# Community-Acquired Pneumonia among Adults

## Studies on selected factors which associate with severe disease and risk of death

**Kristján Godsk Rögnvaldsson**

**Thesis for the degree of Philosophiae Doctor**

**Supervisor and Tutor:**
Magnús Gottfreðsson Professor

**Co-supervisor:**
Agnar Bjarnason Assistant Professor

**Doctoral committee:**
Aðalsteinn Guðmundsson, Inga Sif Ólafsdóttir and Kristján Orri Helgason

June 2023

UNIVERSITY OF ICELAND
SCHOOL OF HEALTH SCIENCES
FACULTY OF MEDICINE

# Samfélagslungnabólga meðal fullorðinna

## Rannsóknir á völdum þáttum sem tengjast horfum og lifun

**Kristján Godsk Rögnvaldsson**

**Ritgerð til doktorsgráðu**

**Leiðbeinandi og umsjónarkennari:**

Magnús Gottfreðsson Prófessor

**Meðleiðbeinandi:**

Agnar Bjarnason lektor

**Doktorsnefnd:**

Aðalsteinn Guðmundsson, Inga Sif Ólafsdóttir and Kristján Orri Helgason

2023

UNIVERSITY OF ICELAND
SCHOOL OF HEALTH SCIENCES
FACULTY OF MEDICINE

ORCID: 0000-0003-4852-8114

Reykjavik, Iceland 2023

# Ágrip

**Inngangur.** Þrátt fyrir að næstum öld sé liðin frá uppgötvun penisillíns og að langt sé liðið síðan bólusetningar hófust gegn *Streptococcus pneumoniae* (pneumokokkum), algengasta orsakavaldi lungnabólgu fullorðinna, er enn um algengan og alvarlegan sjúkdóm að ræða. Með hækkandi aldri verður greining lungnabólgu oft erfiðari; einkenni verða gjarnan ósértækari, erfiðara er að ná góðum myndum af lungum og lengri tíma getur tekið fyrir íferðir í lungum að verða sýnilegar á myndrannsókn. Þrátt fyrir þetta er skortur á rannsóknum sem bera saman þá sem eru með klínísk einkenni lungnabólgu en án greinilegra íferða á lungnamynd við hina sem eru með samfélagslungnabólgu (klínísk einkenni ásamt staðfestri íferð á lungnamynd). Sumar fyrri rannsóknir hafa bent til þess að gjöf asetýlsalicýlsýru (ASA) geti dregið úr dauðsföllum í kjölfar lungnabólgu en aðrar ekki. Meinvaldar lungnabólgu geta skyndilega breyst eins og gerðist í heimsfaraldri SARS-CoV-2 og mikilvægt að bregðast við og lýsa nýjum sjúkdómum, s.s. þeim sem meinvaldurinn veldur, áhættuþáttum og mögulegri meðferð. Upplýsingar skortir um tengsl kæfisvefns við tilurð alvarlegar COVID-19 lungnabólgu, þar sem margir áhættuþættir sjúkdómanna eru sameiginlegir er mikilvægt að leiðrétta fyrir þeim.

**Markmið**. Í fyrsta lagi að bera saman tilfelli með klínísk einkenni lungnabólgu en án greinilegra íferða við tilfelli samfélagslungnabólgu með sérstaka áherslu á dánartíðni (Grein I). Í öðru lagi að kanna hvort ASA tengdist bættri lifun tilfella sem greindust með pneumokokkalungnabólgu (Grein II). Í þriðja lagi að kanna hvort kæfisvefn tengdist alvarlegri COVID-19 lungnabólgu (Grein III).

**Efni og aðferðir.** Þrjú aðskilin gagnasöfn voru notuð. Í fyrsta lagi var gögnum safnað um tilfelli sem lögðust inn með grun um lungnabólgu á framskyggnan máta á eins árs tímabili 2018-2019 (grein 1). Í öðru lagi var notast við afturskyggnt gagnasafn allra staðfestra ífarandi pneumókokkasýkinga 1975-2019 á Íslandi. Í þriðja lagi var gagnasafn um öll tilfelli með COVID-19 á Íslandi árið 2020 notað og upplýsingar frá Landspítala um kæfisvefnstilfelli.

***Grein 1.*** Lógistísk aðhvarfsgreining var notuð til að meta dánartíðni við 30 daga eftir leiðréttingu fyrir aldri, kyni, Charlson stigun á sjúkdómsbyrði og fyrir 1 árs dánartíðni var einnig leiðrétt fyrir reykingum, búsetu á hjúkrunarheimili og tilvist meðferðartakmarkana. Framkvæmdar voru endurteknar tilreiknanir á gagnaeyðum, í 8.5% tilfella vantaði upplýsingar um reykingar.

***Grein 2.*** Öll tilfelli 1975-2019 á Íslandi sem höfðu jákvæða blóðræktun með *S. pneumoniae* og staðfesta lungnabólgu samkvæmt myndrannsókn af lungum

voru í rannsóknarhópnum. Aðalsamanburðurinn fólst í að bera saman lifun við 30-daga, 90-daga og 1-ár með því að notast við líkindaskorsvigtun, eftir því hvort sjúklingarnir voru að taka ASA við greiningu sýkingarinnar.
***Grein 3.*** Öll tilfelli sem greindust með COVID-19 á árinu 2020 voru í úrtakinu, tilfelli sem höfðu farið í svefnskimun og reyndust með ≥5 öndunarhlé á mínútu voru skilgreind sem kæfisvefnstilfelli. Endapunktur rannsóknarinnar var dauði eða sjúkrahúsinnlögn. Framkvæmdar voru lógistískar aðhvarfsgreiningar og líkindaskorsvigtun, fyllt var í gagnaeyður með endurteknum tilreikningum.

**Niðurstöður.**
***Grein 1.*** Klínísk einkenni lungnabólgu en án greinilegra íferða var um helmingi óalgengari innlagnarástæða en samfélagslungnabólga. Tilfelli með samfélagslungnabólgu voru líklegri til að mælast með hækkaðan líkamshita, hærra CRP, greinast með *S. pneumoniae* og að fá sýklalyfjameðferð en ólíklegri til að greinast með sýkingu af völdum öndunarfæraveira. Leiðrétt líkindahlutfall dauða þeirra sem voru með klínísk einkenni lungnabólgu en án íferða miðað við þá sem voru með samfélagslungnabólgu innan 30 daga var 0.86 (95% öryggisbil (ÖB) 0.40-1.85) en 1.25 (95% ÖB 0.81-1.95) við 1 ár.
***Grein 2.*** Tilfellin sem voru að taka ASA við innlögn voru ólík tilfellum sem voru ekki að taka lyfið þegar undirliggjandi sjúkdómar, reykingar, áfengisfíkn og aldur voru skoðuð. Ásættanleg leiðrétting náðist með líkindaskorsvigtun. ASA tilfelli höfðu betri lifun á tímabilinu 0-7 dögum eftir sýkingu (Hættuhlutfall (HH), 0.42, 95% CI 0.19-0.92), en ekki milli 7-30 daga eftir greiningu (HH 1.08, 95% CI 0.46-2.55). Meðal HH yfir 1 ár sýndi betri lifun ASA tilfella en þeirra sem ekki voru á lyfinu (HH 0.48, 9%CI 0.31-0.75).
***Grein 3.*** COVID-19 tilfelli sem höfðu kæfisvefn voru líklegri til að þurfa innlögn eða deyja en tilfelli sem voru með COVID-19 en ekki kæfisvefn í fullleiðréttu módeli (2.0 95% CI 1.2-3.2). Áhrifin voru sterkari í minna leiðréttum módelum. Næmisgreiningar sýndu svipuð áhrif.

**Ályktanir.** Klínísk einkenni lungnabólgu án íferða er algeng ástæða innlagna og þrátt fyrir að íferð sjáist ekki við myndrannsókn var dánartíðnin ekki marktækt lægri. Notkun á ASA tengist lægri dánartíðni þeirra sem greinast með ífarandi pneumókokkalungnabólgu en þörf er á rannsóknum sem leiðrétta fyrir mögulegri skekkju heilbrigðari notenda. Kæfisvefn er áhættuþáttur fyrir sjúkrahúsinnlögn eða dauða meðal þeirra sem greinast með COVID-19 að teknu tilliti til bjögunarþátta.

