty et al. 1967).

ARF can result from derangement of any part of the respiratory system and mechanisms responsible for controlling breathing. Thus, several diseases and risk factors can predispose and lead to ARF. Comparing epidemiologic outcome and clinical studies is difficult because ARF lacks uniform consensus definition. In critical care studies, ARF is usually related to severe oxygenation failure, acute lung injury (ALI), and its more severe form, acute respiratory distress syndrome (ARDS), however only 1.7-19% of all ICU admissions (Brun-Buisson et al. 2004; Irish Critical Care Trials Group 2008; Luhr et al. 1999; Roupie et al. 1999; Villar et al. 2011) and 7.4-23% of patients with MV (Luhr et al. 1999; Roupie et al. 1999; Villar et al. 2011) carry these more severe conditions. Nonetheless, some kind of ventilatory support therapy is needed in 33-74% of ICU patients (Carlucci et al. 2001; Demoule et al. 2006b; Esteban et al. 2002; Metnitz et al. 2009; Pettilä et al. 2002). Because the need for invasive MV in acute disease in general indicates treatment in ICU, and the volume of invasive MV may have an effect on survival (Kahn et al. 2006), the knowledge of epidemiology of ARF with a broader definition than ALI/ARDS is important for future planning of ICU bed capacity. The information may provide a basis for how to quickly organize ICU resources for unexpected increases in admissions, as was seen during the 2009 influenza A(H1N1) pandemic (Webb et al. 2009; Smetanin et al. 2009; Ugarte et al. 2010).

Ventilatory support and other respiratory rescue therapies are essential for most patients suffering from severe ARF. The influence of ventilatory support method (non-invasive vs. invasive ventilation) on outcome has been demonstrated in clinical trials (Brochard et al. 1995; Plant et al. 2000) and meta-analysis (Keenan et al. 2003; Ram et al. 2004) of exacerbation of chronic obstructive pulmonary disease (COPD), in meta-analysis of
cardiogenic pulmonary oedema (Masip et al. 2005), facilitating extubation in COPD patients (Ferrer et al. 2003; Nava et al. 1998), and in immunocompromised patients (Antonelli et al. 2000; Hilbert et al. 2001). In fact, only MV using low tidal volume (Vt) has been associated with decreased mortality in ARDS (ARDS network 2000). Low Vt strategy has been incorporated into sepsis guidelines (Dellinger et al. 2008), and recommended also for other patient groups at risk of ARDS (Schultz et al. 2007), however adherence to this treatment strategy has been poor (Weinert et al. 2003; Young et al. 2004). In Finland, the use of ventilatory methods and settings has only been studied in patients with severe sepsis (Karlsson et al. 2007).

Refractory septic shock warrants hydrocortisone treatment (Dellinger et al. 2008). Similarly, glucocorticoids are considered an established treatment in some types of ARF, such as status asthmaticus and acute exacerbation of COPD, however in severe pulmonary virus infection, the use of corticosteroids is controversial (Chen et al. 2006; Hien et al. 2009; Quispe-Laime et al. 2010; Salluh et al. 2010; Yam et al. 2007). In fact, The World Health Organization (WHO) does not recommend the use of high dose corticosteroids for H1N1 unless for another reason indicated (http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html). Only a few studies have evaluated the impact of corticosteroids on mortality in critically ill H1N1 patients (Brun-Buisson et al. 2011; Kim et al. 2011; Martin-Loeches et al. 2011).

The mortality of ARF increases with the number of coexistent organ failures (Aggarwal et al. 2007; Flaatten et al. 2003a; Vincent et al. 2002). An increasing number of organ failures in septic pediatric ICU patients coincides with lower serum zinc levels (Cvijanovich et al. 2009), and with non-survivors (Wong et al. 2007). In critically ill septic patients, enteral supplementation of zinc with other key pharmaconutrients resulted in faster improvement of organ failure compared to control patients (Beale et al. 2008). In experimental animal models, zinc deficiency was related to more severe lung injury (Gomez et al. 2006; Knoell et al. 2009). Nonetheless, the association of serum zinc with the outcome of ARF has not been previously studied.
Long-term mortality has been studied mostly in subgroups of ARF, namely in ALI/ARDS patients (Angus et al. 2001; Davidson et al. 1999b; Herridge et al. 2011), ARDS and pneumonia (Garland et al. 2004), and in patients with prolonged MV (Bigatello et al. 2007; Combes et al. 2003; Cox et al. 2007a; Douglas et al. 2002). Besides long-term survival, assessing health-related quality of life (HRQOL) of these survivors is recommended (Angus et al. 2003). MV is associated with higher ICU cost of care (Dasta et al. 2005; Tan et al. 2008), and in future the incidence and duration of MV is estimated to increase (Needham et al. 2005). Expensive treatment together with high mortality and decreased long-term health-related quality of life (Angus et al. 2001; Davidson et al. 1999a; Garland et al. 2004; Heyland et al. 2005; Orme et al. 2003; Schelling et al. 2000; Weinert et al. 1997) necessitates an analysis of the cost-effectiveness of ARF.

In these nationwide studies the aims were to study the incidence, treatment, and outcome of ARF in general, and in the specific patient population with H1N1 infection, treated in central and university hospital ICUs in Finland. In H1N1 patients the special reference was in glucocorticoid use. The association of serum zinc with organ failures and outcome was assessed in ARF patients. In addition to ICU and hospital mortality, 90-day and one-year mortality of ARF was evaluated. HRQOL and quality-adjusted life years (QALYs) were assessed for cost-utility analysis.
2 REVIEW OF THE LITERATURE

2.1 Definitions of acute respiratory failure

Acute respiratory failure (ARF) is a condition of sudden oxygenation and/or ventilation failure, which necessitates prompt treatment. The normal range for arterial partial pressure of oxygen (PaO$_2$) is 9.3-13.3 kPa (80-100 mmHg), for pulse oximeter saturation (SpO$_2$) is 94-98%, for arterial carbon dioxide (PaCO$_2$) is 4.7-6.0 kPa (35-45 mmHg), and for pH is 7.35-7.45. Ventilation failure leads to hypercapnia and acidosis. Thus, respiratory failure can be classified as hypoxaemic type I respiratory failure (PaO$_2$<8.0 kPa, 60 mmHg), or type II hypercapnic respiratory failure (PaCO$_2$>6.0 kPa, 45 mmHg), although a combination of both disorders is common (Roussos and Koutsoukou 2003).

In critical care, ARF lacks a uniform definition. The most common criteria for epidemiologic and clinical studies are diagnosis of ALI and/or ARDS (Bersten et al. 2002; Brun-Buisson et al. 2004; Irish Critical Care Trials Group 2008; Rubenfeld et al. 2005), a certain degree of oxygenation impairment (Antonelli et al. 1998; Roupie et al. 1999), the respiratory component of the Sequential Organ Failure Assessment (SOFA) score (Flaatten et al. 2003a; Pettilä et al. 2002; Vincent et al. 2002), and the use of variable durations of ventilatory support (Esteban et al. 2002; Lewandowski et al. 1995; Luhr et al. 1999). In addition to ALI/ARDS, certain other critically ill subgroups of ARF, such as pneumonia (Garland et al. 2004), have been referred to as ARF. ARF cohorts may include patients with acute deterioration of a chronic disease, such as acute exacerbation of COPD or status asthmaticus (Esteban et al. 2002; Garland et al. 2004; Wysocki et al. 1995).

ARDS is a syndrome of tachypnoe, severe impairment of oxygen transport, bilateral infiltrations in chest X-ray, and decreased compliance of the respiratory system, which was first described in 1967 (Ashbaugh et al. 1967). Since that time, the definition has been modified several times. The American-European Consensus Conference (AECC) presented the latest and currently most used definition in 1994 (Bernard et al. 1994). This definition introduced the concept of ALI, which differs of ARDS only by less severe oxygenation
impairment. In ALI PaO$_2$ divided by inspired oxygen fraction (PaO$_2$/FiO$_2$, PF) is below 300 mmHg (40.0 kPa), and in ARDS below 200 mmHg (26.7 kPa). Other required characteristics are acute onset, and bilateral pulmonary infiltrations in chest X-ray without left atrial hypertension. No requirement for the use of ventilator support, or any limit for supplemental oxygen or PEEP is a limitation of this definition (Allardet-Servent et al. 2009; Estenssoro et al. 2003; Villar et al. 2007).

The sequential, or originally sepsis-related, organ failure assessment (SOFA) scores the degree of organ dysfunction of six organ systems (Vincent et al. 1996). Each organ system is graded from 0 to 4 (Table 1). Zero reflects normal condition, 1-2 organ dysfunction, and 3-4 organ failure (Moreno et al. 1999).

Table 1. The SOFA score.

<table>
<thead>
<tr>
<th>SOFA score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$,</td>
<td>≥400</td>
<td>&lt;400</td>
<td>&lt;300 (53.3)</td>
<td>&lt;200 (40.0)</td>
<td>&lt;100 (13.3)</td>
</tr>
<tr>
<td>mmHg (kPa)</td>
<td>(53.3)</td>
<td>(53.3)</td>
<td></td>
<td>with ventilatory</td>
<td>with ventilatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>support</td>
<td>support</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytes x10$^3$/l</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, μmol/l</td>
<td>&lt;20</td>
<td>20-32</td>
<td>33-101</td>
<td>102-204</td>
<td>&gt;204</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adrenergic agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for at least one hour,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μg/kg/minute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP≥70 mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP&lt;70 mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dopamines5 or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dobutamine (any dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dopamine&gt;5 or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adrenalin&gt;0.1 or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>noradrenalin&gt;0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dopamine&gt;15 or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adrenalin&gt;0.1 or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>noradrenalin&gt;0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, μmol/l or urine output</td>
<td>&lt;110</td>
<td>110-170</td>
<td>171-299</td>
<td>300-440 or &lt;500 ml/day</td>
<td>&gt;440 or &lt;200 ml/day</td>
</tr>
</tbody>
</table>

No consensus is available to define the length of MV in the assessment of ARF, relating to the utilization of non-invasive and/or invasive MV, or short-term versus long-term MV. A combination of diagnostic code (acute respiratory distress or failure), and procedural code of MV has been used for ARF incidence estimation in the USA (Behrendt 2000). This study did not have any requirement for the length of MV, but a hospital stay of at least 24 hours was required. The limit of one hour of MV has been used previously in the outcome.
assessment of ARF (Stauffer et al. 1993). A minimum of 12 hours, including both non-invasive and invasive MV, has been used in studies evaluating indications and practices of MV (Esteban et al. 2002; Esteban et al. 2008). Intubation and MV for more than 24 hours has been used as a measure in large epidemiological studies of ARF (Lewandowski et al. 1995; Luhr et al. 1999). Definition of prolonged invasive MV has ranged from 48 hours (Im et al. 2004) to 14 days (Combes et al. 2003), and up to 21 days (at least 6 hours of MV on consecutive days) (MacIntyre et al. 2005).

2.2 Underlying conditions of acute respiratory failure

Disorders leading to oxygenation and/or ventilation failure can derive from pulmonary or extrapulmonary origins. The most frequent extrapulmonary causes of ARF and the need for ventilatory support are related to the ventilatory regulatory system, abdominal diseases, and post-operative state (Esteban et al. 2002; Luhr et al. 1999).

Cases of ARF treated in the ICU are more frequently due to pulmonary reasons, rather than extrapulmonary (Bersten et al. 2002; Luhr et al. 1999; Roupie et al. 1999), the most predominant of which is pneumonia (Esteban et al. 2002; Luhr et al. 1999; Roupie et al. 1999). In community acquired pneumonia (CAP), bacterial aetiology dominates in adults, in contrast to viral aetiology in children (Ruukskanen et al. 2011). In severe CAP, confirmation of microbial aetiology varies widely. Viral origin was detected in only 3-7% of microbiologic samples (Luna et al. 2000; Moine et al. 1994). The advancement of new diagnostic methods has increased the amount of virus infections detected (Ruukskanen et al. 2011). Rapid influenza antigen test, in particular, has increased the number of hospital admissions for influenza (Oliveira et al. 2001). The use of polymerase chain reaction (PCR) test led to virus identification in 22% of patients treated with invasive MV for more than 48 hours (Daubin et al. 2006). Rhinovirus was the most common finding (46%) followed by herpes simplex virus type 1 (22%), and influenza A (16%). Positive virus test, predominantly for influenza virus, was found in 17% of critically ill cardiorespiratory failure patients (Carrat et al. 2006).

Acute lung injury/acute respiratory distress syndrome

The underlying risk factors for ALI/ARDS may be derived from pulmonary (direct), or extrapulmonary (indirect) causes (Bernard et al. 1994). Direct cause is more common than
indirect cause (Bersten et al. 2002; Brun-Buisson et al. 2004). The most common direct risk factors are pneumonia (Bersten et al. 2002; Brun-Buisson et al. 2004; Estenssoro et al. 2002; Rubenfeld et al. 2005), and aspiration (Doyle et al. 1995), whilst sepsis of non-pulmonary origin and severe trauma are the most common indirect factors (Bersten et al. 2002; Ferring and Vincent 1997). In a multicentre study, abdominal sepsis was the most common extrapulmonary etiology of ALI/ARDS (Roupie et al. 1999). Overall, sepsis of any origin is the most common and important risk factor of ALI/ARDS (Doyle et al. 1995; Estenssoro et al. 2002; Rubenfeld et al. 2005). Nonetheless, in ARF and ALI/ARDS several underlying risk factors may be present (Ferguson et al. 2007; Luhr et al. 1999).

**Pandemic Influenza A(H1N1)**

Young people predominate among hospitalized H1N1 patients (Jain et al. 2009; Dawood et al. 2009), a high frequency of cross-reacting antibodies is suggested to protect the elderly (Ikonen et al. 2010). Up to 9% of the critically ill H1N1 patients were pregnant in a recent study (Webb et al. 2009). Underlying conditions were more common in ICU patients compared with hospitalized patients. Of the hospital patients 45-73% (Jain et al. 2009; Nguyen-Van-Tam et al. 2010; Viasus et al. 2011), versus 73-85% of the ICU patients (Dominguez-Cherit et al. 2009; Kim et al. 2011; Viasus et al. 2011), had at least one co-morbid condition or risk factor.

Of the ICU patients, 24-36% were obese (BMI>30 kg/m²) (Dominguez-Cherit et al. 2009; Estenssoro et al. 2010; Fuhrman et al. 2011; Kumar et al. 2009; Rello et al. 2009), and 6-14% were morbidly obese (BMI>40 kg/m²) (Dominguez-Cherit et al. 2009; Fuhrman et al. 2011; Rello et al. 2009). According to observational studies and one meta-analysis, obesity was associated with more severe disease (Fezeu et al. 2011; Kumar et al. 2009; Louie et al. 2009; Nguyen-Van-Tam et al. 2010; Viasus et al. 2011).
2.3 Incidence and prevalence of acute respiratory failure

2.3.1 Acute respiratory failure

Published incidences of ARF (intubation and MV≥24 hours) vary from 77.6/100,000/year in Scandinavia (Luhr et al. 1999) to 88.6/100,000/year in Berlin, Germany (Lewandowski et al. 1995).

2.3.2 Mechanical ventilation

Some kind of ventilatory support is needed in 33-74% of ICU patients (Carlucci et al. 2001; Demoule et al. 2006b; Esteban et al. 2002; Metnitz et al. 2009; Pettilä et al. 2002). In Argentina, most of the patients treated with invasive MV were treated for more than 12 hours (58% of ICU patients) (Estenssoro et al. 2005). Prevalence of ARF ranges from 32% to 47% at ICU admission and from 56% to 63% during ICU stay according to the respiratory component of the SOFA score (≥3) (Flaatten et al. 2003a; Vincent et al. 2002). A more stringent criteria, intubation and MV for more than 24 hours, was fulfilled in only 9% in a Scandinavian study (Luhr et al. 1999).