**Lykilorð:**
Samfélagslungnabólga, lýðgrunduð rannsókn, lifun, asetýlsalicýlsýra, COVID-19

# Abstract

**Introduction.** Despite almost a century passing since the discovery of penicillin and many years since the initiation of vaccinations against *Streptococcus pneumoniae*, this principal cause of pneumonia among adults, pneumonia is still a common and serious disease. Increasing age often complicates the diagnosis of pneumonia with fewer specific symptoms, difficulty obtaining radiographs of sufficient quality and sometimes a lag in infiltrates becoming visible. Studies are lacking comparing cases that have symptoms of pneumonia without radiographic confirmation of an infiltrate (SPWI) with those that have symptoms of pneumonia with radiographic confirmation (community-acquired pneumonia, CAP). Some earlier studies indicated that acetylsalicylic acid (ASA) decreased mortality following pneumonia, but others did not. Pneumonia etiology can suddenly change, as observed recently in the SARS-CoV-2 pandemic, highlighting the importance of timely studies on new or re-emerging pathogens and diseases, risk factors and possible treatments. Information is lacking on the association of obstructive sleep apnea (OSA) with severe COVID-19.

**Goals.** The first goal was to compare clinical characteristics and mortality of SPWI cases to CAP cases (Paper I). Secondly, to examine if ASA was associated with improved survival among those with invasive pneumococcal pneumonia (Paper II). Lastly, to assess if OSA was associated with severe COVID-19 pneumonia (Paper III).

**Methods.** Three different datasets were used. In the first paper we performed a prospective study on cases hospitalized with suspected pneumonia over a one-year period (2018-2019). In the second paper we used a retrospective dataset on all invasive pneumocccal infections 1975-2019 in Iceland. In the third paper we used a dataset on all COVID-19 infections in Iceland in the year 2020 and information on cases from a sleep study from Landspitali- The National University Hospital of Iceland (LUH).

***Paper 1.*** For analysis of mortality at 30 days logistic regression was used adjusting for age, sex and Charlson comorbidity index (CCI); for the 1-year outcome analysis, do not resuscitate directive, smoking, and nursing home residence were added. Multiple imputations were performed on missing data.

***Paper 2.*** All adult cases in Iceland 1975-2019 with a positive blood culture for *S. pneumoniae* along with symptoms and signs of pneumonia were included. The main outcome was survival at 30 and 90 days and at 1 year comparing those using ASA to those not using ASA, using Cox regression with inverse probability weighting for covariate adjustment.
***Paper 3.*** All cases with a COVID-19 diagnosis in 2020 were included, cases with an apnea-hypopnea index (AHI) ≥ 5 per minute were defined as OSA. A combined outcome of hospitalization or death was used as the main outcome. Logistic regression and propensity score weighting were used for adjustment, multiple imputations were performed on missing data.

**Results**

***Paper I.*** The incidence of SPWI requiring hospital admission was one half of that of CAP. CAP cases more frequently had fever (≥38°C), higher CRP value, *S. pneumoniae* as microbial etiology and more frequently received antibiotic therapy, but cases in the CAP group less frequently had a respiratory virus identified. The adjusted odds of mortality for SPWI cases compared with CAP within 30 days was 0.86 (95% confidence interval (CI) 0.40-1.85) but 1.25 (95% CI 0.81-1.95) at 1 year.
***Paper II.*** There were differences between the groups taking ASA or not in terms of underlying illnesses, smoking, alcoholism, and age. After propensity score weighting an accepatable balance was reached. After adjustment, ASA cases had a better survival 0-7 days after diagnosis (HR 0.42, 95% CI 0.19-0.92), but not between 7-30 days (1.08 95% CI 0.46-2.55). Average HR over 1-year showed a better survival for the ASA cases compared to those not on ASA (HR 0.48, 9%CI 0.31-0.75).
***Paper III.*** COVID-19 cases with OSA were more likely to need hospitalization or die than cases that had COVID-19 but without a prior OSA diagnosis in a fully adjusted model (2.0 95% CI 1.2-3.2). The association was stronger in models which adjusted for fewer comorbidities. The effects held in sensitivity analyses.
**Conclusion.** SPWI is a common reason for hospitalization and despite lacking radiographic infiltrates, mortality was not much lower than in CAP. The use of ASA is associated with lower mortality among those diagnosed with invasive pneumococcal pneumonia, but studies adjusting for healthy user bias are needed. OSA is a risk factor for hospitalization or death among those diagnosed with COVID-19.

**Keywords:** Community-acquired pneumonia, population-based, survival, acetylsalicylic acid, COVID-19

# Acknowledgements

First, I want to thank my supervisor and tutor Magnús Gottfreðsson for providing me with a unique opportunity, this Ph.D. project. His guidance through the winding Ph.D. path, which includes tackling multiple setbacks, has been invaluable. His positive and solution-oriented mindset have been of critical importance to this work. I also want to thank Agnar Bjarnason, the co-supervisor of the project, for the support and the fun and fruitful discussions. I want to thank the rest of the PhD committee, Inga Sif Ólafsdóttir for reviewing pneumonia cases with uncertain chest radiography results, Kristján Orri Helgason for his detailed reviews of manuscripts and recommendations regarding pathogen diagnosis. Aðalsteinn Guðmundsson for his important recommendations regarding the planning of the study and the detailed recommendations regarding the older adults. Specially, I want to thank Ubaldo Benitez Hernandez, statistician at Landspitali, for all his great help regarding statistical matters during the course of my Ph.D.. I also want to thank all the other Ph.D. students at the research facility at Landakot and the staff at the Landspitali Library located at Rauðarárstígur (at that time) for great coffee break talks. The staff at the emergency wards at Landspitali were very accomodating and helpful in regards to patient recruitment, for that I want to thank them. My collaborators in the published studies I want to thank for great collaboration, I want to specifically thank Vilhjálmur Steingrímsson, Elías Sæbjörn Eyþórsson and Össur Ingi Emilsson.

I want to thank those that took part in the collection of data or managed the datasets that some of my work is based on. Elías Eyþórsson, who managed the COVID-19 datasbase of patients. Helga Erlendsdóttir, for collecting and managing the unique nationwide dataset of invasive infections at the department of Clinical Microbiology and Virology at LUH. I also want to thank Hörður Tryggvi Bragason, Karl Kristinsson and Sandra Halldórsdóttir, for collecting clinical information from the medical records of patients with invasive pneumococcal disease.

I want to thank my family, my mom and dad for their constant support and encouragement throughout the years, and my siblings for always rooting for me. As well as my friends Vilhjálmur and Andri, grill is chill, thank you for all your help and good humor.

Finally, but not least, I want to thank my life partner Salvör for her unfaltering belief in me during the whole Ph.D. process and for her immense help, both directly related to the research and all the other help. I am not sure our baby Stígur helped much, but he has filled life with pure joy the last months and for that I am very grateful.

I would also like to thank all the institutions that have supported this project and made this project possible:

- The Icelandic Centre for Research (Rannís, grant number 217716-051)
- The Doctoral Grants of The University of Iceland Research Fund
- The Scientific Fund of Landspitali—The National University Hospital of Iceland
- The Scandinavian Society for Antimicrobial Chemotherapy Foundation (SSAC Foundation)
- The Foundation of St. Josef´s Hospital
- The Geriatric council of Iceland (Öldrunarráð Íslands)

# Contents

# List of abbreviations

**ACE=Angiotensin-converting enzyme**

**AHI=Apnea-hypopnea index**

**APACHE II= Acute physiology and chronic health evaluation II**

**ASA=Acetylsalicylic acid**

**ATE=Average treatment effect**

**ATT=Average treatment effect of the treated**

**AUROC= Area under the receiver operating characteristic**

**BALF= Bronchoalveolar lavage fluid**

**CAP=Community-acquired pneumonia**

**CCI=Charlson comorbidity index**

**CI=Confidence interval**

**COPD=Chronic obstructive pulmonary disease**

**COVID-19= Coronavirus disease 2019**

**cPAP= Continuous positive airway pressure**

**CT=Computed tomography**

**CXR=Chest x-ray**

**DM=Diabetes mellitus**

**DNR=Do not resuscitate**

**ECOG= Eastern Cooperative Group performance status**

**HAP=Hospital-acquired pneumonia**

**HIV=Human immunodeficiency virus**

**HR=Hazard ratio**

**ICD=International Classification of Diseases**

**IPD=Invasive pneumococcal disease**

**LRT=Lower respiratory tract**

**LRTI=Lower respiratory tract infection**

**LUH=Landspitali- The National University Hospital of Iceland**

**NAAT= Nucleic acid amplification test**

**PCR= Polymerase chain reaction**

**PET= Positron emission tomography**

**PCV=Pneumococcal conjugate vaccines**

**PPV= Pneumococcal polysaccharide vaccine**

**PSI=Pneumonia severity index**

**qSOFA= quick sepsis related organ failure assessment**

**SPWI=Symptomatic pneumonia without infiltrate**

**SSAC=Scandinavian Society for Antimicrobial Chemotherapy**

**OSA=Obsctructive sleep apnea**

**URT=Upper respiratory tract**

**USA=United States of America**

**WHO=World Health Organization**

# List of figures

# List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-III):

I. Rögnvaldsson, K. G., Bjarnason, A., Ólafsdóttir, I. S., Helgason, K. O., Guðmundsson, A., & Gottfreðsson, M. (2023). Adults with symptoms of pneumonia: a prospective comparison of patients with and without infiltrates on chest radiography. Clinical Microbiology and Infection, 29(1),108.e1-108.e106. doi:https://doi.org/10.1016/j.cmi.2022.07.013

II. Rögnvaldsson, K. G., Bjarnason, A., Kristinsson, K., Bragason, H. T., Erlendsdóttir, H., Þorgeirsson, G., & Gottfreðsson, M. (2022). Acetylsalicylic acid use is associated with improved survival in bacteremic pneumococcal pneumonia: A long-term nationwide study. Journal of Internal Medicine, 292(2), 321-332. doi:https://doi.org/10.1111/joim.13485

III. Rögnvaldsson, K. G., Eyþórsson, E. S., Emilsson, Ö. I., Eysteinsdóttir, B., Pálsson, R., Gottfreðsson, M., Guðmundsson, G., & Steingrímsson, V. (2021). Obstructive sleep apnea is an independent risk factor for severe COVID-19: a population-based study. Sleep, 45(3). doi:https//doi.org/0.1093/sleep/zsab272

In addition, some unpublished data may be presented:

All papers are reprinted by kind permission of the publishers.

# Declaration of contribution

Paper I. Kristján Godsk Rögnvaldsson (KGR), Magnús Gottfreðsson (MG) and Agnar Bjarnason (AB) conceived and planned the study. KGR screened participants, obtained consent, clinical information and respiratory samples and went through medical records for follow-up information. Inclusion criteria was reviewed by Inga Sif Ólafsdótir, AB and KGR. KGR performed the statistical analyses. Writing of the paper was done by KGR and MG. All the authors reviewed and edited the final manuscript.

Paper II. KGR, MG, AB and Guðmundur Þorgeirsson (GÞ) conveived and planned the study. Helga Erlendsdóttir (HE), Karl Kristinsson (KK), Hörður Tryggvi Bragason (HTB) and KGR obtained data from medical records. Statistical analyses were performed by KGR. Writing of the paper was done by MG and KGR and all the authors contributed to editing and reviewing to the final paper.

Paper III. Vilhjálmur Steingrímsson (VS) and KGR came up with the original study plan, Elías Sæbjörn Eyþórsson (ESE) and Össur Ingi Emilsson (ÖIE) contributed greatly to the plan. ESE managed the COVID-19 database. KGR and VS went through medical records of all patients that had gone through a sleep analysis at LUH. Statistical analyses were performed by ESE, VS and KGR. Writing of the original draft of the article was done by KGR, VS, ESE and ÖIE, all the study group edited and reviewed the final manuscript.

# 1 Introduction

## 1.1 Introduction to pneumonia

Like many other medical terms pneumonia is derived from old Greek, roughly translated it means lung illness (Sattar & Sharma, 2021). According to the World Health Organization (WHO): “Pneumonia is a form of acute respiratory infection that affects the lungs” (World Health Organization, 2021). Although, non-infectious pneumonia exists, it is much less common (Waterer, 2021), and is not the focus of this thesis. According to the Global Burden of Disease study, lower respiratory tract (LRT) infections, including pneumonia, led to the loss of 2.4 million lives in 2016 (Troeger et al., 2018). Historically bacteria, especially *Streptococcus pneumoniae* (pneumococci), have been considered the most important cause of pneumonia globally; late in 2019 SARS-CoV-2 emerged and by March 2020 it had been declared a pandemic by WHO with viral pneumonia manifesting as its most severe form of illness (P. Zhou et al., 2020; Zhu et al., 2020). Three years later SARS-CoV-2 is still a very important pneumonia pathogen throughout the world (Hannah Ritchie, 2020; World Health Organization, 2022).

Pneumonia is commonly divided into two groups depending on the origin of the infection: hospital-acquired and community-acquired, with the latter being more common (Torres & Rello, 2010). Hospital-acquired pneumonia (HAP) is usually defined as pneumonia that starts more than 48 hours after admission to a hospital and community-acquired pneumonia (CAP) an infection that occurs in non-hospitalized patients or patients that have not recently been hospitalized (Corrado et al., 2017; Jain et al., 2015). The reason for this categorization lies in important differences in terms of microbial etiology and susceptibility and therefore optimal empirical treatment (Tschernig, 2016; van Vught et al., 2016). An overwhelming majority of pneumonia cases, whether community-acquired or not, are caused by pathogens arriving through the upper respiratory tract (URT) (Waterer, 2021). From the early 2000s to the early 2010s the literature also included a hybrid category, i.e. patients that were not hospitalized but were in frequent contact with the healthcare system, termed healthcare-associated pneumonia. Adjusting for other factors, this third group turned out to be a poor predictor of resistant pathogens and mortality and was therefore made redundant (Chalmers et al., 2013; Jones et al., 2015).

The disease progress of pneumonia is influenced by a combination of host, pathogen, and environmental factors. This includes the direct pathogenicity of the pathogen combined with local and systemic host responses activated upon infection (Chiotan & Chiotan, 2014; Hippenstiel et al., 2006; Quinton et al., 2018; M. I. Restrepo & Reyes, 2018; Waterer, 2021). The pathology of pneumonia usually includes inflammation of alveoli, bronchioles and the lung interstitium (Waterer, 2021). Occasionally lung complications of pneumonia ensue, e.g., empyema or pleural effusion (C. Cillóniz et al., 2012; Waterer, 2021).

Risk factors for pneumonia include chronic obstructive pulmonary disease (COPD), cardio- and cerebrovascular disease, dementia, Parkinson's, epilepsy, dysphagia, malignancies, immunosuppression, HIV, diabetes mellitus (DM), asthma, chronic kidney disease or chronic hepatic disease (Koivula et al., 1994; Torres et al., 2013a; Wong & Evans, 2017). Modifiable risk factors include smoking, air pollution, alcohol overuse, malnutrition, poor oral and dental hygiene and close contact with children (Pirozzi et al., 2017; Torres et al., 2013a; Z. Zhang et al., 2017). Indoor air pollution from burning of biomass increases the risk of pneumonia in children by around 80% (Dherani et al., 2008).

Pneumonia most commonly presents with cough (with or without production of sputum), fever, chest pain, shortness of breath, shaking, chills or sweating. With increasing age, the specificity of these classic presenting symptoms decreases and delirium, falls and loss of appetite become increasingly common (Agnar Bjarnason et al., 2018a; Rothberg, 2022; Takada et al., 2017; Yoshikawa & Marrie, 2000).

This thesis will from now exclusively focus on community-acquired pneumonia among adults.

## 1.2 Pneumonia diagnosis

Optimal empirical treatment depends on accurate diagnosis. Even though specific signs or symptoms have been shown to be unreliable in diagnosing pneumonia, using the overall clinical picture is a time-honored approach to making the diagnosis (Ebell et al., 2020; Hill et al., 2019; J. P. Metlay et al., 1997a; Rothberg, 2022). Nevertheless, no globally recognized definition of pneumonia exists (Mackenzie, 2016), which means studies conducted on this common problem are not always directly comparable. It also means constructing guidelines from available studies is difficult. Current guidelines recommend diagnosing pneumonia based on symptoms and or signs and that

pneumonia is confirmed with a radiographic examination (Hill et al., 2019; Lim et al., 2009; Joshua P. Metlay et al., 2019; NICE, 2019). Most guidelines do not specify which or how many symptoms are required to make the diagnosis. Older adults have fewer and less specific symptoms than younger patients when presenting with pneumonia (Marrie, 2000; J. P. Metlay et al., 1997b). This makes pneumonia diagnosis among older adults especially challenging.

Additionally, guidelines on CAP management in hospital settings commonly rely on studies that are highly selective, excluding large groups of immunocompromised patients and patients without an infiltrate on radiography (Lim et al., 2009; J. P. Metlay et al., 1997a; Joshua P. Metlay et al., 2019). If guidelines are to be applicable to most patients presenting to hospitals with a possible pneumonia, they must be based on studies representative of that population. Excluding patients receiving common immunosuppressive therapy makes studies and thus guidelines based on these studies less representative of the population being managed by clinicians. This is of increasing concern because of the growing number of older adults and immunosuppressed individuals in the last decades in many countries (Joshua P. Metlay et al., 2019; Wallace et al., 2021; World Health Organization, 2015).

### 1.2.1 Coding of pneumonia

Many retrospective pneumonia studies identify cases using the International Classification of Diseases –ninth (ICD-9) or tenth revision (ICD-10) (Azmi et al., 2016; Gupta et al., 2019; Marshall et al., 2018; Marcos I. Restrepo et al., 2010; Szakmany et al., 2021; Trotter et al., 2008). Local traditions regarding diagnostic coding can influence the cohort produced by such an approach. The overall sensitivity of ICD-9-CM codes for diagnosing any pneumonia has been reported at 72% and the specificity at 80% (van de Garde et al., 2007). However, the sensitivity for specific pathogens has a wide range of 14-96% depending on the pathogen (Higgins et al., 2020; van de Garde et al., 2007). Similar results have been noted for the ICD-10 diagnostic codes, with a sensitivity of 80% and specificity of 84% for overall pneumonia diagnosis (Henriksen et al., 2014). An important downside to the ICD-9 and ICD-10 is that they do not distinguish between HAP and CAP.