In a retrospective study, 26% of patients receiving MV needed prolonged ventilation for more than 96 hours (Zilberberg et al. 2009). In a multicentre study, 20% of patients needing MV at ICU admission continued to require MV for at least 7 days (Seneff et al. 1996). A retrospective study from Scotland showed prolonged MV (>21 days) in 4.4% of ICU admissions, and in 6.3% of ICU admissions with MV (Lone and Walsh 2011). In two other retrospective cohorts, 14% of ICU patients (Estenssoro et al. 2005), and 14% of patients ventilated for at least 48 hours (Cox et al. 2007a) received prolonged MV for more than 21 days.
Table 2. Studies of the incidence and prevalence of ARF, and ALI and/or ARDS using the AECC-criteria.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country, type, inclusion criteria</th>
<th>Duration</th>
<th>Incidence/100,000/year</th>
<th>Prevalence ALI/ARDS of admissions</th>
<th>Prevalence ALI/ARDS of MV</th>
<th>ICU mortality</th>
<th>90-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bersten et al. 2002</td>
<td>Australia, multicentre Intubation/mask+MV≥12 h, adults</td>
<td>2 months</td>
<td>34 30</td>
<td>28 19.6 (24h)</td>
<td></td>
<td>32% ALI*</td>
<td>34% ARDS*</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewandowski et al. 1995</td>
<td>Germany, multicentre MV+ intubation ≥24 hours, ≥14 years</td>
<td>2 months</td>
<td>88.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monchi et al. 1998</td>
<td>France, 24-bed medical ICU MV, surviving&gt;24h after ARDS onset</td>
<td>4 years, one ICU</td>
<td>/7.4%</td>
<td></td>
<td></td>
<td>42.7%</td>
<td></td>
</tr>
<tr>
<td>Roupie et al. 1999</td>
<td>French ICUs in 4 countries, multicentre Intubation/mask+MV&gt;6h/day, PaO2/FIO2&lt;300 mmHg (40.0 kPa)</td>
<td>14 days</td>
<td>8.7%/6.9% 19.8%/15.8%</td>
<td></td>
<td></td>
<td>41% all*</td>
<td>60% ARDS*</td>
</tr>
<tr>
<td>Valtta et al. 1999</td>
<td>Finland, single ICU, retrospective</td>
<td>3 years</td>
<td>4.9</td>
<td></td>
<td></td>
<td>37% ARDS</td>
<td></td>
</tr>
<tr>
<td>Luhr et al. 1999</td>
<td>Scandinavia, multicentre, Intubation+MV≥24 hours</td>
<td>8 weeks</td>
<td>77.6 17.9 13.5</td>
<td>2.2%/1.7% 23.3%/18.0%</td>
<td></td>
<td>53.1% ARDS</td>
<td>60.9% ARDS#</td>
</tr>
<tr>
<td>Hughes et al. 2003</td>
<td>Scotland, multicentre, ARDS, &gt;15 years</td>
<td>8 months</td>
<td>16.0</td>
<td>/8.1%</td>
<td></td>
<td>22.6% ALI no ARDS</td>
<td>49.4% ALI no ARDS#</td>
</tr>
<tr>
<td>Brun-Buisson et al. 2004</td>
<td>ICUs of 10 European countries, multicentre, ICU&gt;4h, ALI</td>
<td>2 months</td>
<td>7.1%/6.1% 16.1% (MV+ICU&gt;24h)</td>
<td></td>
<td></td>
<td>22.6% ALI no ARDS</td>
<td>49.4% ALI no ARDS#</td>
</tr>
<tr>
<td>Wind et al. 2007</td>
<td>The Netherlands, multicentre</td>
<td>3 days point prevalence</td>
<td>29.3 24.0</td>
<td>12%/7% 21%/13%</td>
<td></td>
<td>57.9% ARDS#</td>
<td></td>
</tr>
<tr>
<td>Irish Critical Care Trials Group 2008</td>
<td>Ireland, multicentre Intubation+MV</td>
<td>10 weeks</td>
<td>19%</td>
<td>27%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villar et al. 2011</td>
<td>Spain, multicentre, MV&gt;24h, &gt;18 years</td>
<td>1 year</td>
<td>7.2</td>
<td>/2.2% /7.4%</td>
<td></td>
<td>42.7% ARDS</td>
<td>47.8% ARDS #</td>
</tr>
<tr>
<td>Reference</td>
<td>Country, type, inclusion criteria</td>
<td>Duration</td>
<td>Incidence/100,000/year</td>
<td>Prevalence ALI/ARDS of admissions</td>
<td>Prevalence ALI/ARDS of MV</td>
<td>ICU mortality</td>
<td>90-day mortality</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------</td>
<td>------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------</td>
<td>---------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>North America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arroliga et al. 2002</td>
<td>US, Northeast Ohio, retrospective, ARDS, intubation not needed</td>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
<td>47% ARDS</td>
<td>48.5% ARDS*</td>
</tr>
<tr>
<td>Goss et al. 2003</td>
<td>US, multicentre, academic ≥20 bed ICUs, extrapolation</td>
<td>4 years</td>
<td></td>
<td>22.4-64.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. 2011</td>
<td>US, Olmsted county, retrospective, invasive MV or postoperative invasive MV&gt;12 hours</td>
<td>8 years</td>
<td></td>
<td>38.9-82.4</td>
<td></td>
<td>28-45% ARDS#</td>
<td></td>
</tr>
<tr>
<td>Rubenfeld et al. 2005</td>
<td>US, King County, multicentre, Intubation or mask+MV, ARDS</td>
<td>15 months</td>
<td></td>
<td>78.9</td>
<td>58.7</td>
<td>26.2%/19.5%</td>
<td>38.5% ALI#</td>
</tr>
<tr>
<td><strong>South-America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estenssoro et al. 2002</td>
<td>Argentina, 4 ICUs, ICU patients surviving&gt;24h, &gt;14 years</td>
<td>15 months</td>
<td></td>
<td></td>
<td>/7.7%</td>
<td>/19.7%</td>
<td>58% ARDS#</td>
</tr>
<tr>
<td>Fialkow et al. 2002</td>
<td>Brazil, single ICU ICU&gt;24h, adults</td>
<td>12 months</td>
<td></td>
<td>3.8%/2.3%</td>
<td></td>
<td>44.0% ALI</td>
<td>48.0% ALI#</td>
</tr>
</tbody>
</table>

* 28-day mortality
# hospital mortality
2.3.3 Acute lung injury/acute respiratory distress syndrome

Published incidences of ALI/ARDS according to the AECC definition, 4.9-82.4/100,000/year, are presented in Table 2. The lowest incidence of ARDS (4.9/100,000/year) was found in Finland, and it was estimated from one university hospital district area during the years 1993-1995 (Valta et al. 1999). The highest incidence figures are from the United States (Li et al. 2011; Rubenfeld et al. 2005). However, in a single county in the United States, the incidence decreased from 82.4/100,000/year to 38.9/100,000/year during the years 2001-2008 (Li et al. 2011). A recent study from Spain is the first to describe the incidence, 7.2/100,000/year, during lung protective ventilation (Villar et al. 2011). The prevalence of ALI and ARDS in the ICU is presented in Table 2. ALI and ARDS are found in 2.2-19% and 1.7-8.1% of admissions, and 16-27% and 7.4-19.7% of patients with MV, respectively.

2.3.4 Pandemic influenza A(H1N1)

The first critically ill young patients with H1N1 were reported in March-April 2009 (Centers for Disease Control and Prevention 2009; Perez-Padilla et al. 2009). The virus spread rapidly over the world, and a pandemic was declared in June 2009 (http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/print.html). The clinical picture of H1N1 varied from a mild, subclinical infection to a serious critical illness with severe oxygenation failure and ARDS (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza 2010). It was estimated that 12-30% of the population would develop clinical disease, of which 4% would need hospitalization, and 20% of the hospitalized would need ICU care (Patel et al. 2010).

Most of the infections occurred in patients younger than 50 years (Dawood et al. 2009). The highest disease incidence (218.5/100,000) was detected in infants, and the lowest incidence (15.3/100,000) in people over 70 years of age, while the overall incidence was 74.5/100,000 (Baker et al. 2009). The incidence of hospitalization varied from 2.8/100,000 in California, US (Louie et al. 2009) to 22.8/100,000 in New Zealand (Baker et al. 2009). In New Zealand, 31% of the patients were hospitalized (Baker et al. 2009) compared with 17% in the Mayo Clinic in Rochester, US (Venkata et al. 2010). The incidence of ICU admission with H1N1
in Australia and New Zealand was 28.7/1,000,000 (Webb et al. 2009). The highest ICU incidence was detected in infants, however the count of ICU admissions was highest in the 25 to 64 years age group (Webb et al. 2009). ICU admission of hospitalized patients ranged between 7% and 44% (Dominguez-Cherit et al. 2009; Jain et al. 2009; Venkata et al. 2010).

2.4 Treatment of acute respiratory failure

2.4.1 Invasive mechanical ventilation

After successful implementation of manual positive pressure ventilation with tracheostomy for respiratory paralysis due to polio in 1952, the use of invasive MV increased (Ibsen 1954; Trubuhovich 2004). Invasive MV became used for securing the airway and/or ensuring adequate gas exchange in critically ill patients. Patients with ARF of various aetiologies were treated in new respiratory units with a 66% survival rate (Petty et al. 1967). However, patients with severe oxygenation disorder, adult respiratory distress syndrome (now named acute respiratory distress syndrome (ARDS), died despite invasive MV and high inspired oxygen fraction (Ashbaugh et al. 1967; Petty et al. 1967). Positive end expiratory pressure (PEEP) was found essential for achieving adequate oxygenation and survival of these patients (Ashbaugh et al. 1967; Petty and Ashbaugh 1971).

The aim to achieve normal blood gas values, especially in the treatment of severe lung diseases, leads to the use of high tidal volumes and inspiratory pressures. Consequently, pneumothorax became a recognized complication of invasive MV. Toxic concentrations of oxygen and injurious ventilatory therapy were speculated to be involved in the development of lung injury, based on early clinical cases at the time of the first reports of ARDS (Nash et al. 1967). In the next decades, research with animal models showed that high inspiratory pressure and end-expiratory lung volume led to permeability disorders and pulmonary oedema (Dreyfuss et al. 1988; Webb and Tierney 1974), and that PEEP had a protective effect on alveolar epithelium during permeability oedema (Dreyfuss et al.1985). After recognizing the microscopic and macroscopic effects of MV, inflammatory action was studied. Increased cytokine levels were found in lung (Tremblay et al. 1997) and blood (Chiumello et al. 1999) in both animals and patients suffering from ARDS (Ranieri et al. 1999).
Low mortality associated with pressure limited ventilation by reduced tidal volume (Vt) and subsequent permissive hypercapnia in ARDS patients was first reported in 1990 (Hickling et al. 1990). Thereafter, four randomized trials evaluated reduced tidal volumes in invasive MV (Amato et al. 1998; Brochard et al. 1998; Brower et al. 1999; Stewart et al. 1998). Only one study showed survival benefit (Amato et al. 1998), where in addition to lower Vt, PEEP was adjusted according to the lower inflection point of lung compliance, and recruitment manoeuvres were used. The ARDS network conducted a fifth study comparing low and high Vt with similar PEEP in both groups (ARDS Network 2000); the low Vt group had significantly lower mortality. In addition, a recent meta-analysis suggests that volume and pressure limited ventilation in ALI/ARDS is associated with improved survival (Burns et al. 2011). Understandably, lung-protective ventilation with low Vt and pressure limitation is recommended in the treatment of septic patients (Dellinger et al. 2008).

No mortality benefit has been found with randomizing ALI/ARDS patients to low versus high PEEP (Brower et al. 2004; Meade et al. 2008; Mercat et al. 2008), however, according to a recent patient level meta-analysis high PEEP may improve survival in ARDS patients (Briel et al. 2010).

### 2.4.2 Non-invasive ventilation

Non-invasive ventilation (NIV) is a ventilatory support method without endotracheal or tracheostomy tube. In this study NIV refers to non-invasive positive pressure ventilation (NPPV) and continuous positive airway pressure (CPAP) provided by a facial mask. By avoiding invasive MV the occurrence of ventilator-associated pneumonia and other infections can be reduced (Antonelli et al. 1998; Antonelli et al. 2007; Carlucci et al. 2001).

The first randomized controlled trial (RCT) of CPAP versus oxygen therapy in acute cardiogenic pulmonary oedema was published in 1985 (Räsänen et al. 1985). In cardiogenic pulmonary oedema, CPAP improves gas exchange, decreases respiratory work and cardiac stress (Lin et al. 1995; Räsänen et al. 1985), and reduces the need for intubation and MV (Bersten et al. 1991; Lin et al. 1995).
NPPV was first introduced to treat chronic respiratory problems outside intensive care. In 1989, Meduri and colleagues reported the successful use of NPPV in both hypercapnic and hypoxic ARF (Meduri et al. 1989). A few years later, NPPV was found to reduce the need of intubation, the length of hospital stay, and in-hospital mortality in acute exacerbation of COPD treated in ICU (Brochard et al. 1995) and normal ward (Plant et al. 2000). In a systematic review of 15 RCTs, intubation rate, hospital length of stay (LOS), and mortality was reduced in severe cases of COPD (Keenan et al. 2003). Similarly, the British Thoracic Society Guidelines recommend NIV in acute exacerbation of COPD if acidosis persists despite maximal medical treatment (Roberts et al. 2008).

Although NIV also improves gas exchange in hypoxaemic ARF (Antonelli et al. 1998; Antonelli et al. 2007; Ferrer et al. 2003), results for other conditions than COPD, and results for other end points are more diverse (Keenan et al. 2009). For ARF patients not suffering from COPD, NIV reduced the intubation rate, ICU LOS, and mortality in hypercapnic patients (Wysocki et al. 1995). In CAP, survival benefit was found only in the subgroup of COPD patients (Confalonieri et al. 1999). However, an independent association of decreased risk of intubation and 90-day mortality with NIV compared to oxygen therapy was found in severe hypoxemic ARF, excluding hypercapnic patients (Ferrer et al. 2003). The meta-analysis by Keenan and colleagues did not detect outcome benefit of NIV with hypoxaemic ARF (Keenan et al. 2004).

NIV failure in heterogeneous ICU patients is high, 38-40% (Carlucci et al. 2001; Demoule et al. 2006b). An even higher rate has been detected in hypoxaemic ARF, 34-50% in pneumonia (Antonelli et al. 2001; Domenighetti et al. 2002; Jolliet et al. 2001), and 51% in ARDS (Antonelli et al. 2001) compared to 6.6-10% in cardiogenic pulmonary oedema (Antonelli et al. 2001; Domenighetti et al. 2002). NIV failure in observational studies was associated with more severe disease (Antonelli et al. 2001; Carlucci et al. 2001; Demoule et al. 2006a), more severe hypoxaemia (Antonelli et al. 2001; Jolliet et al. 2001; Rana et al. 2006), and shock (Rana et al. 2006).
2.4.3 Respiratory rescue therapies

Prone positioning
In 1977 Douglas and colleagues reported improved oxygenation with prone positioning in patients with ARF (Douglas et al. 1977). Suggested mechanisms of prone positioning are recruitment of atelectasis and improvement of ventilation perfusion distribution (Pappert et al. 1994). The prone position relieves the hydrostatic pressure of overlying lung parenchyma and the compressive effect of the heart on the lungs (Pelosi et al. 2001). Likewise, the incidence of ventilator associated pneumonia may be decreased (Guerin et al. 2004).

RCTs of prone ventilation have been unable to find any beneficial effect on mortality (Gattinoni et al. 2001; Guerin et al. 2004; Mancebo et al. 2006; Taccone et al. 2009). Although improved oxygenation is reported in reviews and meta-analyses, routine prone positioning is not recommended in hypoxemic ARF (Abroug et al. 2008; Sud et al. 2010). Outcome effect in the most severely ill patients is controversial (Gattinoni et al. 2001; Mancebo et al. 2006; Taccone et al. 2009). Meta-analysis of studies concerning severely hypoxemic ARDS patients have shown a 10% reduction in mortality (Gattinoni et al. 2010). Furthermore, a recent meta-analysis suggests, that prone ventilation may be considered for severely hypoxaemic patients (Sud et al. 2010).

Only a few studies have evaluated the use of prone ventilation in every day ICU practice. Charron and colleagues reported high survival with routine prone positioning in severe ARDS (PF<100 mmHg, 13.3 kPa) (Charron et al. 2011). Prone positioning was used, if PF remained below 100 mmHg (13.3 kPa) after 24-48 hours of MV. Of all ARDS patients, 26% were treated with prone positioning according to this practice. In the incidence study of ARF by Luhr and colleagues, prone ventilation was used in 1.4% of the patients (Luhr et al. 1999), however only therapies 24 hours prior and at the time of inclusion were reported. In addition, Esteban and colleagues reported that the use of prone ventilation decreased from 13% to 7% during years 1998 and 2004, respectively (Esteban et al. 2002; Esteban et al. 2008).
Extracorporeal life support (ECLS)

Extracorporeal cardiopulmonary support has been used as a rescue therapy in severe ARF. As early as the 1970s, Zapol and colleagues compared extracorporeal membrane oxygenation (ECMO) with invasive MV in adults (Zapol et al. 1979). ECMO was applied late in the course of MV, and mortality was high in both groups. Moreover, MV did not follow the principles of lung-protective ventilation. Later,Gattinoni and colleagues introduced the technique of low-flow extracorporeal CO₂ removal together with low frequency ventilation avoiding high airway pressures (Gattinoni et al. 1986). A RCT comparing extracorporeal CO₂ removal with pressure controlled inverse-ratio ventilation reported a high complication rate and no benefit to 30-day mortality (Morris et al. 1994). ECLS has remained a treatment option despite discouraging results from the first studies. High survival rate has been reported in severe ARDS patients treated with ECLS according a protocol-driven algorithm after unsuccessful conventional therapy (Hemmila et al. 2004). In this US centre, hospital survival was 52%. In Berlin, Germany, ICU survival of the ECMO group reached 55% (Lewandowski et al. 1997). Hospital survival of ARF patients recorded in the Extracorporeal Life-Support Organisation (ELSO) registry was 50% (Brogan et al. 2009). Recently, long-term survival of early ECMO treatment was higher (63%) compared to conventional MV (47%) on intention-to-treat analysis of a RCT conducted in England (Peek et al. 2009). Many issues of this study, and thus, also generalization of the results have been criticized (Brindley et al. 2010).