The exact codes for pneumonia in the ICD-10 are J12-J18, however a poor quality radiographic study or the lack of such a study means that some cases with pneumonia could be miscoded as other types of acute LRT infections section, J20-J22 (Mackenzie, 2016). Audits or retrospective studies are limited by the radiographs obtained at the time of the disease; meaning there is no

way to assess if these cases in fact were pneumonia if the only radiographs obtained were of poor quality.

### 1.2.2 Utility of imaging in pneumonia diagnosis

As previously mentioned, guidelines have universally suggested that in-hospital CAP should be confirmed with a chest x-ray (CXR) or another equivalent radiological study (Lim et al., 2009; Mandell et al., 2007; Joshua P. Metlay et al., 2019; M. Woodhead et al., 2011). CXRs lack sensitivity and specificity in diagnosing pneumonia compared to chest ultrasound and chest computed tomography (CT) scans (Bourcier et al., 2014; Karimi, 2019; Prendki et al., 2018; Self et al., 2013; Ticinesi et al., 2016; Ye et al., 2015). Additionally, CXRs are commonly nondiagnostic in the first days following pneumonia among older adults (Marrie, 2000).

Use of chest CT scans can improve the specificity of diagnosis in the emergency room setting compared to CXR among patients with a suspected community-acquired pneumonia, by decreasing overdiagnosis of infiltrates described on CXR by 30% and increasing the sensitivity in 15-18% of cases with negative CXRs (Claessens et al., 2015; Prendki et al., 2018). An additional problem with diagnosing pneumonia with a traditional CXR is the low agreement between radiologists, infectious disease specialists and pulmonologists (Novack et al., 2006). For optimal quality of CXRs the patient needs to be standing, or at least sitting (Esayag et al., 2010; Kunz et al., 2018). However, very old or frail patients are more often unably to get out of bed and thus often only a supine image is possible. A supine CXR has a decreased sensitivity compared to a normal standing CXR (Esayag et al., 2010; Kunz et al., 2018). Among patients that were bedridden, chest CT scans significantly increased the sensitivity of pneumonia diagnosis when compared to CXR, yielding a pneumonia diagnosis in 53% of the cases compared to CXR where only 21% of the cases had a discernable pneumonia (Esayag et al., 2010).

## 1.3 Cases with pneumonia symptoms but without infiltrates

A group which has largely been ignored in previous studies, patients hospitalized with symptoms of pneumonia without radiological confirmation of an infiltrate (**S**ymptomatic **P**neumonia **W**ithout **I**nfiltrate, SPWI) despite the sizeable portion of suspected pneumonia cases represented by this group. Studies on hospitalized patients with CAP almost never include patients without radiological confirmation of an infiltrate (Gadsby et al., 2016; Huijskens et al., 2013; Jain et al., 2015; D. M. Musher et al., 2013; Palmu et al., 2014). Studies which compare characteristics, symptoms, risk factors, laboratory

results, etiology, and outcomes of patients with radiologically confirmed pneumonia to SPWI are very sparse. A single study performed in Canada 2000-2001 by Basi et al. addressed this topic (Basi et al., 2004). They found the number of admitted patients with SPWI to be half that of the number of admitted CAP patients. The patients in the SPWI group were older, had higher severity classification, and 8% mortality compared to 10% in the CAP group (p=0.09). Thus, if we project this admission ratio to the data from the EPIC study on CAP incidence, close to 400.000 SPWI cases may be hospitalized every year in the USA (Jain et al., 2015).

There are a few studies which have examined a related clinical entity, patients diagnosed with pneumonia by a CT scan but not by CXR. In one of these retrospective studies roughly 5% of the pneumonia patients had a negative CXR with a positive CT scan (n=94), patients in this group were frailer and more commonly bedridden (Seo et al., 2019). Interestingly, this group had a shorter duration of hospitalization (Seo et al., 2019). In a prospective study 3% (66/2251) had a positive CT scan with a negative CXR (Upchurch et al., 2017). However, 69% of the patients included in the chest x-ray visible infiltrate group were not at risk of being included in the exposure group because they did not receive a CT scan. This latter study found those with a negative CXR but positive CT scan to be older, have a BMI above 30, have chest pain and lower procalcitonin levels but a similar length of stay (Upchurch et al., 2017).

## 1.4 Community-acquired pneumonia incidence

The overall annual incidence of pneumonia requiring hospitalization is 25 per 10,000 adults according to a study performed in five United States hospitals (3 in Chicago and 2 in Nashville); among patients 65-79 years of age it was 63 per 10,000 and among those 80 years of age or older it was 164 per 10,000 (Jain et al., 2015). Another USA study set in Louisville, Kentucky, found a higher incidence of around 71 per 10.000 for all adults, and an incidence of 209 per 10,000 among 65-year-old or older and 431 per 10,000 individuals 85 year old or older (Ramirez et al., 2017). In Europe the incidence was estimated to be around 11-17 per 10,000 adults but around 140 per 10,000 for 65 year old or older (Torres et al., 2013b). In Iceland the yearly incidence of pneumonia requiring hospitalization among adults was found to be 21 per 10,000 adults, and 127 per 10,000 among adults 80 years and older in 2008-2009 (Agnar Bjarnason et al., 2018a). The incidence of pneumonia and mortality increases with advancing age (Marrie, 2000; Sanz et al., 2018; Trotter et al., 2008).

Populations in Europe and North America are ageing (Christensen et al., 2009; World Health Organization, 2015), therefore pneumonia hospitalizations have been forecast to increase. One example is the population of those ≥65 years old in Iceland which has grown considerably, from 11.6% of the population on January 1st, 2008 to 14.4% on January 1st, 2020 (Iceland, 2008, 2020). Reported pneumonia incidence in Europe and the USA seems to range widely from around 10 to 70 cases per 10.000 adults. Explanations for this might include a significant variability in age and other risk factors of pneumonia between populations and the previously mentioned variability in definitions and diagnosis of pneumonia.

Pneumonia hospitalizations in China have been reported to occur at a rate of 71.3 per 10,000 urban inhabitants in a study which included children as well (Sun et al., 2020). In South Korea an incidence of 52 per 10,000 was reported and in Japan it was reported at 96 cases per 10,000 inhabitants (but included all patients diagnosed at a hospital, some of whom were not admitted); in contrast lower rates of 18 to 58 were reported from Thailand (J.-H. Song et al., 2016).

In recent years, many European studies have observed an increase in pneumonia hospitalizations exceeding expectations from ageing alone. In one region in the UK the incidence of CAP increased by 4.2% per year from 1998-2008 and by 8.8% per year from 2009-2014 (Quan et al., 2016) and in Denmark pneumonia related admissions after adjustment for age and sex increased by over 50% between 1997 and 2011, and for pneumonia as a primary diagnosis by around 40% (Søgaard et al., 2014). Interestingly, pneumonia incidence remained stable among adults under 40 years of age, but increased by around 90% among people over 80 (Søgaard et al., 2014). A Spanish study also using hospital diagnostic codes in the period from 2004 to 2013 found an overall increase in pneumonia hospitalizations (de Miguel-Díez et al., 2017). Another study found an increase in hospitalizations with pneumonia from 2002-2009 in Britain (Elston et al., 2012). In contrast, observations from the USA have shown a different trend in recent decades. A decrease in pneumonia incidence leading to hospitalizations has been noted (Griffin et al., 2013; Hayes et al., 2018; Lindenauer et al., 2012; Wuerth et al., 2016), most noticeable in the oldest age groups (Griffin et al., 2013; Hayes et al., 2018; Lindenauer et al., 2012; Wuerth et al., 2016). When expanding our view across the Atlantic, USA studies found a decrease in pneumonia diagnoses among hospitalized adults following the pneumococcal vaccination among children (Griffin et al., 2013; Hayes et al., 2018; Lindenauer et al., 2012; Wuerth et al., 2016). This was most noticeable among the oldest age group,

85 year old or older (Griffin et al., 2013). One of the USA studies found a decrease in hospitalizations due to pneumonia as a primary diagnosis according to diagnostic codes, but an increase in diagnosis of pneumonia as a secondary diagnosis to respiratory failure or sepsis. Taken together the incidence of these diagnoses decreased by 12.5% from 2003 to 2009 (Lindenauer et al., 2012). However, an earlier study set in the USA showed a decrease in hospitalizations among adults due to pneumococcal pneumonia following pneumococcal vaccinations among children but failed to show a significant decrease for all pneumonia cases in adults (Grijalva et al., 2007). Another USA study found that hospitalizations due to *Haemophilus influenzae* and pneumococcal pneumonia decreased from 2002-2011 but increased for *Klebsiella* spp.*, Pseudomonas* spp., *and S. aureus* (Wuerth et al., 2016). A recent Danish study also found a high rate of *H. influenzae* among hospitalized patients.