Inhaled nitric oxide (iNO)
iNO is a selective pulmonary vasodilator. It reduces pulmonary arterial pressure and selectively dilates vessels in ventilated lung units, which improves ventilation-perfusion mismatch and oxygenation. All these effects would be desired in ARDS, and thus, several clinical trials have been performed. The first RCT showed improved oxygenation in the first 4 hours (Dellinger et al. 1998). In 2007, a meta-analysis of 12 randomized trials of iNO in ARDS, of which two evaluated paediatric patients, showed only a temporary improvement in oxygenation (Adhikari et al. 2007). iNO had no effect on the length of MV, survival, and increased the risk of renal failure. Similarly, a recent Cochrane analysis does not recommend iNO for hypoxaemic ARF due to only a transient improvement in oxygenation, no mortality benefit, and the possibility of adverse effects (Afshari et al. 2010).
High frequency oscillatory ventilation (HFOV)

HFOV improves gas exchange by using higher mean airway pressure and smaller Vt than conventional MV, and thus may help to provide lung protective ventilation. Only 2 RCTs have evaluated the outcome of HFOV, and no outcome benefit has been found (Bollen et al. 2005; Derdak et al. 2002). A review of these two RCTs and other clinical studies cannot confirm a benefit of HFOV (Chan et al. 2007).

2.4.4 Pharmacological adjuvant therapies

Corticosteroid treatment

Corticosteroids are involved in many physiological systems. Corticosteroid insufficiency in itself can lead to critical illness, but conversely, severe illness may lead to relative insufficiency (Cooper et al. 2003). The anti-inflammatory effect of corticosteroid therapy has advocated its use in various pulmonary conditions leading to ARF, such as exacerbation of COPD and severe asthma (Jantz and Sahn 1999).

ALI/ARDS is a syndrome of inflammation (Bernard et al. 1994), and pulmonary inflammatory responses can lead to fibrosis in later stages (Ware and Matthay 2000). The impact of corticosteroids has been studied during different time frames of ARDS to examine their effects. The first RCTs used high dose and short duration methylprednisolone treatment (30 mg/kg x 4/day for 24-48 hours) (Bernard et al. 1987; Bone et al. 1987; Luce et al. 1988; Weigelt et al. 1985). In patients at high risk of ARDS, the development of ARDS could not be decreased with corticosteroid treatment (Bone et al. 1987; Luce et al. 1988; Weigelt et al. 1985). In established ARDS, corticosteroid therapy did not affect mortality (Bernard et al. 1987). Indeed, the AECC report in 1998 suggested that corticosteroids are not useful in early sepsis and ARDS (Artigas et al. 1998). Later, a meta-analysis even found a trend of increased risk of ARDS from a preventive use of corticosteroids (Peter et al. 2008).

In later studies, the dose and duration of corticosteroid changed. Prolonged methylprednisolone treatment was found to suppress systemic inflammation (Meduri et al. 2002), and to decrease fibrogenesis in ARDS (Meduri et al. 1998b). Prolonged moderate-dose methylprednisolone treatment (a loading dose of 2 mg/kg followed by an infusion of 2 mg/kg/day for two weeks, and tapered of during 32 days) improved lung function and
outcome in unresolving ARDS (Meduri et al. 1998a). Hospital mortality was 12% in the treatment group versus 62% in the control group. In a study by the ARDS Network, ventilator-free and shock-free days were increased, and oxygenation improved, during the first 28 days (Steinberg et al. 2006), however, the 60-day mortality was similar in the treatment and control groups, and starting treatment after 14 days of ARDS was associated with increased mortality. In a cohort study of late ALI, administration of 120 mg/day methylprednisolone resulted in similar 30-day mortality rates in treatment (19%) and control groups (20%) (Varpula et al. 2000). In early ARDS, low-dose methylprednisolone infusion (1 mg/kg/day for 28 days) down-regulated systemic inflammation, and improved pulmonary and extrapulmonary dysfunction in early ARDS (Meduri et al. 2007). In addition, days of MV were fewer, and ICU LOS and mortality were lower in the corticosteroid group, however, the difference in hospital mortality did not reach statistical significance.

In severe CAP, early hydrocortisone treatment (hydrocortisone intravenous bolus 200 mg followed by 240 mg/day infusion for 7 days) was associated with shorter hospital LOS and lower mortality (Confalonieri et al. 2005). Treatment with prednisolone (40 mg daily for 7 days) did not improve outcome in hospitalized CAP (Snijders et al. 2010). In severe and less severe CAP, corticosteroid improved oxygenation (Confalonieri et al. 2005; Fernandez-Serrano et al. 2011). According to a systematic review corticosteroids are not routinely recommended in severe CAP (Salluh et al. 2008). Corticosteroid for severe acute respiratory syndrome is controversial (Auyeung et al. 2005; Yam et al. 2007). Hydrocortisone has been associated with high positive culture rate (Yam et al. 2007), and methylprednisolone treatment is not associated with better survival in avian H5N1 influenza (Hien et al. 2009).

Patients with severe sepsis, and thus at high risk of ARDS, did not benefit from high-dose corticosteroid (Bone et al. 1987; Luce et al. 1988; Weigelt et al. 1985). Low-dose hydrocortisone produced a 10% reduction in mortality in patients with inadequate adrenal response (Annane et al. 2002). Later, the CORTICUS-study could not demonstrate improved survival or reversal of shock with hydrocortisone treatment (Sprung et al. 2008). Accordingly, the guideline regarding hydrocortisone in severe sepsis has changed to recommend hydrocortisone in vasopressor resistant septic shock (Dellinger et al. 2008).
Neuromuscular blocking agents (NMBAs)

Applications for NMBAs in critical care include facilitating invasive MV, managing increased intracerebral pressure, treating muscle spasms, and decreasing oxygen consumption when other means are not successful (Murray et al. 2002). NMBAs have also been used for providing respiratory rescue therapies (Arroliga et al. 2005). NMBAs are administered to 25-45% of ALI/ARDS patients (Forel et al. 2009). Approximately 13% of invasively ventilated patients in a large multicentre cohort were treated with NMBAs (Arroliga et al. 2005). Nonetheless, prolonged use of intermediate-acting NMBAs is associated with the risk of critical illness polyneuropathy in septic patients (Garnacho-Montero et al. 2001), and muscle weakness and myopathy in mechanically ventilated asthma patients (Adnet et al. 2001; Leatherman et al. 1996). The risk of muscle weakness increases with the simultaneous use of corticosteroids and the risk is not decreased with the use of nonsteroidal NMBA cis-atracurium compared to steroidal NMBAs, vecuronium, and pancuronium (Leatherman et al. 1996).

Later studies have demonstrated the beneficial effects of NMBAs. The administration of NMBA for 48 hours has been shown to improve oxygenation in ARDS patients ventilated with volume-controlled ventilation (Gainnier et al. 2004). In addition, NMBA treatment combined with lung protective ventilation can decrease pro-inflammatory marker levels (Forel et al. 2006). Recently, Papazian and colleagues reported a lower 90-day mortality after cis-atracurium treatment for ARDS when compared to placebo (Papazian et al. 2010).

2.5 Respiratory failure in influenza A(H1N1)

Rapid progression to severe respiratory failure is characteristic in H1N1 (Chowell et al. 2009; Patel et al. 2010). On hospital admission, 83% had findings typical for pneumonia in chest X-ray (Xi et al. 2010). Subsequently at ICU admission, bilateral infiltrates have been seen in most patients (71-96%) (Dominguez-Cherit et al. 2009; Kumar et al. 2009; Rello et al. 2009), 93% have shown three or more involved lung zones (Agarwal et al. 2009), and in two other studies almost half of the patients (41-47%) had four-quadrant involvement (Kumar et al. 2009; Rello et al. 2009). Among pneumonia patients, ARDS was diagnosed in 51% (Bai et al. 2011). At the onset of critical illness 73% have reported ALI, and ARDS was diagnosed in 36-74% of the ICU patients (Table 2). In patients treated with invasive MV,
ARDS was diagnosed in 88%, and PF was ≤100 mmHg (13.3 kPa) for nearly half of them (Estenssoro et al. 2010). Patients with H1N1-related ARDS had a higher lung injury score, and needed more rescue therapies than other ARDS patients (Riscili et al. 2011).

The use of respiratory and rescue treatments, and other therapies in ICU patients during the pandemic is presented in Table 3.

Respiratory treatments
Although only 23% of the hospitalized H1N1 patients with pneumonia required non-invasive and/or invasive MV (Chien et al. 2010), the majority of the ICU patients (63-93%) were treated with ventilator support (Table 3). Almost all patients treated with invasive ventilation were intubated already within a few hours of ICU admission (Brun-Buisson et al. 2011), and within median (range) 1 (0-6) day (Chien et al. 2010).

An expert panel strongly recommended against the use of NIV in the treatment of influenza pneumonia, in patients with a high risk of progression to ARDS, and in patients with concomitant organ failures due to fear of unnecessary delay of inevitable invasive MV (http://www.ersnet.org/index.php?option=com_flexicontent&view=items&id=4016:h1n1-resource-centre-); however, this recommendation states that NIV may be considered in patients with exacerbation of underlying chronic diseases. Accordingly, Winck and colleagues presented successful NIV treatment in a H1N1 infected patient with concomitant severe left ventricular failure (Winck et al. 2010).

NIV was the initial treatment for patients needing MV in 7-82% of cases (Grasselli et al. 2011; Kumar et al. 2009; Rello et al. 2009; Ugarte et al. 2010; Venkata et al. 2010), however, NIV failure rate has been high (Dominguez-Cherit et al. 2009; Kumar et al. 2009). In the study by Miller and colleagues, 43% of ARDS patients were treated with NIV with a failure rate of 85% (Miller et al. 2010). In Beijing, all ARDS patients were initially treated with NIV, and this study reports the highest (54%) success of NIV (Bai et al. 2011).

Interest in ECLS and other rescue therapies, and preparedness to apply them, increased during the 2009 H1N1 pandemic due to severe respiratory insufficiency (Webb et al. 2009; Kumar et al. 2009). During the pandemic, ELSO provided supplemental guidelines for
ECLS use in severe H1N1 (http://www.elso.med.umich.edu/Guidelines.html), however, the treatment is not evidence-based, and the availability of advanced technologies is limited (Estenssoro et al. 2010).

The first experience of ECMO was reported from Australia and New Zealand during the pandemic of the southern hemisphere. Of the patients on MV, 12% were treated with ECMO (Webb et al. 2009). In the referral ICUs of ECMO treatment, ECMO was used in 34% (n=68) in Australia and New Zealand, and 39% (n=60) in Italy (Davies et al. 2009; Patroniti et al. 2011). ECMO was successfully initiated in referral centres without complications during transfer (Davies et al. 2009; Ciapetti et al. 2011). Most of the ECMO cases were treated with veno-venous ECMO (Chan et al. 2010; Freed et al. 2010; Grasselli et al. 2011; Roch et al. 2010). A few patients were treated with pumpless lung assist (Freed et al. 2010). Length of MV before ECMO was an independent predictor of mortality (Patroniti et al. 2011).

Generally, hypoxaemia was severe before ECMO. In Australia and New Zealand, median (IQR) PF was 56 [48-64] mmHg (7.5 [6.4-8.5] kPa), and PEEP 18 [15-20] cmH2O (Davies et al. 2009). The respective values in Hong Kong were 56 [53-71] mmHg (7.5 [7.1-9.5] kPa), and 16 [15-19] cmH2O (Chan et al. 2010). In the Canadian case series, mean PF was 61 mmHg (8.1 kPa), PEEP was 20 cmH2O, and patients were hypercapnic (Freed et al. 2010).

Other rescue therapies, including prone positioning and iNO, were frequently applied before ECMO (Davies et al. 2009; Grasselli et al. 2011; Patroniti et al. 2011; Roch et al. 2010). In severe H1N1, recruitment with prone positioning was shown to improve oxygenation in refractory hypoxaemia (Biatto et al. 2010; Sundar et al. 2011). The use of prone ventilation varied from 0% to 25% in ICU patients (Rello et al. 2009; Venkata et al. 2010), and from 7% to 79% in patients treated with MV (Dominguez-Cherit et al. 2009; Sundar et al. 2011).

Only few observational studies report the use of NMBAs in treating H1N1 patients. In the United States, 47% of ICU patients received NMBAs for more than 48 hours, and ventilatory rescue therapies were not used (Miller et al. 2010). Sundar and colleagues reported a frequent use of prone ventilation without the need for NMBAs in refractory
hypoxaemia (Sundar et al. 2011). In Canada, all ECLS patients received NMBAs at ICU admission (Freed et al. 2010).

**Corticosteroids**

In severe H1N1, the immune system is strongly activated (Berdal et al. 2011; Bermejo-Martin et al. 2009). In the most severe cases, patients developing ARDS or non-survivors, higher plasma levels of proinflammatory cytokines and chemokines, and slower clearance of viral load were found compared to milder cases (To et al. 2010). Thus, a rationale for immunomodulatory agents in severely ill patients has been suggested (Annane 2011).

In the early stages of the H1N1 pandemic, Quispe-Laime and colleagues reported low mortality without major adverse effects with routine hydrocortisone treatment in these patients (Quispe-Laime et al. 2010). The importance of low to moderate dose corticosteroid in patients unresponsive to antivirals and other supportive therapies has been discussed (Confalonieri et al. 2010a; Confalonieri et al. 2010b; Kidd et al. 2009). Two case reports demonstrated successful responses to late high-dose methylprednisolone (Biatto et al. 2010; Roberts et al. 2010). In paediatric patients with severe H1N1 pneumonia, high dose methylprednisolone was associated with faster pneumonia resolution, compared to patients not receiving this treatment in two other hospitals (Kil et al. 2011).

Although not recommended by the WHO, 36% of hospitalized patients (Jain et al. 2009), 28-48% of pneumonia patients (Perez-Badilla 2009, Bai 2011), and 10-69% of ICU patients (Webb et al. 2009; Dominguez-Cherit et al. 2009; Grasselli et al. 2011; Kim et al. 2011; Kumar et al. 2009; Martin-Loeches et al. 2011; Miller et al. 2010; Sundar et al. 2011; Venkata et al. 2010) received corticosteroids. In most of the hospitalized patients, the indication that corticosteroid administration was needed in the acute state was underlying asthma, COPD, or other chronic lung respiratory disease (Nguyen-Van-Tam et al. 2010). Shock was a frequent indication in ICU patients (Grasselli et al. 2011; Sundar et al. 2011).

No improvement in survival of critically ill H1N1 patients has been seen due to corticosteroids (Brun-Buisson et al. 2011; Kim et al. 2011; Martin-Loeches et al. 2011), however, all of these studies had different viewpoints on corticosteroid use. Martin-Loeches and colleagues only evaluated patients with early corticosteroid (Martin-Loeches et al. 2011; Sundar et al. 2011).
2011), Brun-Buisson and colleagues evaluated only ARDS patients and excluded patients with other indications for corticosteroid (Brun-Buisson et al. 2011), and Kim and colleagues reported all patients receiving corticosteroids (Kim et al. 2011). In all three studies, hospital acquired infections were more common in the corticosteroid group (Brun-Buisson et al. 2011; Kim et al. 2011; Martin-Loeches et al. 2011). In the study of Martin-Loeches and colleagues, mortality was not increased after adjustment for disease severity and underlying diseases (Martin-Loeches et al. 2011). On the contrary, corticosteroid use remained independently associated with mortality in the other two studies (Brun-Buisson et al. 2011; Kim et al. 2011).

2.6 Co-existing organ dysfunction and failure

Multiple organ dysfunction syndrome (MODS) is defined as the presence of altered organ function in a patient who is acutely ill and in whom homeostasis cannot be maintained without intervention (Bone et al. 1992). Several scoring systems have been developed for describing the severity and course of MODS. The SOFA score is one of the most commonly used organ dysfunction scores (Vincent and Moreno 2010), which was developed to describe the degree of organ dysfunction in critically ill patients (Vincent et al. 1996). Six organ systems (respiratory, cardiovascular, renal, hepatic, central nervous, coagulation) are assessed (Table 1). The worst daily values of each organ system are summed to form the SOFA score. The simplicity of daily calculation enables its use for organ failure development during ICU stay (Vincent et al. 1998).

At ICU admission, 35-60% of ARF patients do not have co-existing organ failure (Aggarwal et al. 2007; Flaatten et al. 2003a). During the ICU stay, 14-34% of patients remain with single organ ARF (Flaatten et al. 2003a; Pettilä et al. 2002; Vincent et al. 2002). Renal failure varies from 11% to 22%, and neurologic failure from 6% to 37% (Aggarwal et al. 2007; Pettilä et al. 2002; Vincent et al. 2002). In the Finnish study, cardiovascular failure occurred in 76% of patients (Pettilä et al. 2002). The prevalence of co-existing organ failures was different, although the same organ failure assessment was used. In patients receiving over 12 hours of MV, shock was detected in 22% and renal failure in 19% (Esteban et al. 2002)
In ALI/ARDS the presence of co-existing organ dysfunction/failure increases compared with other hypoxaemic ARF patients (Roupie et al. 1999). Haemodynamic failure (42-55%) and renal failure (43-75%) are most frequent (Brun-Buisson et al. 2004; Ferring and Vincent 1997). Of the ARDS patients, 82% had an extrapulmonary organ dysfunction and septic shock was present in 51% (Roupie et al. 1999).

Autopsy of patients dying with H1N1 showed distinct pathological findings in the lungs, but the findings in other organs were mainly secondary to multiple organ failure (Mauad et al. 2010). Based on SOFA score assessment, shock and nonpulmonary acute organ dysfunction were common (Kumar et al. 2009). Of the ICU patients, one or more additional organ failures were found in 53-75% of patients (Grasselli et al. 2011; Rello et al. 2009). Of H1N1 pneumonia patients, 39% developed multi organ failure (Perez-Padilla et al. 2009). Most of the H1N1 patients with ARDS (87%) developed at least one other organ dysfunction, and 23% had four or more organ dysfunctions (Miller et al. 2010). In Italy, H1N1 patients with ECMO had similar non-respiratory organ dysfunctions compared to other ECMO patients (Patroniti et al. 2011).

Acute kidney injury (AKI) was present in 10-33% of hospitalized H1N1 patients (Perez-Padilla et al. 2009; Xi et al. 2010), and was more common (29-51%) in critically ill patients (Jung et al. 2011; Nin et al. 2011; Pettilä et al. 2011). Haemodialysis or renal replacement therapy was needed in 5% of hospitalized patients (Bai et al. 2011), and in 17-24% of ICU patients (Estenssoro et al. 2010; Nin et al. 2011; Rello et al. 2009). Of hospitalized patients, 12% had septic shock (Xi et al. 2010), and up to 72% of ICU patients with MV had shock (Estenssoro et al. 2010).

2.7 Serum zinc, organ dysfunction, and acute respiratory failure

Zinc is an essential trace element, which is important in many biological functions including immune function, DNA and protein synthesis, wound healing, and growth. Zinc is required for the activities of approximately 300 enzymes (Prasad 1995). Severe zinc deficiency occurs in acrodermatitis enteropathica, in excessive use of alcohol, and following total parenteral nutrition without zinc (Prasad 2008). Zinc deficient persons have immune dysfunctions (Prasad 2008), and increased susceptibility to infections (Meydani et al. 2007;
Shankar et al. 1998). In experimental studies, zinc may have a role in maintaining pulmonary cell integrity (Bao et al. 2006; Truong-Tran et al. 2000). The incidence of pneumonia, length of disease, and mortality were reduced with zinc supplementation in elderly nursing home patients (Meydani et al. 2007). A recent Cochrane review found a therapeutic and preventive effect of zinc on the common cold (Singh and Das 2011). In critically ill burn patients, zinc supplementation reduced the incidence of nosocomial pneumonia (Berger et al. 2006).

Zinc homeostasis may be altered at the genome-level in septic shock (Wong et al. 2007). In a model of sepsis, mortality and level of organ failure was higher in zinc deficient animals (Knoell et al. 2009). In critically ill paediatric patients, a low level of serum zinc has been associated with organ failures (Cvijanovich et al. 2009), and worse outcome (Wong et al. 2007). In adult medical ICU patients, plasma zinc levels had an inverse relation to the innate immune response, organ failure, and sepsis severity (Besecker et al. 2011).

### 2.8 Outcome in acute respiratory failure

#### 2.8.1 Short-term mortality

**ARF and MV**

Mortality in critical illness with ARF is higher than the mortality without ARF (Vincent et al. 2002). The ICU mortality has varied between 22% and 31% (Flaatten et al. 2003a; Vincent et al. 2002). In a retrospective study from the United States, the hospital mortality of ARF was 36% (Behrendt 2000). In hypoxaemic ARF (PF<300 mmHg, 40.0 kPa) 28-day mortality was 40% (Roupie et al. 1999). In patients with MV (>12 hours) a constant ICU mortality of 31% was detected in two different cohorts (Esteban et al. 2002; Esteban et al. 2008). Hospital mortality in patients receiving MV for more than 24 hours was 47% (Douglas et al. 2002). Mortality varied from 27% (MV>21 days) (Estenssoro et al. 2005) to 44% (Combes et al. 2003) in prolonged MV.

The 90-day mortality for all ARF patients (intubation and MV>24 hours) was 41%; 42% for ALI (not fulfilling ARDS), and 41% for ARDS, in a Scandinavian study (Luhr et al. 1999). For prolonged MV (MV>96 hours with tracheostomy or MV>21 days) the 90-day mortality has been 29% (Unroe et al. 2010).
The hospital mortality of ARF without co-existing organ failures varies from 7% to 17%, and increases with the number of co-existing organ failures (Flaatten et al. 2003a; Pettilä et al. 2002; Vincent et al. 2002). The 90-day mortality was 75% when ARF was associated with 4 or 5 additional organ failures (Flaatten et al. 2003a). In fact, the outcome of ARF is more dependent on dysfunction in other vital organs than on the severity of the respiratory failure (Esteban et al. 2008; Flaatten et al. 2003a; Luhr et al. 1999). The type of cause of ARF was associated with survival outcome (Stauffer et al. 1993). The underlying severity of respiratory disease did not influence hospital mortality in acute exacerbation of COPD needing MV (Esteban et al. 2008). Hospital survival of acute exacerbation of COPD is relatively good (75%) even among ICU patients of which 95% needed invasive MV (Ai-Ping et al. 2005).

In ARF, regardless of the definition, age and acute disease severity score are independent predictors of mortality (Brun-Buisson et al. 2004; Esteban et al. 2002; Luhr et al. 1999; Vincent et al. 2002). Shock on admission was independently associated with mortality in the study of Vincent and colleagues (Vincent et al. 2002), however, septic shock and severity of acute disease were associated with mortality in hypoxaemic ARF (Roupie et al. 1999).

**ALI/ARDS**

The mortality of ARDS has changed over time, but still remains high (Abel et al. 1998; Milberg et al. 1995; Zambon and Vincent 2008). According to a systematic review, the overall pooled mortality of ARDS was 44% (Phua et al. 2008). Mortality in RCTs with strict patient selection has been lower (Erickson et al. 2009), than mortality of ALI/ARDS in epidemiologic studies using the AECC criteria (Table 2). The 60-day mortality of patients enrolled in the ARDS Network RCTs decreased from 35% in 1996-1997, to 26% in 2004-2005 (Erickson et al. 2009). Furthermore, a meta-regression analysis of 72 studies between 1994 and 2006 suggested an approximately 1.1%/year reduction in overall mortality (Zambon and Vincent 2008). In contrast, decrease in mortality was found only in observational studies before the year 1994 (Phua et al. 2008). Improvement in general patient care has been suggested to explain the decreased mortality (Abel et al. 1998; Erickson et al. 2009).
Sepsis and/or MODS are major causes (40-69%) of death in ARDS, while respiratory failure as a sole cause is responsible for only 9-16% of deaths (Bersten et al. 2002; Estenssoro et al. 2002; Ferring and Vincent 1997). In the CESAR-study (ECMO for ARDS), 27% died of respiratory failure, and 17% of MODS in the conventional treatment group, while the corresponding values were 9% and 16% in the ECMO group (Peek et al. 2009). One per cent of deaths were related to ECMO. Hospital mortality of pneumonia together with shock was 72% in the ALIVE-study (Brun-Buisson et al. 2004), and the 28-day mortality was 73% of patients with septic shock at admission in the French study (Roupie et al. 1999). In a Finnish study, the number of organ failures at the onset of ARDS did not differ in survivors and non-survivors (Valta et al. 1999). Lower mortality of trauma patients compared with patients with sepsis has been reported (Brun-Buisson et al. 2004; Hughes et al. 2003; Rubenfeld et al. 2005). After controlling for other prognostic variables the cause of lung injury was not associated with mortality (Brun-Buisson et al. 2004).

The association of hypoxaemia with outcome has varied. In a few studies, mortality of ALI patients has been lower compared to patients with ARDS (Bersten et al. 2002; Brun-Buisson et al. 2004; Roupie et al. 1999; Rubenfeld et al. 2005), while in others no difference has been detected (Luhr et al. 1999; Zilberberg et al. 1998). Although mortality in ALI and ARDS patients was similar in one study, severe hypoxaemia (PF<100mmHg, 13.3 kPa) in ARDS patients was independently associated with mortality (Luhr et al. 1999). The severity of oxygenation impairment was independently associated with mortality in an Irish study (Irish Critical Care Trials Group 2008). The early response of hypoxaemia may identify patients with better survival (Bone et al. 1989; Estenssoro et al. 2002).

**H1N1**

Mortality in hospitalized H1N1 patients has varied from 7% to 11% (Jain et al. 2009; Louie et al. 2009), in ICU patients from 13% to 41%, patients on MV from 46% to 58% (Table 3), and patients treated with ECMO from 14% to 56% (Davies et al. 2009; Chan et al. 2010; Freed et al. 2010; Grasselli et al. 2011; Patroniti et al. 2011; Roch et al. 2010).

The most common direct cause of death was respiratory failure (76%) according to an English study (Donaldson et al. 2009). Diffuse alveolar damage is characteristic in autopsy (Bai et al. 2011; Mauad et al. 2010; Perez-Padilla et al. 2009). Hyaline membranes,
necrotizing bronchiolitis, and fibroblast proliferation are also found (Bai et al. 2011; Mauad et al. 2010). A high SOFA score in H1N1 patients was not associated with as high mortality as in other ICU patients (Shahpori et al. 2011). Multi-organ failure was the cause of death for 18% of patients in England (Donaldson et al. 2009). In the ECMO group in Italy, 57% died of MODS, and 21% of septic shock (Patroniti et al. 2011). More than two thirds of the non-survivors had at least one underlying medical condition (Donaldson et al. 2009; Louie et al. 2009). In contrast, 59% were previously healthy according to a report from United Kingdom (Nguyen-Van-Tam et al. 2010). Obesity was related to more severe disease (Fuhrman et al. 2011), but not to death (Brun-Buisson et al. 2011).

2.8.2 Long-term mortality

ICU and hospital mortality may not reflect the long-term outcome and overall burden of critical illness (Angus et al. 2003). The risk of death after critical illness is higher for several years after hospital discharge in comparison with the general population (Cuthbertson et al. 2010; Williams et al. 2008; Wright et al. 2003). Mortality after hospital discharge differs according to the aetiology of ARF. The six-month mortality of ARF (pneumonia or ARDS) was 52% (Hamel et al. 2000). During long-term follow-up mortality increased deeply during the first year, and after that more slowly (Garland et al. 2004). In COPD, good hospital survival was achieved with ICU treatment, but readmissions were common, and long-term mortality was high due to the underlying disease; one-year mortality was 61%, and 5-year mortality was 76% (Ai-Ping et al. 2005). In contrast, hospital survivors of ARDS all survived 8 months after acute illness in the Finnish study (Valta et al. 1999). An expert panel recommends follow-up of at least six months after intensive care treatment in order to evaluate a comprehensive impact of critical illness on survival (Angus et al. 2003).

The one-year cumulative mortality for patients on MV for more than 24 hours was 65% for all; 50% for MV 24-96 hours, and 66% for MV over 96 hours (Douglas et al. 2002). In another study, the one-year mortality for patients on MV for more than 48 hours was 56% (Chelluri et al. 2004). The one-year mortality for patients that had received prolonged MV for more than 96 hours with tracheostomy was 48% compared with 58% for those receiving prolonged MV for more than 21 days (Cox et al. 2007a).
Table 3. Treatments and mortality of influenza A(H1N1) patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country, centre</th>
<th>Patients</th>
<th>Setting</th>
<th>ARDS</th>
<th>MV</th>
<th>Prone</th>
<th>ECMO</th>
<th>iNO</th>
<th>HFOV</th>
<th>Cortico- steroid</th>
<th>NMBA</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webb et al. 2009</td>
<td>AUS, NZ</td>
<td>722</td>
<td>ICU</td>
<td>49%</td>
<td>65%*</td>
<td>NR</td>
<td>11%</td>
<td>NR</td>
<td>NR</td>
<td>18%</td>
<td>NR</td>
<td>14% (H)</td>
</tr>
<tr>
<td>Kumar et al. 2009</td>
<td>Canada</td>
<td>215</td>
<td>ICU</td>
<td>73%  (ALI)</td>
<td>81% (D 1)</td>
<td>3 %</td>
<td>4 %</td>
<td>14%</td>
<td>12%</td>
<td>51%</td>
<td>28%</td>
<td>14% (28-day)</td>
</tr>
<tr>
<td>Rello et al. 2009</td>
<td>Spain</td>
<td>32</td>
<td>ICU</td>
<td>NR</td>
<td>75%</td>
<td>25%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>19% (28-day)</td>
</tr>
<tr>
<td>Jain et al. 2009</td>
<td>US</td>
<td>67</td>
<td>ICU</td>
<td>36%</td>
<td>63%*</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>36% of hospitalized with data</td>
<td>NR</td>
<td>28%</td>
</tr>
<tr>
<td>Dominguez-Cherit et al. 2009</td>
<td>Mexico</td>
<td>58</td>
<td>ICU</td>
<td>NR</td>
<td>93%</td>
<td>7% of MV</td>
<td>0</td>
<td>0</td>
<td>1.7%</td>
<td>69%</td>
<td>NR</td>
<td>41.4% (60-day)</td>
</tr>
<tr>
<td>Miller et al. 2010</td>
<td>US</td>
<td>47</td>
<td>ICU</td>
<td>79%  (ALI)</td>
<td>64% (ARDS)</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>55% of ARDS</td>
<td>47%</td>
<td>17% (H)</td>
</tr>
<tr>
<td>Estenssoro et al. 2010</td>
<td>Argentina</td>
<td>337</td>
<td>ICU+MV</td>
<td>88%</td>
<td>100%</td>
<td>13%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>46% (H)</td>
</tr>
<tr>
<td>Ugarte et al. 2010</td>
<td>Chile</td>
<td>75</td>
<td>ICU</td>
<td>NR</td>
<td>75%</td>
<td>24%</td>
<td>6%</td>
<td>NR</td>
<td>11%</td>
<td>NR</td>
<td>NR</td>
<td>26% (ICU)</td>
</tr>
<tr>
<td>Venkata et al. 2010</td>
<td>US, Mayo Clinic in Rochester</td>
<td>29</td>
<td>ICU</td>
<td>55%</td>
<td>79%</td>
<td>7%</td>
<td>0</td>
<td>14%</td>
<td>13%</td>
<td>10%</td>
<td>NR</td>
<td>8% (H)</td>
</tr>
<tr>
<td>Chien et al. 2010</td>
<td>Taiwan</td>
<td>22</td>
<td>pneumonia+ MV</td>
<td>100%</td>
<td>100%</td>
<td>NR</td>
<td>41% (mort 56%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fuhrman et al. 2011</td>
<td>France</td>
<td>1065</td>
<td>ICU</td>
<td>49%</td>
<td>67% (mort 28%)</td>
<td>NR</td>
<td>7% (mort 49%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Viasus et al. 2011</td>
<td>Spain</td>
<td>75</td>
<td>ICU</td>
<td>NR</td>
<td>73%*</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>13% (H)</td>
</tr>
<tr>
<td>Grasselli et al. 2011</td>
<td>Italy, Monza</td>
<td>19</td>
<td>ICU</td>
<td>58%</td>
<td>84%</td>
<td>26%</td>
<td>42%</td>
<td>16%</td>
<td>NR</td>
<td>32%</td>
<td>NR</td>
<td>16% (ICU)</td>
</tr>
<tr>
<td>Reference</td>
<td>Country, centre</td>
<td>Patients</td>
<td>Setting</td>
<td>ARDS</td>
<td>MV</td>
<td>Prone</td>
<td>ECMO</td>
<td>iNO</td>
<td>HFOV</td>
<td>Corticosteroid</td>
<td>NMBA</td>
<td>Mortality</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------</td>
<td>----------</td>
<td>----------------------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
<td>------</td>
<td>-----</td>
<td>------</td>
<td>----------------</td>
<td>------</td>
<td>------------------</td>
</tr>
<tr>
<td>Martin-Löeches et al. 2011</td>
<td>Europe</td>
<td>220</td>
<td>ICU</td>
<td>74 %</td>
<td>78 %</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>57% (on adm)</td>
<td>NR</td>
<td>31% (ICU) 34% (H)</td>
</tr>
<tr>
<td>Brun-Buisson et al. 2011</td>
<td>France</td>
<td>208</td>
<td>ICU+ARDS (steroid for other indication excluded)</td>
<td>100 %</td>
<td>100 %</td>
<td>21 %</td>
<td>26 %</td>
<td>27 %</td>
<td>NR</td>
<td>40 %</td>
<td>NR</td>
<td>24% (ICU)</td>
</tr>
<tr>
<td>Kim et al. 2011</td>
<td>Korea</td>
<td>245</td>
<td>ICU</td>
<td>56% (on adm)</td>
<td>71 %</td>
<td>NR</td>
<td>5 %</td>
<td>NR</td>
<td>NR</td>
<td>44 %</td>
<td>NR</td>
<td>33% (30-day) 40% (90-day)</td>
</tr>
</tbody>
</table>