### 1.4.1 Incidence trends following vaccinations among children

The results of these previous studies need to be viewed in the context of routine childhood pneumococcal vaccinations which were initiated in some parts of Spain in 2001, in the UK in 2006 and in Denmark and Sweden in October 2007 (Foster et al., 2011; Galanis et al., 2016; Griffin et al., 2013; Harboe et al., 2013; Pérez-Trallero et al., 2009). In comparison, childhood pneumocccal vaccinations were implemented in the USA in the year 2000 (Griffin et al., 2013). In Sweden a decrease in the incidence of invasive pneumococcal disease (IPD) was observed among older children and adults following pneumococcal vaccinations among children but not specifically among 65 year old or older (Galanis et al., 2016). While infections due to vaccine type pneumococci decreased this was somewhat balanced by an increase in non-vaccine type pneumococci, especially among older adults (Galanis et al., 2016).These results were echoed elsewhere; a British study also found a decrease in overall IPD cases following childhood pneumococcal vaccinations but not in the subgroup of the oldest individuals (Moore et al., 2014), and a population based study in Iceland found that both pneumonia and IPD decreased overall for the whole population but not specifically for the oldest age group (Eythorsson et al., 2021). A previous Dutch study did not find a decrease in IPD among adults after vaccinations started among children (Rodenburg et al., 2010). Interestingly, a British study found an overall increase in IPD despite increasing uptake of pneumococcal vaccine among children and adults in the period studied (2002-2009), even though a decrease in vaccine type IPD was observed (Elston et al., 2012). Finally, a study performed in the USA reported a decrease in IPD among adults following

vaccinations in children (Whitney et al., 2003). Likewise a systematic review mostly based on studies from North America and the UK found an overall protective effect of childhood pneumcoccal vaccinations on IPD among adults, especially among those 65 year old or older (Tsaban & Ben-Shimol, 2017). It could be that the previously mentioned studies that did not find an effect among the oldest age group were not large enough to identify a protective effect among this subgroup.

It is important to note that many of these studies are based on diagnostic codes at discharge (ICD-9 or 10) raising questions regarding the accuracy of the results given the limitations of diagnostic codes with respect to sensitivity and specificity of the pneumonia diagnosis.

Despite pneumococcal vaccinations having been administered for more than a decade in both Europe and the US, the incidence of pneumonia has developed differently in the continents (Agnar Bjarnason et al., 2018a; Jain et al., 2015; Quan et al., 2016; Shoar & Musher, 2020; Søgaard et al., 2014). Several reasons have been proposed for these differences; a faster increase in non-vaccine serotypes, changes in diagnostic codes (e.g. from ICD-9 to ICD-10), increased hospitalizations of less-severe pneumonia, individuals with high levels of comorbidity living longer, changes in how physicians code LRT infections, an increase in repeated pneumonia events or readmissions of same event (many studies exclude repeated events of same individuals) or diagnostics with higher sensitivity being performed (de Miguel-Díez et al., 2017; Quan et al., 2016; Søgaard et al., 2014). Pneumoccci seem to be the causative agent in a higher fraction of pneumonia in Europe compared to the USA (Daniel M Musher et al., 2017; Shoar & Musher, 2020). Could the difference in the share of pneumonia caused by pneumococcal pneumonia explain the differences in incidence trends? We also wonder if the different life-expectancy could partially explain this. Life-expectancy among high-income countries is lowest in the USA (Braveman, 2013), on top of that, life-expectancy has increased the least in the USA in recent years when 17 high-income countries are compared (J. Y. Ho & Hendi, 2018).

Extending our view to the globe, from 1990-2017 there was a 5.8% decrease in the age- standardized incidence of LRT infections worldwide among all age groups including children, according to the 2017 Global Burden of Disease study (James et al., 2018).

The USA and Europe comprise only a small part of the world's population. Globally tuberculosis, gram negative pathogens and even HIV/AIDS associated infections accompany pneumococci as the most common LRT

pathogens (Aston, 2017; Aston et al., 2019; Iroezindu et al., 2014; J.-H. Song et al., 2016). However, studies on pneumonia incidence and etiology are lacking in many parts of Asia and Africa (J.-H. Song et al., 2016; J.-H. Song et al., 2011). Nevertheless, a reduction in pneumonia among children has been seen in studies assessing the effects of pneumococcal vaccination in Kenya (Silaba et al., 2019) and Gambia (Cutts et al., 2005).

## 1.5 Pneumonia in older adults

The curious nature of pneumonia among older adults in comparison with younger patients has sparked a special interest among physicians and researchers particularly revolving around the difference in symptoms (fewer specific symptoms, acute delirium, malaise, loss of appetite etc.) and the higher incidence and mortality rates (Berk, 1984; Marrie, 1996; Shi et al., 2019). This was even noted by William Osler in the *Principles and Practice of Medicine* published in 1892, who pointed out the frequent delirium observed among older adults with pneumonia compared to younger patients (Berk, 1984). The oldest age groups and patients in nursing homes also have the highest incidence rates of pneumonia which (Jackson et al., 2004; Jain et al., 2015; Loeb et al., 1999) increase almost exponentially with advancing age (A Bjarnason et al., 2018b; Rivero-Calle et al., 2017). Pneumonia incidence in nursing homes has been reported to be as high as one pneumonia per 1000 person-days (Yoshikawa & Marrie, 2000), that is one episode of pneumonia on average every three years.

As previously mentioned, older adults commonly have fewer and less specific symptoms, more frequently are slower to develop visible infiltrates on CXR and more commonly receive a supine CXR imaging study, all these factors challenge the diagnosis of pneumonia (Esayag et al., 2010; Kunz et al., 2018; Marrie, 2000; J. P. Metlay et al., 1997b). This can delay administration of appropriate treatment (Claessens et al., 2015) and, conversely, lead to the overuse of antibiotics in a group especially vulnerable to adverse drug events and other complications from unnecessary antibiotics, e.g. *Clostridioides difficile* infection and antibiotic resistance (Davies et al., 2009; Jump, 2013; Pirmohamed et al., 2004).

Some researchers have made prediction models predicting pneumonia diagnosis based on signs and symptoms (Takada et al., 2017; van Vugt et al., 2013). These models have modest discriminatory abilities ranging from 0.55-0.71 area under receiver operating characteristics curve (AUROC) but increase to around 0.77 when CRP or procalcitonin is added to the symptoms

and signs (van Vugt et al., 2013). However, among older adults adding symptoms of loss of appetite to the models increased the discriminatory ability (Takada et al., 2017).

Recovery after pneumonia takes longer among older adults the elderly and especially among those that are frail. It can take several months to return to baseline if those patients ever fully recover (Yoshikawa & Marrie, 2000).

With increasing age daily activities often get more difficult to perform, however, this functional decline is not a direct effect of age and varies drastically between individuals. Research has even shown that functional decline caused by the lack of exercise can be partially regained (Shur et al., 2021). With increasing age sarcopenia becomes more common, it is the loss of muscle mass and strength, it has gained increased interest in relation to pneumonia in recent years (Okazaki et al., 2020). Sarcopenia could lead to an interruption of normal physiological responses of aspiration, by decreasing the strength and function of swallowing muscles and muscles responsible for coughing (Okazaki et al., 2020). More studies are still needed on the association but a study found an association between the incidence of pneumonia and sarcopenia (Altuna-Venegas et al., 2019) and another study found that respiratory muscle strength, tongue strength and the size of trunk muscles were negatively associated with incidence of pneumonia (Okazaki et al., 2021)

In relation to pneumonia outcomes functional status is a strong predictor of mortality following infection (Ma et al., 2011; Sanz et al., 2018). Barthel's daily activity index had a better prognostic ability for mortality among pneumonia patients than age and underlying illnesses in one study on pneumonia mortality (Sanz et al., 2018). Patients that had a Barthel‘s functional index of less than 80 prior to developing a pneumonia event had an adjusted odds ratio (aOR) of 3.9 (95% confidence interval (CI) 1.4-10.5) for 30-day mortality (Murcia et al., 2010). Another study assessing mortality following pneumonia found that adding functional performance assessment of ECOG (Eastern Cooperative Oncology Group) to CRB-65 significantly improved the predictive ability of the model (Jeon et al., 2017). Even patients with a low score of CURB-65 (0-2) had a high risk of mortality if they had a high ECOG performance score (Pieralli et al., 2018). Both the CURB-65 and the PSI pneumonia mortality scores were developed in younger populations than the current Western populations are today, in the CURB-65 study the mean age of participants was 64 years of age and in the PSI study 43% were younger than 50 years of age (Fine et al., 1997; Lim et al., 2003a). These results indicate

that functional status is an important but sometimes overlooked predictor of mortality, especially among older adults.