**ECLS/ECMO reports**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country, centre</th>
<th>Patients</th>
<th>Setting</th>
<th>ARDS</th>
<th>MV</th>
<th>Prone</th>
<th>ECMO</th>
<th>iNO</th>
<th>HFOV</th>
<th>Corticosteroid</th>
<th>NMBA</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al. 2009</td>
<td>AUS, NZ</td>
<td>61</td>
<td>ECMO</td>
<td>100 %</td>
<td>100%*</td>
<td>20% (of MV)</td>
<td>32 %</td>
<td>32 %</td>
<td>5 %</td>
<td>NR</td>
<td>NR</td>
<td>23% (H)</td>
</tr>
<tr>
<td>Freed et al. 2010</td>
<td>Canada</td>
<td>4 2</td>
<td>ECMO ECLS</td>
<td>NR</td>
<td>NR</td>
<td>33% (on adm)</td>
<td>3% (of ICU)</td>
<td>100% (on adm)</td>
<td>50% (on adm)</td>
<td>33 %</td>
<td>100% (on adm)</td>
<td>33% (28-day)</td>
</tr>
<tr>
<td>Chan et al. 2010</td>
<td>China, Hong Kong</td>
<td>7</td>
<td>ECMO</td>
<td>100 %</td>
<td>100%*</td>
<td>14 %</td>
<td>6% (of MV)</td>
<td>0</td>
<td>0</td>
<td>29 %</td>
<td>43 %</td>
<td>14% (H)</td>
</tr>
<tr>
<td>Roch et al. 2010</td>
<td>France, Marseille</td>
<td>9</td>
<td>ECMO</td>
<td>100 %</td>
<td>100%*</td>
<td>22 %</td>
<td>41% (of MV)</td>
<td>67 %</td>
<td>0</td>
<td>56 %</td>
<td>100 %</td>
<td>56% (H)</td>
</tr>
<tr>
<td>Patroniti et al. 2011</td>
<td>Italy</td>
<td>49</td>
<td>ECMO</td>
<td>100 %</td>
<td>NR</td>
<td>28 %</td>
<td>32% (of ICU)</td>
<td>15 %</td>
<td>4 %</td>
<td>33 %</td>
<td>NR</td>
<td>29% (H)</td>
</tr>
</tbody>
</table>

NR, not reported; D 1, day one; H, hospital
MV includes non-invasive and invasive ventilation except for marked with *where data not specified
The positive effect of NIV can still be observed after one year in patients with acute exacerbation of COPD compared with historic controls of conventional treatment (Confalonieri et al. 1996). NIV remained associated with improved survival compared with invasive MV after 5-years follow-up (Berkius et al. 2010). However, 5-year survival was poor (17%) even in the NIV group. In an earlier study from Spain, 15% of COPD patients receiving long-term oxygen therapy were alive at 5 years (Anon et al. 1999). In cardiogenic pulmonary oedema, NIV (CPAP or NPPV) did not affect short- or long-term mortality compared with standard therapy (Goodacre et al. 2011; Gray et al. 2008).

Factors impacting on short- and long-term outcomes are different. The acute severity of illness is associated with short-term mortality, while age and chronic health state (Chelluri et al. 2004; Davidson et al. 1999b; Garland et al. 2004), and pre-admission functional status (Garland et al. 2004; Sligl et al. 2011; Williams et al. 2008) are associated with long-term mortality. In patients with prolonged MV (>48 hours), pre-admission functional status was also associated with short-term mortality (Chelluri et al. 2004). After controlling for age, risk factor of ARDS, chronic co-morbidity, and acute illness severity, the survival of ARDS was similar to matched controls (sepsis and trauma) (Davidson et al. 1999b).

### 2.8.3 Quality of life and quality-adjusted life years

Short- or long-term mortality does not give an in-depth picture of the burden of critical illness. ICU treatment may have serious long-term consequences, and thus, long-term quality of life (QOL) assessment is recommended (Angus et al. 2003). The Short Form 36-item questionnaire (SF-36) and Euro-QOL-5D (EQ-5D) are the most suitable for multicentre trials of critically ill patients (Angus et al. 2003).

SF-36 is a multi-purpose generic health survey, which assesses 8 domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions (Ware and Sherbourne 1992). All dimensions are measured on the range 0-100, where higher score represents better health. SF-36 has been widely used in critically ill patients with ARF (Chelluri et al. 2004; Cox et al. 2007a; Davidson et al. 1999a; Herridge

EQ-5D is a generic preference-based instrument for health evaluation. The questionnaire consists of 5 domains: mobility, self-care, usual activities, anxiety and/or depression and bodily pain, and a visual analogue scale (VAS) (EuroQolGroup 1990). Each domain is rated with a three-level scale: no, some, or severe problems. The subjective 5-digit health profile is converted to a health index score, which can be used in cost-utility analysis. The EQ-5D questionnaire has been used for HRQOL assessment in the critically ill, especially when cost-utility analysis has been calculated (Gray et al. 2009; Peek et al. 2009; Unroe et al. 2010; van Hoek et al. 2011). It has been found suitable for proxy assessment (Badia et al. 2001). Similar HRQOL outcome profiles were found with EQ-5D and SF-36 in a Swedish study (Orwelius et al. 2005).

The effect of ICU-related factors on HRQOL is contradictory. A recent study of critically ill patients in Sweden (>24 hours in the ICU) did not find association of ICU LOS or length of ventilator treatment with HRQOL (Orwelius et al. 2005). In the United States, short-term MV patients had better functional status than long-term MV (>96 hours) patients (Douglas et al. 2002). Only 9% of hospital survivors of prolonged MV are independently functioning at one year (Unroe et al. 2010). Half of the short-term, but only 27% of the long-term MV patients are discharged home (Douglas et al. 2002). However, 89% of patients living at home before illness are able to live at home at one year after ICU treatment (Chelluri et al. 2004). According to another study, almost all patients with prolonged MV were living at home after three years (Combes et al. 2003). Nearly half of the long-term MV patients have been discharged to a nursing home (Douglas et al. 2002), or needed caregiver assistance one year after discharge (Chelluri et al. 2004).

In cardiogenic pulmonary oedema, survivors have reduced HRQOL irrespective of standard treatment or NIV (Goodacre et al. 2011). In COPD patients needing intensive care, long-term mortality is influenced by low pre-admission quality of life (QOL) (Rivera-Fernandez et al. 2006). Survivors have worse long-term HRQOL compared with their pre-admission state, but 75% of survivors manage without help from others.
ARDS survivors have reduced HRQOL compared with normal controls (Heyland et al. 2005; Hopkins et al. 2005; Masclans et al. 2011; Schelling et al. 2000; Weinert et al. 1997), and compared with other ICU patients (Davidson et al. 1999a). When matched with age, previous health state, and severity of disease, ARDS survivors had similar QOL to other ICU patients (Granja et al. 2003). In the study of Cooper and colleagues, HRQOL and physical function were similar to patients with chronic diseases (Cooper et al. 1999). Although HRQOL starts to improve after hospital discharge (Herridge et al. 2003; Hopkins et al. 2005), HRQOL and physical function remain reduced at one year and further (Cheung et al. 2006; Cooper et al. 1999; Herridge et al. 2003; Herridge et al. 2011; Heyland et al. 2005). In the study of Heyland and colleagues, 57% of patients had not returned to normal activity by 12 months (Heyland et al. 2005). ARDS survivors treated with ECMO did not have disabilities after 6 months (Peek et al. 2009). In critically ill patients, physical health reached pre-morbid levels at one year, but thereafter fell again (Cuthbertson et al. 2010). Overall, the majority of long-term survivors rate their HRQOL as good (Hamel et al. 2000; Schelling et al. 2000).

Most impairment found in ARDS patients has been observed in physical functioning and pulmonary symptoms (Davidson et al. 1999a). In a French single centre study, QOL was the same regardless of having ARDS or not, but ARDS patients had more respiratory symptoms (Combes et al. 2003). Pulmonary symptoms correlated with reduced HRQOL in ARDS (Heyland et al. 2005; Orme et al. 2003), and in ARDS treated with ECMO (Linden et al. 2009). In a Canadian ARDS cohort, nearly normal lung function was detected at one year, and this persisted until 5-year follow-up (Herridge et al. 2003; Herridge et al. 2011). Most patients suffered from extrapulmonary disorders, and functional status at one year was associated with the absence of use of systemic corticosteroids, no acquired illness during ICU stay, and rapid resolution of organ functions (Herridge et al. 2003). Although physical function remains lower than in the normal population throughout the 5-year period, almost all had returned to work during this time (Herridge et al. 2011).

QALY is the product of QOL assessed with a generic preference-based health state instrument (scale from zero to one, where one indicates best health state) and gained or expected life years after intervention, and thus QALY indicates both quality and quantity of life years. In intensive care patients all gained life-years and QALYs are usually assumed to
be of benefit to ICU treatment (Sznajder et al. 2001, Karlsson et al. 2009, Peek et al. 2009). For example, a patient surviving for 5 years with a QOL of 1 reaches 5 QALYs, while patients with similar survival with reduced QOL of 0.5 or 0.1 reach 2.5 or 0.5 QALYs, respectively. QALYs are used for comparing health interventions and treatments (Talmor et al. 2006), however studies evaluating QALYs of patients with ARF are limited.

In previously healthy ARDS patients quality adjusted survival is poor (Angus et al. 2001). Patients requiring ventilator support for pneumonia and ARDS gain reasonable QALYs if survival probability is high (Hamel et al. 2000). ARDS patients referred for consideration of ECMO gained 0.03 QALYs at 6 months compared with conventional MV (Peek et al. 2009). In influenza, QALY loss is minor for individual patients, but estimated total burden of the disease was substantial when compared to other infectious diseases (van Hoek et al. 2011).

2.9 Cost, cost-effectiveness, and cost-utility analysis

ICUs consume up to 30% of hospital costs (Feng et al. 2009; Halpern et al. 2004; Moerer et al. 2007). In Norway, the average cost per ICU day was €2,601, and €14,223 for ICU stay (Flaatten et al. 2003b). In a study from the Netherlands, average daily cost was €1,911, and the range of individual patient costs were €751-€11,116 (Tan et al. 2008). In France, mean ICU cost was $14,130 (Sznajder 2001), whilst in Finland, the mean total cost for a surviving patient with severe sepsis was €32,563 (Karlsson et al. 2009). Nurse and physician wages (Flaatten et al. 2003b) and overheads (Tan et al. 2008) comprise the largest single costs.

ICU cost is increased in patients treated with MV compared to ICU patients not needing MV (Dasta et al. 2005; Tan et al. 2008). The mean total cost of patients requiring renal replacement therapy (RRT) was even higher (Tan et al. 2008). Costs increase with the time spent on MV (Cox et al. 2007b), nearly one-quarter of the charges of all MV patients are spent on those receiving MV for more than 96 hours with tracheostomy (Cox et al. 2004). In a study by Zilberberg and colleagues, the median hospital cost for patients receiving MV for less than 96 hours was $13,434, while the cost of prolonged MV was $40,903 (Zilberberg et al. 2008). Moreover, MV for more than 21 days is even more expensive (Cox et al. 2007b). The mean total one-year costs for prolonged MV were $306,135 (SD $285,467) (Unroe et al. 2010). Charges to produce a long-term MV survivor were almost twice the charges of short-
term MV survivor (Douglas et al. 2002). Mean health-care costs per patient were more than
twice as high for patients in the group considering ECMO compared with the conventional
management group (Peak et al. 2009). The critical care cost of H1N1 has been evaluated in
one study, and the ICU cost was found to be higher than previously published for an average
ICU admission (Higgins et al. 2011).

Cost-effectiveness analysis calculates the ratio of incremental cost and health benefit,
usually gained life years. Cost-utility analysis uses QALYs as a denominator, and takes into
account the quality of resulting years. A cost of $50,000 to $100,000 per QALY is usually
considered cost-effective in the United States, versus £20,000 to £30,000 per QALY in the
United Kingdom (Laupacis et al. 1992; Talmor et al. 2006).

In a Canadian study, the cost per saved life-year was Can $4,350 compared with ICU
patients where active treatment was stopped (Heyland et al. 1998). In a French study, the
incremental cost per life-year saved was $1,150 (Sznajder et al. 2001). In Norway, the cost
of year of survival was €684 (Flaatten et al. 2003b). According to modelling, the incremental
cost per life-year saved was $55,460 for prolonged MV (Cox et al. 2007b).

Only a few cost-utility analyses of ARF patients are available. The estimated cost per QALY
in acute exacerbation of severe COPD requiring MV ranged from $26,283 to $44,602 (Anon
et al. 1999). According to a theoretical model, NIV in acute exacerbation of COPD is cost-
effective compared with standard therapy alone (Keenan et al. 2000). Incremental cost
effectiveness analysis of NIV in acute exacerbation of COPD found NIV to reduce total
costs and hospital mortality was improved (Plant et al. 2003). Cost saving was mainly a
result of the reduced use of ICUs. In cardiogenic pulmonary oedema, more QALYs were
gained with NIV compared with standard therapy, but costs were higher (Gray et al. 2009).
In patients with pneumonia or ARDS, the incremental cost per QALY ranged from $19,000
to $200,000 according to estimated 2 months survival probability and sensitivity analysis
(Hamel et al. 2000). Sensitivity analysis assessed how different estimates of cost, QOL, and
annual mortality affected cost per QALY. For prolonged MV, a cost per QALY of $82,411
has been reported (Cox et al. 2007b). A lifetime model predicted a cost of £19,252 (95% CI
£7,622-59,200) per QALY of ECMO at a discount rate of 3.5% (Peak et al. 2009)
3 AIMS OF THE STUDY

The objective of this study was to evaluate the epidemiology, treatment, and short- and long-term outcomes of ARF in central and university hospital ICUs in Finland. The specific aims were:

1. To study the incidence, treatments, and outcome of acute respiratory failure in ICUs. (Studies I, IV)

2. To assess the long-term mortality and health-related quality of life, quality adjusted life-years, and cost-utility in one-year survivors of acute respiratory failure (Study II)

3. To assess the association of serum zinc with organ failures and mortality in acute respiratory failure. (Study III)

4. To evaluate the incidence, patient characteristics, treatment, and short-term outcome in pandemic influenza A(H1N1) patients treated in ICUs. (Study IV)
4 PATIENTS AND METHODS

4.1 Patients

Studies I-IV comprised altogether 1090 patients (Table 4).

Studies I, II, and III
Altogether 958 adult patients in 25 Finnish central and university hospital ICUs from 16 April to 10 June 2007 comprised the FINNALI study cohort of acute respiratory failure patients (ARF). All of these 958 patients were included in study I. Study II evaluated the long-term outcome of the FINNALI patients. Six hundred nineteen patients were alive at one-year. HRQOL was assessed of 288 survivors with consent. Study III comprised 551 patients with serum zinc analysis after consent and exclusions. Flowchart of studies I-III is presented in Figure 1A.

Study IV
Study IV assessed all 229 patients admitted to Finnish central and university hospital ICUs with suspected or confirmed H1N1 during the 2009 epidemic (from 11 October to 31 December 2009). Out of the 229 patients, 132 tested positive for H1N1 by PCR, and these patients comprised the study cohort. The flowchart of included patients is presented in Figure 1B. Demographics of the FINNALI and H1N1 patients are presented in Table 4.
Figure 1. Flowchart of the patients in Studies I-III (A) and Study IV (B).

Table 4. Characteristics of the patients in Studies I-IV.