## 1.6 Etiology

In recent years a change in the etiology of hospitalized CAP has been observed, at least among cases with any pathogens detected. Interestingly, there is still a large portion of cases with CAP that are without an identified microbial etiology (Agnar Bjarnason et al., 2018a; Fally et al., 2021; Jain et al., 2015). While tests based on nucleic acid amplification (NAAT), such as polymerase chain reaction (PCR) analyses, are increasingly being applied on samples from pneumonia patients and thus leading to an increase in the identification of viral pathogens, *S. pneumoniae* is still the most commonly detected pneumonia pathogen almost everywhere (Aston et al., 2019; Fally et al., 2021; Jain et al., 2015; Daniel M Musher et al., 2017; J.-H. Song et al., 2016). However, the rates of pneumococci in pneumonia are declining, most notably in the United States (Shoar & Musher, 2020), but also in countries which have implemented widespread pneumococcal vaccinations (Hanquet et al., 2019).

Studies on the etiology of CAP have identified likely pathogens in 38-63% of cases (Agnar Bjarnason et al., 2018a; Fally et al., 2021; J. C. Holter et al., 2015; Jain et al., 2015; D. M. Musher et al., 2013). Microbial etiology can be established in up to 87% of cases providing sputum for PCR testing, however, far from all patients with pneumonia can produce good quality sputum at the time of admission (Fally et al., 2021; Gadsby et al., 2016; Huijskens et al., 2014; Neill et al., 1996; Wolff et al., 2017). In patients that had not received prior antibiotics, etiological diagnosis could be made in 79% (J. C. Holter et al., 2015). Prior to the widespread use of antibiotics, less than 5% of pneumonia patients did not have an etiological diagnosis (Daniel M Musher et al., 2017).

While most studies identify likely pathogens in around half of patients with CAP the rate is lower in routine clinical practice (Shoar & Musher, 2020). This has major practical implications, as improved pathogen detection can lead to more targeted antibiotic treatment, a topic that is especially important in this era of increasing antimicrobial resistance.

The most common pathogens identified in patients admitted due to CAP in Iceland 2008-2009 were *S. pneumoniae* in 20% of cases, viruses were identified in 15% and *Mycoplasma pneumoniae* in 12% of cases (Agnar Bjarnason et al., 2018a). Jain et al. reported that rhinovirus, influenza A or B and *S. pneumoniae,* were the most common pathogens found in CAP in five

United States hospitals (Jain et al., 2015). In Malawi the most common pathogen of CAP among adults was *Mycobacterium tuberculosis* closely followed by *S. pneumoniae* (Aston et al., 2019). In Asia and the Pacific region, in addition to the globally typical pathogens *S. pneumoniae, M. pneumoniae* and *Haemophilus influenzae, Klebsiella pneumoniae* and *Burkholderia pseudomallei* are relevant (J.-H. Song et al., 2016). There is a notable difference in the percentage of *S. pneumoniae* (5%) in the study by Jain et al. compared to the Icelandic study as well as studies performed in the era before widespread antibiotic use (Daniel M Musher et al., 2017). There even seems to be an important difference in pneumonia etiology within the Nordic countries (Agnar Bjarnason et al., 2018a; Fally et al., 2021; J. C. Holter et al., 2015).

This underscores the need for local and regular updates on pathogen prevalence and microbial resistance patterns to guide treatment recommendations and further stresses the importance of methodology when studies are compared, e.g. a globally accepted pneumonia criteria. A Norwegian study performed in 2008-2011 found a possible etiology in 63% of cases; *S. pneumoniae* was the most common pathogen identified, in 30% of cases (J. C. Holter et al., 2015). Some of these studies have been criticized by Shoar et al. for reporting etiology fractions using the overall number of patients as the denominator even though the specific diagnostic tests needed to diagnose some of the pathogens were not performed in all cases (Shoar & Musher, 2020). Some have argued that the introduction of guidelines and the administration of early empiric antibiotics have inadvertently lead to a decreased emphasis on etiological diagnosis of pneumonia (Daniel M Musher et al., 2017). Whatever the reason it might be prudent to keep obtaining samples for etiological diagnosis of pneumonia and antimicrobial resistance analysis, at least among those hospitalized. Despite this the 2019 guidelines by the American Thoracic Society and Infectious Diseases Society of America, only recommend routine culture of sputum and blood among those with severe CAP or at increased risk of harboring a pathogen that is not covered by empiric treatment (Joshua P. Metlay et al., 2019). However, routine testing of influenza virus is recommended during seasons of high influenza activity (Joshua P. Metlay et al., 2019).

This is important so that treatment of individual patients can be adjusted. Furthermore, for surveillance purposes so that local guidelines can be updated if significant changes are observed to the detected pathogens or their antimicrobial resistance; lastly this practice is also vital in identifying and monitoring emerging epidemics.

### 1.6.1 The role of viruses

The exact role of viruses in CAP is not fully understood, even though viruses constitute a large part of pathogens detected in pneumonia patients (Alimi et al., 2017; Fally et al., 2021; Jain et al., 2015; Wolff et al., 2017). A meta-analysis reported that 26% of hospitalized CAP cases had a viral etiology, drawing on information from 25 individual studies (Burk et al., 2016). Recently, Coronavirus Disease 2019 (COVID-19) caused by the SARS-CoV-2 virus has pushed viral pneumonia to the top of the research agenda. Viral pneumonia is associated with symptoms, outcomes and radiological findings that overlap with bacterial pneumonia. Studies are lacking on the value of PCR diagnosis among patients with pneumonia other than COVID-19. It is known that detection of viruses from the URT among asymptomatic participants is low; one study showed around 4% positivity rate, of those around 3% were rhinovirus (Sundell et al., 2019). Nevertheless, studies comparing the etiological results using PCR diagnostics among patients with pneumonia to a control group of patients without pneumonia, are lacking (Self et al., 2015; Tatarelli et al., 2020). Such a comparison could help establish if certain viruses are innocent bystanders or active pathogens. Unfortunately, the identification of a viral agent in LRT samples does not rule out a concurrent or a secondary bacterial infection (Jain et al., 2015; Jennings et al., 2008; Shoar & Musher, 2020). In fact, many pneumonia cases have more than one microbial agent identified (Agnar Bjarnason et al., 2018a; Jain et al., 2015; Jennings et al., 2008). Importantly, CAP patients diagnosed with a concomitant viral and bacterial infection had a higher risk of dying according to a meta-analysis of prior studies OR=2.1 (95% confidence interval (CI) 1.32-3.31) (Burk et al., 2016).

## 1.7 Etiologic diagnostics - PCR

Commercially available PCR diagnostic panels have become more widely available in recent years along with increasingly elaborate in-house PCRs. PCR analyses play an increasing role in identifying viral and “atypical” bacterial pathogens causing respiratory tract infections (Caliendo, 2011; Gadsby et al., 2016; Olofsson et al., 2011). The role of PCR on URT samples in finding “typical” bacteria like *S. pneumoniae* and *H. influenzae* is not clear. Bacterial detection by PCR is not as sensitive to recent antibiotic treatment as is detection by culture (A. M. Harris et al., 2017; Lee et al., 2019), since PCR can detect the presence of nucleic acids from nonviable organisms (Josephson et al., 1993; Satzke et al., 2013). On the other hand, a PCR diagnosis of a pathogen from the URT does not nessesarly mean an acute infection is

ongoing, it can also mean an infection has recently occured or colonization without infection (Almirall et al., 2008; Arnold & Fuqua, 2020). Quantitative real-time PCR can be used to estimate rough numbers of pathogens in the sample (Baggett et al., 2017; Greiner et al., 2001). For detection of *S. pneumoniae* carriage, the WHO working group recommends real-time PCR targeting *lytA* (Satzke et al., 2013). PCR methods targeting both *lytA* and *piaB* genes were almost 100% specific but *cpsA*, *ply, Spn9802, zmpC* lacked specificity (Wyllie et al., 2017). Non-typeable pneumococci usually lack the gene *piaB*, making its use suboptimal (D. A. Tavares et al., 2019). However, the *lytA* primer is thought to have lower specificity (88%) when used on oropharyngeal samples but had 95% specificity in nasopharyngeal samples (Boelsen et al., 2020). A previous study has shown favorable results for oropharyngeal sampling compared to nasopharyngeal sampling for PCR analysis of *S. pneumoniae* (Trzcinski et al., 2013). The transcriptional regulator SP2020, a part of the core genome of *S. pneumoniae,* has been proposed as a potential marker for this organism with a reported 100% sensitivity and 99.8% specificity (Croxen et al., 2018; D. A. Tavares et al., 2019).