<table>
<thead>
<tr>
<th></th>
<th>All study patients</th>
<th>Study I-II FINNALI</th>
<th>Study III FINNALI</th>
<th>Study IV H1N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>1090</td>
<td>958</td>
<td>551 of 958</td>
<td>132</td>
</tr>
<tr>
<td>Male</td>
<td>722 (66%)</td>
<td>637 (66%)</td>
<td>265 (66%)</td>
<td>85 (64%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>60 [48-73]</td>
<td>63 [51-74]</td>
<td>65 [53-74]</td>
<td>49 [34-56]</td>
</tr>
<tr>
<td>SOFA at 24 hours</td>
<td>8 [5-10]</td>
<td>8 [6-10]</td>
<td>8 [5-10]</td>
<td>4 [2-8]</td>
</tr>
<tr>
<td>ALI/ARDS</td>
<td>130 [12%]</td>
<td>68 (7%)</td>
<td>46 (8%)</td>
<td>62 (50%)</td>
</tr>
<tr>
<td>ICU LOS, days</td>
<td>3.2 [1.7-7.1]</td>
<td>3.2 [1.7-6.8]</td>
<td>3.3 [1.7-6.9]</td>
<td>4.1 [1.9-11.5]</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>125 (12%)</td>
<td>120 (13%)</td>
<td>58 (11%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>240 (22%)</td>
<td>230 [24%]</td>
<td>122 (22%)*</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>295 [31%]</td>
<td>158 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-year mortality</td>
<td>339 [35%]</td>
<td>185 (34%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*30-day mortality in Study III
Data are expressed as number (percentage) or median [interquartile range]
4.2 Study designs

Studies I-III

The epidemiology, treatment, outcome, and HRQOL of ARF patients were evaluated in a prospective observational cohort study in 25 central and university hospital ICUs in Finland during an 8-week period. After subtracting the adult population of two non-participating hospitals, the total reference population was 4,164,980, and this covered over 97% of the Finnish adult population (≥16 years) (Figure 2). All consecutive adult patients admitted to ICUs were assessed for ventilatory support treatment. ARF was defined as the need for ventilatory support for more than 6 hours, and the fulfilment of this time was considered as study baseline. In cases of multiple admissions only the first one was included in the incidence calculation. Patients with ventilatory support for less than 6 hours and foreign patients were excluded. ARF was fulfilled in 958 patients according to study criteria, and these patients were included in the FINNALI-study.

Patient characteristics and risk factors for ARF were assessed upon entry to the study entry. Risk factors 48 hours preceding ARF included chronic obstructive and restrictive pulmonary disease, chronic heart condition, diabetes mellitus, pneumonia, other respiratory infection, sepsis, pancreatitis, operation, trauma, massive blood transfusion, witnessed or suspected aspiration, and decreased consciousness. Local study nurses and investigators recorded cardiovascular and respiratory variables, and applied treatments at participating ICUs daily. ALI and ARDS according to the AECC criteria (Bernard et al. 1994) was evaluated throughout the ICU stay.

Previous health state, performance of daily life, ICU admission reason with primary diagnosis, severity of acute illness, daily organ function score with original values, LOS and ICU and hospital mortality were obtained from the quality database (The Finnish Quality Consortium, Intensium Ltd., Kuopio, Finland).
In study II, the one-year mortality of the FINNALI patients was assessed with data acquired from Statistics Finland. Patient HRQOL was evaluated at ICU admission and at one-year with a generic EuroQOL-5-dimensional (EQ-5D) instrument (The EuroQol Group 1990). Consent was given by 288 patients who answered the HRQOL assessment. Quality adjusted life years (QALYs) and cost per QALY was estimated from the reference values of age- and gender-matched respondents. The mean cost for one QALY was calculated by using the mean ICU and hospital cost of the study patients and dividing the sum by acquired QALYs gained. All gained life-years/QALYs were calculated as the benefit of intensive care with the assumption that ARF patients most probably will die without ICU admission and ventilator support (Karlsson et al. 2009; Sznajder et al. 2001).
Study III

Study III was a substudy of study I. All FINNALI patients with consent for blood samples were eligible for the study. Blood samples for zinc analysis were obtained from 598 patients. After exclusions, 551 zinc measurements were included in the analysis. The aim was to assess the association of serum zinc with 30-day mortality, organ dysfunction, length of ventilatory support, and/or ICU LOS in adult patients with ARF.

Study IV

Study IV evaluated the epidemiology, treatment, and outcome of H1N1 during the Finnish outbreak of the 2009 pandemic. The study period was from 11th of October to 31st of December 2009. In December 2009, the population of Finland was 5,353,427. All 299 ICU patients with suspected or confirmed H1N1 were recorded. Of the 299 patients, 132 were PCR positive for H1N1.

4.3 Laboratory measurements

Serum zinc (Zn) (III)

Blood sample for serum Zn analysis was obtained after informed consent at 6 hours after ventilatory treatment start. The samples were drawn in zinc-free tubes and processed according to laboratory instruction. The samples were frozen and stored at -80°C for later analysis. Serum zinc was analysed with atomic absorption spectrophotometry. All samples were analysed in the laboratory of Oulu University Hospital. The normal range of serum zinc is 11-22 µmol/l (72-144 µg/dl). To assess the effect of haemodilution on zinc levels we corrected zinc values with haematocrit (Hct) by calculating zinc/Hct-ratio. C-reactive protein (CRP) of the day of zinc sample was extracted from the patient data system. Hct and leukocytes were obtained from the SAPS II and APACHE II data.

4.4 Data collection

Patient identification codes were used to avoid admitting patients repeatedly to incidence calculations and to obtain survival status and time of death for one-year outcome assessment. Otherwise the data were managed anonymously with admission number.
Data was recorded with an internet-based interface for making clinical reports and the data was collected in the national ICU quality database. Patient characteristics and risk factors for ARF were assessed at study entry. Risk factors 48 hours preceding ARF included chronic obstructive and restrictive pulmonary disease, chronic heart condition, diabetes mellitus, pneumonia, other respiratory infection, sepsis, pancreatitis, operation, trauma, massive blood transfusion, witnessed or suspected aspiration and decreased consciousness. Local study nurses and investigators recorded cardiovascular and respiratory variables and applied treatments in participating ICUs daily. Clinical syndromes throughout the ICU stay were recorded.

4.5 Scoring for the severity of illness

*Sequential Organ Failure Assessment (SOFA)*

SOFA score (Vincent et al. 1998) was used to assess the number and severity of organ dysfunction/failure. Six organ systems (respiration, cardiovascular, coagulation, renal, hepatic and central nervous system) are evaluated and graded from 0 to 4 yielding in a maximal score of 24. Zero indicates no organ dysfunction. Points 1 and 2 reflect organ dysfunction. Organ failure is defined as points 3 and 4.

*Simplified Acute Physiology Score (SAPS) II and Acute Physiology and Chronic Health Evaluation (APACHE) II*

SAPS II (Le Gall et al. 1993) and APACHE II (Knaus et al. 1985) use physiology and laboratory data for disease severity adjustment. Acute disease severity was assessed with the SAPS II score. The underlying data for SAPS II and APACHE II score were available.

4.6 Outcome measures

*Length of ventilatory support*

Length of ventilatory support was calculated in days when either non-invasive or invasive ventilation was used.
Hospital and ICU length of stay (LOS)
When a patient was transported directly from one ICU/hospital to another, the LOS was calculated as a sum of all treatment periods.

Mortality
Data for ICU and hospital mortality (I-IV) was acquired from ICU and hospital records. Data for 30-day (III), 90-day (I), and one-year mortality (II) was obtained from Statistics Finland. The follow-up time was calculated from the beginning of ARF.

The standardized mortality ratio (SMR)
The SMR was calculated as the ratio of observed hospital deaths and predicted deaths based on the SAPS II model.

Health-related quality of life (HRQOL)
HRQOL was assessed with the EuroQol 5-dimensional (EQ-5D) instrument (EuroQol Group 1990). The questionnaire consists of evaluation of five domains and perceived health state by visual analogy scale. The five domains in EQ-5D are: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is graded from 1 to 3, where 1= no problems, 2= moderate problems, and 3= severe problems.

4.7 Interventions
Patients were treated according to general practice guidelines and protocols of the participating ICUs without therapeutic study interventions. Blood samples for the study and HRQOL assessment of one-year survivors were obtained from patients after informed consent.

4.8 Statistical analyses
Data are presented as number (percentages), absolute values and percentages with 95% confidence intervals (CIs), mean (±SD) or medians and 25th to 75th percentiles, interquartile range [IQR] where appropriate. The 95% CIs were calculated for incidences. In Study I,
p≤0.01 was considered significant due to multiple comparisons. The level of p<0.05 was considered statistically significant in all tests in Studies II-IV. All statistical analyses were performed with SPSS 15.0, SPSS 16.0, SPSS 17.0 or PASW 18.0 software (SPSS Inc, Chicago, Illinois).

The Kolmogorow-Smirnov test was used for testing normality of continuous variables (III).

Chi-Square or Fisher's exact test were used for comparing categorical variables in all studies. Fisher’s exact test was used if the number of events was below five.

Kaplan-Meier test was used to evaluate one-year survival according to oxygenation impairment.

Kendall rank correlation test was used to test correlation of non-normally distributed data (III).

Kruskal-Wallis test was used for comparison of several groups (III).

Mann-Whitney U test was used for comparison of non-parametric continuous data between two independent groups. It was used to test patient characteristics (I-IV) and laboratory data (III).

Wilcoxon’s signed matched pair test was used for analysing EQ-5D index and reference values (II).

Multiple (stepwise forward) logistic regression analysis was used to test independent effect of the variables on the outcome (I), and independent factors predicting treatment with corticosteroids (IV). Logistic regression analysis was used to calculate the odds ratio (OR) with 95% CI for corticosteroid use adjusting for association with SAPS II (IV).

Receiver operating characteristics (ROC) curve analysis and area under curve (AUC) with 95% CIs were constructed to assess the accuracy for the final multivariate model (I), and predictive power of zinc regarding 30-day mortality (III).
4.9 Ethical aspects

Studies I, II, and III
Ethics committees of each participating hospital approved the study. An informed consent was obtained from the patient or next of kin for laboratory samples and quality of life assessment.

Study II
The EuroQol group permitted the use of the EQ-5D questionnaire.

Study IV
The National Institute of Health and Welfare obligated all hospitals and ICUs in Finland to report all patients of suspected or confirmed H1N1 infections. The Ethics Committee of the Operative Division of Helsinki University Hospital approved the study.

An informed consent was waived for extracting data from standard clinical information systems and patient charts to the registered data files of this study project (Studies I, II, III and IV).

Authors of the studies have declared no conflict of interests.
5 RESULTS

5.1 Incidence of acute respiratory failure (ARF) (I, IV)

5.1.1 Overall incidence of ARF

During the 8-week study period in 2007, 2,473 adult patients were treated in the 25 participating ICUs. Either non-invasive or invasive ventilatory support was recorded on 1,310 occasions. After exclusions, ARF was assessed according to study criteria in 958 of the 2,473 patients (39%). These 958 patients comprised the FINNALI study cohort.

The incidence of ARF estimated from the 8-week study period was 149.5/100,000 population/year. Of the 958 patients, 300 (31%) were treated with ventilation support for less than 24 hours. The incidence of these patients was 102.7/100,000/year. ALI was present in 68 patients and ARDS in 32. The calculated incidences of ALI and ARDS were 10.6 and 5.0/100,000/year, respectively. Incidences of patients with hypoxemic ARF were 90.4/100,00/year for oxygenation criteria of ALI (PF≤300mmHg, 40.0 kPa) and 48.4/100,00/year for oxygenation criteria of ARDS (PF≤200mmHg, 26.7 kPa). Pneumonia, or other respiratory infection, 48 hours before ARF was present in 192 (20% of 958) patients, however, only one patient was admitted for viral pneumonia (data not shown in the original study).

5.1.2 Incidence of pandemic influenza A(H1N1)

During the defined 12-week period in the fall of 2009, 132 patients with confirmed (PCR test positive) H1N1 were treated in Finnish ICUs. Eleven patients (8.3%) were under 16 years, and three (2.3%) were pregnant. The incidence of ICU treated H1N1 influenza during the outbreak was 24.7 (95% CI, 16.7 to 36.5) per million inhabitants. ALI or ARDS was present in 62 (50%) and ARDS in 58 (44%) patients.

Figure 3 presents ICU admissions and incidence of ARF (A) and H1N1 (B) according to age groups (data not shown in the original studies). Chronic co-morbidity was present in
60% of patients in both cohorts. Obesity was recorded in 8% of ARF, and 27% of H1N1 patients (body mass index > 35 kg/m²).

Figure 3. Number of ICU admissions and incidence according to age in acute respiratory failure in the FINNALI-study (A) and influenza A(H1N1) (data not shown in the original study) in the H1N1-study (B).

5.2 Ventilatory treatments (I, IV)

According to the study definition, all ARF patients were treated with ventilatory support. At study baseline, 81% were on invasive MV, 15% on NIV, and 4% were intubated after unsuccessful NIV. For H1N1 patients, ventilatory treatment was needed in 103 (78% of the 132) during the study period: only NIV in 36 patients, and invasive
MV in 67 patients, of which 82% also received NIV. Table 5 shows characteristics and treatments of patients with ARF in the FINNALI-study and H1N1 patients.

Table 5. Characteristics and treatments of patients with acute respiratory failure and influenza A(H1N1) with subgroups of ARDS.

<table>
<thead>
<tr>
<th></th>
<th>FINNALI ARDS</th>
<th>FINNALI ARDS</th>
<th>H1N1 ARDS</th>
<th>H1N1 ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=958</td>
<td>N=32</td>
<td>N=132</td>
<td>N=58</td>
</tr>
<tr>
<td>Age</td>
<td>63 [51-74]</td>
<td>55 [47-69]</td>
<td>49 [34-56]</td>
<td>50 [40-56]</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>230 (24%)</td>
<td>12 (38%)</td>
<td>10 (8%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>PaO₂/FiO₂, mmHg</td>
<td>250 [174-338]</td>
<td>145 [89-264]</td>
<td>140 [102-245]</td>
<td>76 [61-100]</td>
</tr>
<tr>
<td>Vt/PBW, ml/kg</td>
<td>8.6 [7.6-9.9]</td>
<td>8.4 [7.2-10.8]</td>
<td>8.2 [6.5-10.0]</td>
<td>8.4 [6.5-10.5]</td>
</tr>
<tr>
<td>PEEP, cmH₂O</td>
<td>6.0 [5.0-8.0]</td>
<td>8.6 [6.0-12.0]</td>
<td>8 [6.0-10.0]</td>
<td>8.0 [6.5-10.0]</td>
</tr>
<tr>
<td>Corticosteroid for shock</td>
<td>107 (11%)</td>
<td>13 (9.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid for ARDS</td>
<td>20 (63%)</td>
<td></td>
<td></td>
<td>28 (48%)</td>
</tr>
<tr>
<td>Prone position</td>
<td>12 (1.2%)</td>
<td>3 (9.4%)</td>
<td>20 (15%)</td>
<td>17 (29%)</td>
</tr>
<tr>
<td>iNO</td>
<td>9 (0.9%)</td>
<td>2 (6.3%)</td>
<td>6 (4.5%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>NMBB</td>
<td>104 (10%)</td>
<td>15 (47%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ECLS/ECMO</td>
<td>3 (0.3%)</td>
<td>0</td>
<td>1 (0.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*baseline: 6 hours after start of ventilatory therapy
Data are expressed as number (percentage) or median [interquartile range]

At baseline of FINNALI-patients with available measurement, 64% had PF≤300 mmHg (40.0 kPa) and 30% had PF≤200 mmHg (26.7 kPa) without accounting PEEP. Respective percentages were 60% and 26% when only patients with PEEP≥5 cmH₂O were taken into account. At baseline, 89% of measured PEEP values (CPAP, NIV or invasive MV) were ≥5 cmH₂O. After baseline, 95% of PEEP values were ≥5 mH₂O. In H1N1 patients, baseline PEEP≥5 cmH₂O was detected in 95%.
5.3 Other treatments (I, IV)

Of all 958 ARF patients, 107 (11%) were treated with corticosteroid for septic shock. Corticosteroid was prescribed for 63% (20 of 32) of ARDS patients. NMBA for ventilatory treatment was used for 104 (10%), iNO for 9 (0.9%), prone position for 12 (1.2%), RRT for 89 (9.3%), and ECLS/ECMO for 3 (0.3%) patients. ARDS was not the indication for iNO or ECLS/ECMO in any of the cases.

Fifty five per cent of H1N1 patients received corticosteroid. Pulmonary obstruction was the most common indication (30 patients). Corticosteroid for ARDS was given to 28 (21% of all and 48% of ARDS) patients primarily or after commencing corticosteroid therapy for obstruction or shock. Septic shock was the initial reason for corticosteroid therapy in 12 (9.1%) patients; whilst the 13th patient suffering septic shock was initially treated for obstruction. Patients who received corticosteroids were significantly more severely ill than those not given corticosteroids. Impaired oxygenation was independently associated with the probability of corticosteroid treatment. One H1N1 patient was treated with ECMO due to severe obstruction and hypercapnia. Prone position was used for 17 (29%) of the H1N1 ARDS patients.