While upper respiratory tract (URT) samples can be collected from most patients regardless of whether they can produce sputum or not, the results are often difficult to interpret. Accurate data are lacking from non-selected patient groups examining the agreement between upper and lower airway test results in the context of CAP. A study found that certain viruses were associated with CAP among hospitalized children and adults when compared to asymptomatic outpatient controls using PCR on URT samples: influenza, respiratory syncytial virus and human metapneumovirus were strongly associated with CAP but rhinovirus was only associated with CAP among adults but not children (Self et al., 2015). This study did not perform PCR analyses of bacteria and only utilized outpatients as controls. In another study utilizing PCR analyses pneumococci were found in 22% of sputum and 8% of nasopharyngeal (NP) samples from CAP cases, however, among cases with an acute respiratory tract infection but no sign of pneumonia, sputum was positive in 3% and NP samples in 1% of adult cases (Saukkoriipi et al., 2017). This suggests upper respiratory tract samples have a low sensitivity for the identification of pneumococci in the setting of pneumonia. Studies comparing upper respiratory tract diagnosis of pneumococci among pneumonia patients to patients without signs and symptoms of respiratory tract are lacking.

## 1.8 Diagnostics based on metagenomics

Current nucleic acid-based methods in clinical use rely on PCR primers that

bind to specific genetic sequences of a target microbe, subsequent amplification signals its presence (Josephson et al., 1993). Shotgun metagenomics is a method where specific primers are usually not required; most of the genetic material of the sample is amplified. The registered genetic sequences are then screened for previously known and unknown microbes using databases of pathogen genetic sequences (Graf et al., 2016). Its main use has been searching for previously unknown pathogens or to examine microbial flora (Miao et al., 2018). Cheaper, faster, and more sensitive genetic sequencing has spurred interest in the possible application of this unbiased approach for accurate etiological diagnosis and rapid antibiotic resistance results (Bal et al., 2018; Graf et al., 2016; Ruppe et al., 2017; Schlaberg et al., 2017). Studies performing metagenomics have mostly been performed using bronchoalveolar lavage fluid (BALF), a recent study using BALF yielded a microbial diagnosis in 74% of hospitalized pneumonia patients (H. Zhou et al., 2021) and another study on BALF from CAP patients hospitalized in the ICU yielded a microbial diagnosis in 91% of the patients (X. Wu et al., 2020b). A recent meta-analysis and systematic review among pneumonia patients found that using metagenomic sequencing of samples around 80% of patients received an etiological diagnosis compared with 46% using traditional methods (Lv et al., 2023). Yet another study performing metagenomic analysis on BALF from pneumonia patients found an increased detection of bacteria and viruses but not fungi compared to traditional diagnostic methods (N. Li et al., 2022). In those with severe pneumonia metagenomic analysis on blood samples simultanesously with BALF helped confirm the diagnosis of a specific pathogen and served as an early indication of bloodstream infection (J. Chen et al., 2021).

These studies were limited by the lack of a control group and the focus on BALF and therefore causal inferences in relation to hospitalized CAP in general are hard to make. Another hurdle for metagenomic-based diagnostic methods on respiratory samples is the high amount of human genetic material in these samples (Charalampous et al., 2019).

## 1.9 Pneumonia treatment

Guidelines for the treatment of pneumonia all recommend antimicrobial treatment (Eccles et al., 2014; Lim et al., 2009; Joshua P. Metlay et al., 2019; M. Woodhead et al., 2011), but guidelines for other LRTIs, for example bronchitis, generally do not recommend antibiotics (Kinkade & Long, 2016; NICE, 2019; M. Woodhead et al., 2011). Studies have shown that pneumonia management guidelines and protocols may shorten admissions, duration of

antibiotic treatment and even decrease mortality (Marrie, 2000; McCabe et al., 2009). CAP treatment guidelines at Landspitali University Hospital (LUH) do not recommend atypical coverage or diagnostic tests for respiratory virus and atypical bacteria when the CURB-65 severity score is below 2 unless there is an ongoing outbreak (Kristjánsson, 2017). The average CURB-65 score in the 2008-9 Icelandic pneumonia study was 1.3 and a large proportion had CURB-65 score below 2 (Agnar Bjarnason et al., 2018a). Interestingly, *M. pneumoniae* was commonly identified (12% of cases) in the 2008-2009 cohort (Agnar Bjarnason et al., 2018a).

Two prospective studies, from Switzerland and the Netherlands did not find a difference in the prognosis of patients with non-severe CAP treated with beta-lactams compared to treatment also covering atypical bacterial pathogens (N. Garin et al., 2014; Postma et al., 2015). In severe CAP, treatment with broader spectrum antibiotics is associated with more favorable outcome (N. Garin et al., 2014; Horita et al., 2016). A meta-analysis indicated that beta-lactam monotherapy had a higher failure rate than treatment which was effective against atypical bacteria (Eljaaly et al., 2017). Another meta-analysis found higher mortality in patients treated with beta-lactam monotherapy compared with beta-lactam and macrolide combination therapy (Vardakas et al., 2017). In non-severe CAP narrow-spectrum antibiotic treatment seems to be equivalent to a broad-spectrum regimen with respect to mortality. However, mortality rates are perhaps not the best endpoints for comparing the efficacy of antibiotic treatments in non-severe CAP considering the generally low mortality rates, unless the sample size is very large.

## 1.10 Risk factors associated with mortality

In this discussion we define short-term mortality as in-hospital or death within 30-days of admission due to pneumonia and long-term mortality as mortality 1-year or more from admission due to pneumonia.

### 1.10.1 Risk factors associated with short-term mortality

Risk factors for short-term mortality following pneumonia have been frequently studied (Flanders et al., 1999; Lim et al., 2003b); increasing age is a strong risk factor for 30-day mortality, nursing home residence, performance status, do not resuscitate (DNR) order, heart failure, cerebrovascular disease and current malignancy are all frequently reported risk factors for short-term mortality following CAP (Flanders et al., 1999; Hamaguchi et al., 2018; Lim et al., 2003b; Murcia et al., 2010). Current smoking has been linked to increased short-term mortality following pneumonia (Drijkoningen & Rohde, 2014). In the

widely used PSI risk assessment for pneumonia mortality Fine et al. incorporated age, sex, nursing home residence, malignancy, liver disease, cerebrovascular disease, heart failure and kidney failure along with 5 examination variables (Fine et al., 1997). The other widely used pneumonia mortality index CURB-65 includes confusion (delirium), urea, respiratory rate, blood pressure and age greater than 65 years (Lim et al., 2003a). These risk scores are used to predict which patients with pneumonia have the highest risk of short-term mortality and, in combination with other factors used by clinicians to help decide which patients may be safely treated as outpatients (Kristjánsson, 2017). The Charlson-comorbidity index (CCI) has also been reported to be a strong risk factor of short-term mortality following pneumonia (Nguyen et al., 2019; S. Song et al., 2018; Tokgoz Akyil et al., 2018).

### 1.10.2 Risk factors associated with long-term mortality

There is a fundamental difference between short-term mortality and long-term mortality following an episode of pneumonia. Short-term mortality is generally thought to be due to the disease itself and/or its acute complications, but as time passes from the infection it may intuitively become less likely that death can be contributed to this single and increasingly remote event. Nevertheless, the effect of pneumonia on longer term mortality has been increasingly studied in the last two decades. One of the possible explanations for increased long-term mortality is the fact that invasive pneumococcal pneumonia increases the risk of myocardial infarction and cerebrovascular disease for several years following the event (Daniel M. Musher et al., 2019). There even seems to be an association between the severity of the respiratory tract infection and how great the increased cardiovascular risk is and for how long it lasts (Daniel M. Musher et al., 2019). Increased long-term risk of cardiovascular diseases has been observed following COVID-19 also in a severity associated manner, those that were hospitalized had a higher risk than those that were not hospitalized (Xie et al., 2022).

Several risk factors influencing long-term mortality following pneumonia have been identified: age, sex, belonging to an ethnic minority, nursing home residence, education, characteristics of the pneumonia e.g pleural effusion, absence of fever, symptoms of delirium, gram-negative etiology, disease-severity, low albumin levels, inflammatory and cardiovascular markers, neurocognitive disorders, cardiovascular diseases, COPD, malignancy, deficient nutritional status, high CCI, glucocorticosteroid therapy, immunization, use of statins and do not resuscitate order (Aliberti et al., 2015; Bruns et al., 2011; Jan C. Holter et al., 2016; Koskela et al., 2014; Marcos I.

Restrepo et al., 2013; Yousufuddin et al., 2018). Long-term mortality following hospitalization due to pneumonia has been reported to be similar or higher than that following hospitalization due to congestive heart failure, cerebrovascular event and major fracture, and only lower than hospitalization due to a cancer diagnosis (Yende et al., 2007).

## 1.11 Trends in pneumonia mortality

A range of previous studies have assessed recent trends in pneumonia mortality, but prospective studies directly comparing the short-term mortality of pneumonia to other diseases leading to hospitalization are lacking.