5.4 Association of serum zinc with organ dysfunction and outcome (III)

The median [IQR] serum zinc level was 4.7 [3.0-6.9] µmol/l in all patients. Serum zinc was low in 95.8% at the onset of ARF. Only 20 (3.8%) samples were within the normal range (11-22 µmol/l). Baseline serum zinc did not differ according to acute disease severity, and were not associated with ventilatory support time (p=0.98) or ICU length of stay (p=0.053). Zinc levels decreased with increasing severity of cardiovascular organ failure (p<0.001). Survivors and non-survivors had similar serum zinc levels, 4.7 [2.8-6.9] µmol/l and 5.2 [3.3-7.0] µmol/l (p=0.12), respectively. AUC for serum zinc regarding 30-day mortality was 0.55 (95% CI 0.49-0.60).
5.5 Short and long-term mortality (I, II, IV)

Hospital and 90-day mortality (95% CI) for ARF were 24% (21-27%), and 32% (28-34%). The 90-day mortality for ALI/ARDS was 47% (35-59%), whilst one-year mortality for ARF and ALI/ARDS were, 35% (32-38%) and 51% (39-64%), respectively. The outcome of other time points, and mortality for various length of ventilator support is presented in Figure 4. The type of ventilatory support was associated with mortality: lowest mortality, 33% (30 to 36%), was found in patients treated only with invasive ventilation, and highest mortality, 60% (45 to 76%) in patients with NIV failure during the first six hours (p=0.001). SAPS II score minus score for oxygenation, chronic heart disease, suspected infection preceding ARF, baseline PF, and intoxication were independently related to outcome. Figure 5 shows Kaplan-Meier survival curves for one-year survival in PF quintiles.

The hospital mortality for all H1N1 patients was 8% (95% CI 3-12%). All non-survivors had severe co-morbidities. Three patients had chronic heart disease, two haematological malignancy, two chronic renal and/or liver disease, one COPD, one diabetes mellitus, and one had chromosomal abnormality.

![Figure 4. Mortality of all patients with ARF, subgroups of ALI/ARDS, and patients according to the ventilatory treatment time.](image-url)
5.6 Quality of life (II)

The percentage of patients with problems in each of the five dimensions is presented in Figure 6. Half of the patients did not have problems with mobility, and two thirds of the patients did not have problems in self-care and usual activities before ICU admission. Severe problems in mobility were seen for 14%, and 17% had problems with their usual activities.

Of 619 one-year survivors, 292 EQ-5D questionnaires were received, out of which 288 (47% of the one-year survivors) EQ-5D sum indices could be calculated. The EQ-5D index was lower than age and sex-matched reference values, (0.70 (0.45 to 0.89) versus 0.84 (0.81 to 0.88), p < 0.001). The median (IQR) EQ-5D sum index for the total population after adjustment for missing values was 0.60 (0.49-0.72).
5.7 Quality adjusted life-years (II)

The mean (SD) predicted life-years and lifetime QALYs for the 288 one-year survivors were 22.9 (14.4) and 15.4 (13.3), and for the total ARF cohort were 16.8 (17.2) and 11.3 (13.0), respectively. QALYs declined with increasing age (Figure 7).
5.8 Cost-effectiveness (II)

The estimated total costs for survivors responding to the EQ-5D questionnaire were €4,830,402. The respective cost for all 958 ARF patients was €15,098,158. The overall calculated cost (survivors and non-survivors) for ICU and hospital stay was €20,739 per hospital survivor (n=728).

The average cost of younger patients was below €20,000, and over €25,000 in patients older than 80 years. The proportion of ICU costs with regard to the total hospital cost (ICU and ward cost) was highest in non-survivors: 73% for all, 69% for survivors, and 87% for non-survivors (p<0.001).

The cost per one predicted lifetime QALY for the respondents was €1,089 and €1,390 estimated for the whole cohort. The cost of QALY increased with age, and was twice as high in patients over 80 years compared with patients from 74 to 80 years. Cost per hospital survivor and cost per QALY varied according to age, pre-admission health-state, severity of illness, and predisposing risk factor for ARF (Figure 8).
Figure 8. Cost per hospital survivor and cost per QALY in different categories.
The incidence of ARDS was low in this study, however the age-adjusted incidence of H1N1 was similar to previous reports. The mortality of ARF and H1N1 patients was low, and the average cost per QALY of ARF was €1,390.

**Incidence of ARF and ALI/ARDS**

Different definitions of ARF make comparisons of incidence, treatment, and outcome difficult. A definition of ventilator support for more than 6 hours was chosen for this study to obtain a general impression and incidence of ARF, and resources needed for treating patients with non-invasive and invasive MV. Almost one third of the study patients only required ventilation for less than 24 hours, and this in part explains the higher incidence compared with previous studies of ARF (intubation and MV >24 hours) (Lewandowski et al. 1995; Luhr et al. 1999). The incidence of the subgroup that received MV for more than 24 hours was similar to, but higher than, previously reported incidences. The proportion of patients that received MV for more than 21 days was lower than previously reported (Cox et al. 2007a; Estenssoro et al. 2005). In addition to different requirements for minimum time of ventilator support for incidence calculation, this study also included patients treated only with NIV. Although invasive MV is usually an indication for ICU admission, COPD and cardiogenic pulmonary oedema are generally treated with NIV outside ICUs. Therefore, the total incidence of ARF, calculated by using the definition of this study, may even be underestimated (Okkonen et al. 2009).

Despite the uniform definition, the incidence of ALI/ARDS varies widely, from 4.9/100,000 to 82.4/100,000, (Li et al. 2011; Luhr et al. 1999; Rubenfeld et al. 2005; Valta et al. 1999; Villar et al. 2011). Highest incidence has been found in the United States (Li et al. 2011; Rubenfeld et al. 2005), although the incidence has decreased during recent years (Li et al. 2011). The low incidence in the present study was similar to a previous report from Finland (Valta et al. 1999) and a recent multicentre study from Spain (Villar et al. 2011). Seasonal variation (Arroliga et al. 2002) cannot be excluded due to the fairly short study period during spring months, however, the 3-year study period in the earlier Finnish study (Valta et al. 1999) most likely eliminated the influence of seasonal variation.
The AECC criteria for ALI/ARDS have several problems. Oxygenation criteria is assessed regardless of FiO₂, need for MV, or ventilator settings. According to pulmonary models and mathematical calculations, the oxygenation criteria (PF) can be manipulated with FiO₂ (Aboab et al. 2006). In a clinical situation, the diagnosis of ALI/ARDS changes with varying FiO₂ (Allardet-Servent et al. 2009; Villar et al. 2007). Larger variations are detected in patients with true shunt greater than 30% (Allardet-Servent et al. 2009; Gowda and Klocke 1997). With an increase in FiO₂ from 0.5 to 1.0, two-thirds of the patients moved from ARDS to ALI (Allardet-Servent et al. 2009).

In addition to FiO₂, other ventilator settings also significantly influence ALI/ARDS diagnosis (Allardet-Servent et al. 2009; Estenssoro et al. 2003; Villar et al. 2007). PEEP was omitted from the AECC oxygenation criteria due to inconsistent and time-dependent effects on pulmonary shunt and oxygenation (Bernard et al. 1994). Applying PEEP to patients fulfilling oxygenation criteria for ARDS without PEEP, however, increased the PF above the ARDS-level; after 6 hours half of the patients, and after 24 hours 62% of the patients, had a PF over 200 mmHg (26.7 kPa) (Estenssoro et al. 2003). With standardized ventilator settings for 30 minutes (Vt 7-8 ml/kg, PEEP 10 cmH₂O and FiO₂ 1.0), only 42% persisted with PF lower than 200 mmHg (26.7 kPa) (Ferguson et al. 2004). Villar and colleagues and Allard-Servent and colleagues suggested PEEP over 10 cmH₂O with FiO₂ over 0.5 to be clinically relevant for screening ARDS (Allardet-Servent et al. 2009; Villar et al. 2007).

The time frame of the ALI/ARDS assessment period, and ICU treatments may influence the detection, and thus, the incidence of ALI/ARDS (Determann et al. 2010; Gajic et al. 2004; Gajic et al. 2007; Li et al. 2011; Vincent et al. 2010). ALI/ARDS diagnosis is mostly made by the second day after ICU admission (Hughes et al. 2003; Luhr et al. 1999; Vincent et al. 2010). In this study, ALI/ARDS were assessed during the whole ICU stay, but conclusions of ventilatory or other treatments were not possible. At least some level of PEEP applied to every patient, and genetic predisposition may potentially impact on the low incidence and prevalence.

**Incidence of H1N1**

The incidence of H1N1 requiring ICU treatment (24.7/1,000,000) during the pandemic was similar to the incidence reported from Australia and New Zealand (Webb et al. 2009).
Approximately the same amount of patients was treated due to suspected H1N1 without confirmation of H1N1. Unfortunately, the aetiology was not otherwise systematically investigated to allow incidence calculation of other respiratory infections during the pandemic. Historical comparison in Australia and New Zealand showed a 3-fold increase in ICU admissions compared with the previous 4 years during the same months (Webb et al. 2009). During the 8 week FINNALI-study, only one patient was admitted for viral pneumonia, however, without routine viral diagnostics this may not reflect the true prevalence (Bertolini et al. 2011; Carrat et al. 2006).

Similar to the study by Webb and colleagues, age-specific incidence was highest in infants (Webb et al. 2009). In Canada, 30% of the ICU patients were children, and in France, 87% of the ICU patients were younger than 64 years (Fuhrman et al. 2011). Cross-reacting antibodies against the H1N1 virus in the elderly (Ikonen et al. 2010) may explain the low incidence in this age cohort.

A quarter of the patients in the present study were obese (BMI>35 kg/m²), as also reported in Australia and New Zealand (Webb et al. 2009). In other studies, one third of the ICU patients were obese with a different definition, BMI>30kg/m² (Domínguez-Cherit et al. 2009; Estenssoro et al. 2010; Kumar et al. 2009; Rello et al. 2009). Unlike in other countries (Webb et al. 2009; Estenssoro et al. 2010; Fuhrman et al. 2011; Miller et al. 2010; Rello et al. 2009; Ugarte et al. 2010), only 2.3% of patients were pregnant. The vaccination of pregnant women against pandemic influenza started in the beginning of the pandemic, which may give reason for incidence speculation.

**Characteristic of ARF and H1N1**

Only a few studies have compared pandemic influenza with seasonal influenza or other severe respiratory failure. Pandemic H1N1 pneumonia affects younger patients, and leads to severe disease more often than seasonal influenza (Chowell et al. 2009; Riquelme et al. 2011). In an Italian study, H1N1 patients with pneumonia were younger than patients with CAP (Bertolini et al. 2011). The median age of H1N1 patients in the present study was lower, and the age-specific incidence of H1N1 patients was different compared to the ARF cohort (Figure 3).
The characteristic of pandemic influenza was severe respiratory failure and viral pneumonitis/ARDS leading to ICU admission, ventilator support, and high mortality in a minority of patients (Chowell et al. 2009; Perez-Padilla et al. 2009). Compared with seasonal influenza, the need for non-invasive and invasive MV was more frequent in pandemic influenza (Riquelme et al. 2011). PF less than 100 mmHg (13.3 kPa) was more frequent in H1N1 pneumonia than in CAP (Bertolini et al. 2011). Oxygenation impairment and degree of lung injury score were more severe in H1N1 associated ARDS than in other ARDS (Riscili et al. 2011). Similarly, PF in the early phase of H1N1 compared with ARF, as well as in subgroups of ARDS, was lower. Admission SOFA score and SAPS II score in H1N1 were lower than in ARF, however.

In Finland, ARDS was more frequent (n=58) in H1N1 than ARDS (n=32) in ARF patients during the FINNALI-study period. The proportion of ARDS among H1N1 patients (44%) was at the lower range of previously reported viral pneumonitis/ARDS (36-74%) (Webb et al. 2009; Fuhrman et al. 2011; Grasselli et al. 2011; Jain et al. 2009; Kim et al. 2011; Martin-Loeches et al. 2011; Miller et al. 2010; Venkata et al. 2010).

Treatments
The effect of low Vt on mortality has been shown in ARDS (ARDS Network 2000), and a review of Vt in non-ALI suggests that low Vt is also beneficial in these patients (Schultz et al. 2007). In ARF and H1N1, Vt per actual body weight (ABW) and airway pressures adhered to lung protective ventilation strategy, but Vt per predicted body weight (PBW) exceeded the recommended volume (Dellinger et al. 2008). A minority of the ARF-patients had ARDS, and lack of consensus recommendation for non-ARDS patients may in part explain these results. Low Vt was not fulfilled even in the subgroup of ALI/ARDS, however, other reasons may be speculated. Moderate airway pressure in the majority might have resulted in overlooking the need for low Vt (Eichacker et al. 2002). In addition, the equation of PBW is not adopted to everyday clinical practice (Tallach et al. 2006). Using ABW or estimate of weight leads to over 30% higher weight compared to PBW (Young et al. 2004). A high proportion of obesity may have impacted the setting of the Vt, especially in H1N1 patients, however, after two years of the FINNALI-study, in the cohort of H1N1 patients, Vt/ABW were lower than in ARF patients, but Vt/PBW remained over 6-7 ml/kg.
The frequency of first line NIV (19%) was similar to previous European studies (16-23%) (Carlucci et al. 2001; Domenighetti et al. 2002). In this study, 11% of ARF patients were treated only with NIV. NIV failure was at the same level as in ARDS (46%) (Antonelli et al. 2001), but higher than in CAP (21%) (Confalonieri et al. 1999), however NIV failure may reach 70% in ALI (Rana et al. 2006). NIV failure is clearly lower in cardiogenic pulmonary oedema (Domenighetti et al. 2002) and COPD (Carlucci et al. 2001).

Against recommendations (Ramsey et al. 2010), 62% of H1N1 patients were initially treated with NIV. The higher initial use compared with the FINNALI-cohort is most likely due to different admission categories of patients, and cohort policy, which probably lead to ICU admission of some milder cases in ICU. In contrast, the report of one of the largest H1N1 cohorts did not include the use of NIV (Webb et al. 2009). Multicentre studies report NIV use in 6-38% of ICU patients with a high failure rate, 75-85% (Dominguez-Cherit et al. 2009; Kumar et al. 2009; Rello et al. 2009). First-line NIV was more common in single centres (41-86%), with a slightly lower failure rate (50-68%) (Grasselli et al. 2011; Timenetsky et al. 2011; Venkata et al. 2010). In a Beijing hospital, all H1N1 related ARDS patients needing ventilator support (73%) were initially treated with NIV (Bai et al. 2011). Similarly, as in other ARDS patients, NIV was successful in half (Antonelli et al. 2001; Bai et al. 2011). From the health care personal perspective, a proper facility for NIV and protective actions seem to make NIV safe in influenza patients (Bai et al. 2011; Timenetsky et al. 2011).

Compared to CAP, rescue therapies were more frequent in H1N1 pneumonia (Bertolini et al. 2011). The high mortality in previously healthy young patients (Chowell et al. 2009; Perez-Padilla et al. 2009) may have increased the interest in advanced ventilatory therapies. The increased use of ECMO during the pandemic began in Australia and New Zealand (Webb et al. 2009; Davies et al. 2009). Before ECMO, most of the patients received other rescue therapies, which were emphasised in treatments with technical devices (Davies et al. 2009; Freed et al. 2010). Although Finnish ICUs were prepared for an increased need for ECMO, only one H1N1 patient was treated with it. In contrast to other studies (Davies et al. 2009; Chan et al. 2010; Patroniti et al. 2011; Roch et al. 2010), ARDS was not the indication. In addition to ECMO, other technologies were also available, but prone ventilation was the
most frequent rescue therapy for ARDS in ARF and for ARDS in H1N1. The use of prone ventilation increased in H1N1 patients, whereas ECMO was rare in both cohorts.

Although the effect of corticosteroids in ARDS is controversial (Meduri et al. 2009; Steinberg et al. 2006; Tang et al. 2009), most of the studies report corticosteroid use in approximately half of the H1N1 patients (Brun-Buisson et al. 2011; Dominguez-Cherit et al. 2009; Jain et al. 2009; Kim et al. 2011; Kumar et al. 2009; Martin-Loeches et al. 2011; Miller et al. 2010). In Finland more than 50% of treatments were given for indications described by the WHO guidelines (Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza 2010), but contradictory to the guidelines, the majority of ARDS patients received corticosteroids. In this study, mortality was similar regardless of corticosteroid treatment, although patients with corticosteroid treatment were more severely ill, and harmful effects have been reported previously. In hospitalized H1N1 patients, a trend towards higher mortality was detected in the group treated with corticosteroid (Xi et al. 2010). This agrees with a Korean study, where corticosteroid treatment was independently associated with increased 90-day mortality (Kim et al. 2011), and a French study where early corticosteroid therapy was associated with secondary pneumonia (Brun-Buisson et al. 2011).

**Zinc in ARF**

The low serum zinc levels found in ARF were most likely the result of an acute phase response. Acute illness (Craig et al. 1990), surgery (Fraser et al. 1989), and sepsis (Gaetke et al. 1997) lead to a fast decrease in serum zinc. In a research frame, zinc may have favourable effect in respiratory diseases (Bao et al. 2006; Knoell et al. 2009; Truong-Tran et al. 2000), however, the effects of zinc or depletion of zinc on respiratory infections is difficult to evaluate in clinical situations due to problems in measuring true zinc deficiency (Craig et al. 1990; King 1990). Low serum zinc levels in the acute phase cannot be directly interpreted as a need for zinc supplementation (Craig et al. 1990), and it may even be a beneficial response to prevent bacterial proliferation (Sugarman et al. 1982). Zinc supplementation in critically ill patients, however, has been shown to be associated with a nonsignificant reduction in mortality in aggregate data from 4 RCTs (Heyland et al. 2008). Beale and colleagues has shown faster organ dysfunction recovery with early enteral supplementation of key pharmaconutrients including zinc (Beale et al. 2008). The predictive value of zinc
demonstrated in paediatric severe sepsis (Wong et al. 2007) could not be shown in this study, however.

**Mortality**

The mortality of ARF was lower than in previous studies (Esteban et al. 2002; Esteban et al. 2008; Flaatten et al. 2003a; Lewandowski et al. 1995; Luhr et al. 1999; Vincent et al. 2002). The lack of exclusion criteria for certain patient cohorts or length of ICU stay (Brun-Buisson et al. 2004; Vincent et al. 2002), and shorter requirement for ventilator therapy (Esteban et al. 2002; Esteban et al. 2008; Lewandowski et al. 1995; Luhr et al. 1999) might cause the low mortality in this study. In patients treated with MV, mortality may vary according to case-mix of ARF. In the study of Esteban and colleagues, mortality was 31% for all patients, 22% for COPD, and 52% for ARDS (Esteban et al. 2002). Despite the fairly large section of short-term ventilator support, patients of this study were severely ill according to acute disease severity score and organ failure score, and 60% had an oxygenation impairment degree below the criteria of ALI (PF<300 mmHg, 40.0 kPa) at baseline.

The hospital mortality of ALI/ARDS (41%) was similar to most of the previous epidemiologic studies (Arroliga et al. 2002; Bersten et al. 2002; Brun-Buisson et al. 2004; Rubenfeld et al. 2005). The 90-day mortality was also comparable to results from other Scandinavian studies (Luhr et al. 1999). In RCTs with selected patient cohorts, mortality has been reported to be lower, 26-40% (Brower et al. 2004; Wiedemann et al. 2006; ARDS Network 2000). In ARDS, however, ICU mortality as high as 60% and 65% has been reported (Monchi et al. 1998; Roupie et al. 1999). The hospital mortality of ARDS has been reported to be 58% in Argentina and 61% in Scotland (Estenssoro et al. 2002). These higher mortalities may be due to studying only ARDS patients, however outcome differences between ALI and ARDS are contradictory. In the study of Luhr et al., mortality was similar in ALI and ARDS (Luhr et al. 1999). In contrast, the mortality of ALI, not reaching the severity of ARDS, has been recorded as lower (27% vs. 41% and 31% vs. 60%) (Roupie et al. 1999; Rubenfeld et al. 2005). In ARF, oxygenation was independently associated with 90-day outcome. Similar results were found during lung protective ventilation in ARDS in Ireland (Irish Critical Care Trials Group 2008) and in H1N1-related ARDS in Argentina (Estenssoro et al. 2010).
In contrast to ARDS (Bersten et al. 2002; Estenssoro et al. 2002; Valta et al. 1999; Vincent et al. 2003), the main cause of mortality in H1N1 is refractory hypoxaemia (Bai et al. 2011), and low PF is independently associated with mortality (Estenssoro et al. 2010). Although organ failures are common in H1N1 (Dominguez-Cherit et al. 2009; Kumar et al. 2009), a high SOFA score is not associated with as high risk of mortality as in other critically ill patients (Shahpori et al. 2011). Contrary to the first outcome report (Perez-Padilla et al. 2009), non-survivors in this and other studies during the on-going pandemic had other underlying health conditions (Donaldson et al. 2009; Jain et al. 2009). In future epidemics, commencement of antiviral medication without delay, at least in risk groups, is recommended based on less severe disease and risk of mortality during pandemic H1N1 (Chien et al. 2010; Dominguez-Cherit et al. 2009; Donaldson et al. 2009; Fuhrman et al. 2011; Jain et al. 2009; Louie et al. 2009; Viasus et al. 2011).

Age is a generally known risk factor for outcome in ARF and ARDS (Brun-Buisson et al. 2004; Hughes et al. 2003; Rubenfeld et al. 2005; Vincent et al. 2002). In patients receiving MV, age and length of MV has been associated with mortality (Combes et al. 2003; Feng et al. 2009). In a small study of elderly patients (≥80 years) who received MV for more than 3 days, survival was poor if the sum of age and length of MV exceeded 100 (Cohen et al. 1993). In this study, the effect of age alone was not evaluated because it is a component of the SAPS II score, which was independently associated with 90-day mortality.

**Long-term outcome and HRQOL**

One-year mortality was low in the present study, 35% in patients receiving MV for more than 24 hours, versus 56-65% for those over 48 hours MV (Chelluri et al. 2004; Douglas et al. 2002). Results differed from the study of Douglas et al. (Douglas et al. 2002), as mortality was similar regardless of length of ventilator therapy. The one-year survival of ARDS patients was, however, at the same level as estimated in the study of Angus and colleagues (Angus et al. 2001). Similarly, mortality did not change between 6 months and one year in ARDS (Angus et al. 2001). As in the previous Finnish study of ARDS (Valta et al. 1999), mortality did not markedly increase after hospital discharge.

Similar to ARDS (Orme et al. 2003; Schelling et al. 2000) and prolonged MV (Combes et al. 2003), the HRQOL in the present study was impaired compared with matched general
population. In the oldest age group however, the long-term survivors did not rate their HRQOL worse than age- and sex-matched population values. The selection of elderly patients with good pre-hospital functional status may explain the result, as poor pre-hospital functional status is associated with worse outcome (Chelluri et al. 2004; Garland et al. 2004; Hofhuis et al. 2007; Rivera-Fernandez et al. 2001). In addition, a relatively high proportion of elective postoperative patients may bias the result (Badia et al. 2001). In ARDS (Davidson et al. 1999a; Herridge et al. 2003; Schelling et al. 2000), as well as in general ICU patients, physiologic functioning is the most affected. Similarly, the proportion of severe problems in the present study was found in the dimensions of mobility and usual activities. Overall, the percentage of patients with severe problems was low.

Long-term effects of H1N1 are scarce and unfortunately not yet studied in the Finnish H1N1 cohort. After 3 months, ground glass opacities in chest X-rays, and reduced diffusion capacities have previously been found in H1N1 survivors, however (Bai et al. 2011).

**Cost and cost-utility**

No uniformly accepted gold standards for QOL measure, calculation method, or time scale for calculation of QALY in ARF patients exist. In the present study, the average cost of a hospital survivor (€20,739) was lower than the cost of a surviving sepsis patient in Finland (€32,563) (Karlsson et al. 2009), but comparable to medical ICU survivors in Germany (€14,130) (Graf et al. 2005), and mixed ICU patients in Norway (€14,223) (Flaatten et al. 2003b). No exact limit for cost-effective treatment has been set, but in the United Kingdom an intervention of £5,000-15,000 cost per QALY is unlikely rejected (Rawlins et al. 2004), but even a cost of $100,000 per QALY has been considered elsewhere (Laupacis et al. 1992). Compared to these figures, the average cost per estimated QALY (€1,391) was reasonable, and also remained at €10,000 in octogenarians. The cost per estimated QALY is comparable to €684 per year of survival reported from Norway (Flaatten et al. 2003b). In contrast, clearly higher cost per QALY (>€100,000) has been estimated for patients with prolonged MV (Cox et al. 2007b), and severe ARF (Hamel et al. 2000), when predicted one-year mortality is greater than 50%. High-technology treatment such as ECMO for severe ARDS is recently suggested to be cost-effective ( Peek et al. 2009), although contradictory opinions have been presented (Moran et al. 2010).
Strengths and limitations of the study

The strength of the FINNALI study is the nearly total nationwide coverage of the studied subjects. In the study of ARF, ICUs covering 97% of the adult population participated in this study. While the university level referral centre of the two non-participating ICUs was involved, it is likely that the coverage of the most severely ill patients was satisfactory. The observational nature of these patient cohorts is both a strength and limitation. This study gave a comprehensive picture of underlying conditions, treatments, resource use, and outcome for a wide range of patients with ARF treated in ICUs. Unfortunately, characteristics and incidence of ARF patients treated in emergency departments and other locations outside ICUs were not covered. The observational nature of these patient cohorts is both a strength and limitation.

Some other limitations of the FINNALI study (I) warrant mention. The eight-week study period in spring can be criticized for being susceptible to seasonal variation of ARF. Furthermore, the definition of ARF used in this study, more than 6 hours of ventilator support, is not in general use. Thus, direct comparisons with previous studies must be made with prudence. The limit of 6 hours may have increased the number of postoperative patients with a probability of a more favourable outcome, but also the most severely ill patients dying before the more commonly used time limit of 24 hours was included in the study. The short time limit was required to ascertain all of the resources (e.g., beds) required for patients requiring ventilator support. In addition, the limit of 6 hours enabled the evaluation of treatments, and biomarkers early in the course of ARF and ALI/ARDS. Despite the good amplitude of the study, the number of the most severely ill ARF patients, namely ARDS patients, was low in further analysis. Moreover, ventilator and other treatments were assessed on a daily basis without exact records of their use in hours.

In Study II, the number of HRQOL responses was only 47% for the one-year survivors, and thus, may affect the overview of HRQOL of long-term survivors. In addition, the evolution of the health index at different time points during the year was not possible, and the mean cost of care was calculated using average cost per TISS point and cost per hospital day in Finnish ICUs. The use of TISS score may have overlooked the use of expensive interventions. Actual cost per patient during the hospital stay, as well as the post discharge costs, was not available. Estimations of the HRQOL assessment for QALY calculations were
made due to moderately low HRQOL response rate. The assumption of non-survival without ICU admission for cost-utility analysis may not apply for all patients, however, acute severity illness score of the study patients indicated critical illness in the ARF cohort.

In Study III, the lack of serial measurements of serum zinc was a limitation of the study. Simultaneous serum albumin and CRP analysis would have improved the interpretation of serum zinc levels.

In the study of H1N1 (IV), all ICUs responsible for treating these patients, including paediatric patients, participated in the study. The low mortality and number of H1N1 patients was not sufficient for propensity score analysis.

**Clinical implications and future perspectives**

This study gave a comprehensive view of the use of ventilator treatments in Finnish ICUs, however, for epidemiologic comparison as well as for intervention studies, consensus definition of ARF, MV, and ALI/ARDS are needed. A sufficiently-long study period would take into account the possible seasonal variation of ARF, but also enable sufficiently large subgroups for treatment and outcome comparison. An update of the epidemiology of ARF is necessary for future preparedness of epidemics, pandemics, and other catastrophes causing sudden increases in critically ill patients.

The revision of the ALI/ARDS criteria to better reflect the severity of respiratory impairment is needed. Accordingly, previous studies of incidence and mortality need to be re-evaluated. It remains to be seen in further studies if simple patient-specific characteristics could be used for ventilator settings instead of fixed low Vt. The prospect of extracorporeal techniques, for facilitating more lung-protection, has been speculated, but controlled clinical studies have not been performed.

Further development of a reliable system for routine recording for both standard and extensive therapies, and diseases, and HRQOL related to ICU treatment, would be valuable. In this study, mortality did not increase between six months and one-year follow-up, thus a six-month follow-up, regarding mortality, seems sufficient in critically ill patients. Studies evaluating HRQOL however, need to be extended beyond 6-12 months. Assessment of
physical and pulmonary well-being might give a wider perspective for understanding long-term HRQOL and outcomes.

A more precise and standardized method for cost calculation together with long-term outcome and HRQOL is necessary for cost-utility analysis. The costs should be evaluated in a wider concept comprising all pre- and post hospitalization charges, effect on personal and social expense, and impact on care givers and other social effects. Larger patient cohorts could make HRQOL and cost-utility comparison possible between different age groups, aetiology of critical illness, and treatments.
7 CONCLUSIONS

Based on these studies the following conclusions can be drawn:

1. The incidence of ARF in the ICU was higher, but the incidence of ALI/ARDS was lower, than previously published. The 90-day mortality of ARF was 31%. Lung protective ventilation with avoidance of high airway pressures was applied, but tidal volumes per predicted body weight were higher than recommended. Prone position was used for severe hypoxemic ARF. Other respiratory rescue therapies were infrequent.

2. One-year mortality of ARF was 35%. HRQOL one-year after ARF was lower than in sex- and age-matched general population. Cost per hospital survivor and lifetime cost-utility were reasonable.

3. Serum zinc had a weak correlation with admission and maximal SOFA score, but did not differ according to the respiratory SOFA score. Serum zinc has no value in predicting 30-day mortality.

4. Age-related incidence of H1N1 was similar to that previously reported. Oxygenation impairment was severe. Corticosteroid treatment and NIV were frequently used. Respiratory rescue techniques other than prone ventilation were rare. Hospital mortality of H1N1 was 8%.
8 ACKNOWLEDGEMENTS

This research project would not have been possible without the support of many people.

I wish to express my great gratitude to my supervisors Docent Ville Pettilä and Docent Tero Varpula. I greatly appreciate your expertise in research and clinical work in intensive care. Your encouragement, guidance and help made this dissertation possible.

I sincerely thank Professor Per Rosenberg for his advice and interest in my thesis.

I thank the official reviewers Docent Pirkko Brander and Docent Ari Uusaro for constructive comments and valuable remarks, which certainly improved the dissertation.

I am really impressed with the quick and expert language editing of Dr Jennifer Rowland.

I owe my warmest thanks to my coworker Marjatta Okkonen, MD, for sharing the ups and downs of this study project. I also express my sincere thanks to all of my coauthors Professor Esko Ruokonen, Professor Tero Ala-Kokko, Docent Ilkka Parviainen, Docent Jyrki Tenhunen, Docent Juha Pettilä, Docent Raili Suojaranta-Ylinen, Sari Karlsson, Ph.D, Vesa Lund, Ph.D, Matti Reinikainen, MD, and Kari Saarinen, MD, for their invaluable support and contributions to this work.

I am tremendously grateful to all study investigators and nurses for their hard work in all participating ICUs. Collaboration with the Finnish ICUs has been pleasant and productive. My warmest thanks goes to study nurses Raija Niemi, Sari Sutinen, Leena Pettilä, and Eeva-Liisa Piiparinen of Meilahti Intensive Care Unit for dedication to the FINNALI project.

I thank Professor Markku Hynynen for giving me the opportunity to work in Jorvi Hospital during the FINNALI-study, and Docent Anne Vakkuri, Docent Anne Kuitunen, and Elina Riihioja, MD, for the arrangeents to work in Meilahti Intensive Care Unit, which got me acquainted with the swineflu epidemic and facilitated study IV.
I wish to express my sincerest gratitude to Ulla-Maija Lehtonen, MD, the former head of Department of Anaesthesiology at Peijas Hospital, for recruiting me there. Your governance and attitude towards employees, as well as patients, was admirable. Year after year you encouraged me to expand my anaesthesiologic knowledge from the scientific aspect, and finally I got involved with this project.

I am extremely grateful to all present and former anaesthetist colleagues of Peijas Hospital for support, advice, and understanding over these years. I also want to thank all other colleagues with whom I have had the pleasure to work with.

I am grateful to all my friends and colleagues, in particular Marjut for conversations during our long runs in the woods and fells, and Sini and her family for memorable orienteering and skiing vacations.

Anu, I most greatly appreciate your friendship and support during this project.

I am deeply grateful to my father Pekka and my late mother Yu-Yen for love and support, as well as showing me the way to combine scientific research with everyday life. Many thanks to my brother Eric and sister Susan and their families for always being around when needed. I also want thank Aulis and Sinikka for the opportunities to spend writing and other vacations in their full-service country house.

Most of all, I owe my warmest gratitude to Ari-Pekka for endless support, patience and encouragement during these years.

Financial support from the Helsinki University Central Hospital EVO grants (TYH 7250 and TYH8240), the Instrumentarium Science Foundation, and the Finnish Society of Intensive Care, is gratefully acknowledged. The financial support of the National Institute for Health and Welfare made the study of influenza A(H1N1) ICU patients possible.

Helsinki 17.03.2012

Rita Linko
9 REFERENCES


83


Confalonieri M, D’Agaro P and Campello C (2010b) Corticosteroids do not cause harmful increase of viral load in severe H1N1 virus infection. Intensive Care Med 36: 1780-1781


Davidson TA, Caldwell ES, Curtis JR, Hudson LD and Steinberg KP (1999a) Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. JAMA 281: 354-360


results of a randomized phase II trial. Inhaled Nitric oxide in ARDS Study Group. Crit Care Med 26: 15-23


Flaatten H, Gjerde S, Guttormsen AB, Haugen O, Hoivik T, Onarheim H and Aardal S (2003a) Outcome after acute respiratory failure is more dependent on dysfunction in other vital organs than on the severity of the respiratory failure. Crit Care 7: R72-R77


88


92


inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. Am J Respir Crit Care Med 165: 983-991


99


http://www.elso.med.umich.edu/Guidelines.html