Globally there was a 19.5% (22.3%-16.9%) decrease in mortality caused by lower respiratory tract adjusted for age according to the Global Burden of Disease study between 2005 and 2015 (H. Wang et al., 2016) overall, that is in all age groups combined.

A study published in 2018, assessing the mortality trend from pneumonia in Europe, using the European mortality database and ICD-10, found the median decrease in mortality was 31.0% from 2001-2014 (Marshall et al., 2018). Mortality rates were age and sex standardized to the European Standard population, this means adjustments for other risk factors of pneumonia mortality were not made (Marshall et al., 2018). No information was available regarding time from pneumonia to death.

A large USA study adjusting for age and sex found that mortality due to pneumonia among adults decreased from 8.9% to 4.1% from 1993 to 2005 (Ruhnke et al., 2010). This trend was also seen among older adults in the USA after adjusting for age and sex (Ruhnke et al., 2011). A British study analyzing administrative data also found decreased mortality from 2009 to 2014 (Daniel et al., 2016), the authors believed this was due to shortening of treatment delay (improved door to antibiotics time). Older studies had found that early antibiotic administration was associated with improved 30-day survival (Houck et al., 2004; Meehan et al., 1997). Newer studies on sepsis have confirmed the importance of door to antibiotics time in terms of mortality (Peltan et al., 2019).

One of the few prospective observational studies assessing changes to mortality among adults hospitalized with CAP in recent years was a study conducted in Barcelona from 1995-2014 (Simonetti et al., 2016). The study reported an unadjusted change in mortality from 9.6% to 4.1% over the period. The decrease in mortality was even greater after adjusting for risk factors (Simonetti et al., 2016). This study was not population-based and could therefore not assess incidence. A retrospective study using prospectively

obtained data assessed patients hospitalized with CAP and a “clinical diagnosis of *S. pneumoniae”* over a 20 year period that ended in December 2016 did not find a significant difference in mortality between the four 5-year periods after adjusting for underlying factors (Catia Cillóniz et al., 2018).

Taken together, globally there seems to have been a modest decrease in overall mortality due to lower respiratory tract infections in the last decade, however, there seems to be a notable locational, etiological and age-associated variation to this trend.

### 1.11.1 Coding of pneumonia mortality

A drawback to using ICD-10 codes in the Causes of Death Registry to identify pneumonia-related mortality is that if a patient had a chronic disease which resulted in pneumonia and ultimately in the death of the patient, the primary underlying cause of death registered would be the chronic underlying disease and the pneumonia would be registered as a contributing factor (Marshall et al., 2018; Skull et al., 2008). Therefore, when assessing pneumonia mortality with diagnostic codes it is important not only to assess the primary underlying cause of death, but also all registered contributing causes of death. In addition, pneumonia can exacerbate underlying illnesses and cause severe complications like cardiovascular diseases. These complications will often be registered as the primary underlying cause of death even though they were caused or greatly influenced by the infection. This coding is understandable as it is impossible to know in which cases the cardiovascular event (or other complication from the infection) would have occurred regardless of the pneumonia. A notable exception to this was observed during the COVID-19 pandemic, where all deaths immediately following a disease syndrome that fit with COVID-19 and the patient had a “probable or confirmed diagnosis” of COVID-19 and these deaths according to WHO “…should be counted independently of pre-existing conditions that are suspected of triggering a severe course of COVID-19.” (Organization, 2020).

These are important limitations to studies reporting on pneumonia related mortality using Causes of Death Registries, especially if only the primary underlying cause of death is reported.

## 1.12 Cardiovascular complications of pneumonia

Complications following pneumonia diagnosis are frequent as previously mentioned, cardiovascular related complications are reported in around 30% of patients hospitalized with pneumonia (V. F. Corrales-Medina et al., 2012;

Violi et al., 2017), the observed risk is highest in the first 1-2 days (V. F. Corrales-Medina et al., 2012). The increase in cardiovascular events is most evident in patients with severe pneumonia, as measured by invasiveness: patients with bacteremic pneumonia have the highest risk and it can remain elevated for months and even years following the event (V. F. Corrales-Medina et al., 2015; Daniel M. Musher et al., 2019). Patients with less severe respiratory tract infections have been reported to have an increase in the baseline risk of cardiovascular disease to a lesser extent and for a shorter duration than those with a more severe respiratory tract infection (Daniel M. Musher et al., 2019). The exact role of different pathogens is unclear but pneumonia caused by *S. pneumoniae* has most commonly been associated with cardiovascular events (Daniel M Musher et al., 2017; M. I. Restrepo & Reyes, 2018; Shenoy et al., 2018). A Danish retrospective study published in 2020 found a roughly 20-fold increase in the risk of mycardial infarction (this included mild infarctions) and a 26-fold risk of stroke in the first three days after invasive pneumococcal infection compared to a control period in the same individual (Ohland et al., 2020). Similar trends were noted with respiratory viral infections, especially with influenza, although the risk was not as dramatically increased (Ohland et al., 2020). This study by Ohland et al. was limited by the fact that only infections by five viruses and one bacteria were assessed, it lacked a control disease without a proposed risk of myocardial infarction, information lacked about disease syndromes and the endpoint included diagnostic codes ICD I21 and I23 which contain mild myocardial infarctions (Ohland et al., 2020). Interestingly, pulmonary inflammation in general has been associated with cardiovascular diseases (Van Eeden et al., 2012).

The exact pathophysiology behind cardiovascular complications following pneumonia is not fully understood, it is thought to be caused by the combination of several different factors. This includes decreased oxygen transportation, direct damage to the cardiovascular system, increased inflammatory activity, activation of platelets and a decrease in perfusion of coronary arteries (R. Cangemi et al., 2014b; Rae et al., 2016; M. I. Restrepo & Reyes, 2018). The perseverance of *S. pneumoniae* antigens following the infection could contribute to the persistence of inflammation (Charles Feldman & Anderson, 2020; C. Feldman et al., 2019). The persistence of inflammation is thought to be an important factor among older adults, as a disruption in the resolution of acute inflammation following infection has been observed with ageing (Doyle et al., 2018). Higher levels of inflammatory markers at discharge have been associated with a higher mortality following pneumonia (Yende et al., 2008; Yende et al., 2011). Another more recent study using PET (positron

emission tomography) CT scans found increased metabolic activity suggestive of inflammation in the majory of CAP patients 30-45 days post discharge compared to healthy controls (Vicente F. Corrales-Medina et al., 2021). This also supports the hypothesis of persistence of inflammation.

Some of these cardiovascular events following pneumonia are thought to be type-2 myocardial infarction (T2MI), which has been defined as infarction caused by shortage of oxygen when the myocardium is in great need of oxygen, rather then a clear thrombotic event like the classical type 1 myocardial infarction (Landes et al., 2016). In a recent study, around 30% of those categorized as having a T2MI had a “plaque rupture” and the mortality was higher among those with T2MI than among those with T1MI (Landes et al., 2016).

## 1.13 Acetylsalicylic acid

Aspirin or Acetylsalicylic acid (ASA), is an inhibitor of cyclooxygenase 1 and prostaglandin production (Desborough & Keeling, 2017). Aspirin is one of the historically most used drugs, it has been in use for more than 2400 years, for most of that time mainly for its analgesic properties in higher doses (Awtry & Loscalzo, 2000; Desborough & Keeling, 2017). One of the key current roles of aspirin is secondary prevention of myocardial and cerebral infarctions due to it‘s ability to decrease aggregation of platelets (Antithrombotic Trialists' Collaboration, 2002; Desborough & Keeling, 2017). Aspirin is a generic drug, therefore quite cheap and it is still sold over the counter in many countries (Awtry & Loscalzo, 2000; Desborough & Keeling, 2017).

Due to the elevated risk of cardiovascular diseases following pneumonia and especially myocardial infarction, and the fact that a large portion of these complications occur very soon after the advent of pneumonia, researchers raised the question whether administration of aspirin could reduce mortality linked to pneumonia. Prior studies have reported mixed results, a number of them indicated that ASA was associated with a decrease in short-term mortality (Falcone et al., 2015; Falcone et al., 2019b), but other studies did not find such an association (R. Cangemi et al., 2014b; Chalmers et al., 2008). A recent study in primary care found an association with ASA and decreased risk of cardiovascular complications following CAP (Hamilton et al., 2021).

A study performed in Turkey randomized hospitalized CAP patients with ≥2 cardiovascular risk factors to receive 300mg of ASA daily for 30 days in addition to routine pneumonia treatment. The control group received routine care (i.e., no placebo group and the study was not blinded). The final groups

included 91 and 94 patients, respectively out of 1223 patients originally screened; cases with a coronary artery disease, malignancy, and heart failure were excluded (Oz et al., 2013). The study only presented per protocol statistical analysis but not intention to treat results. Those treated with ASA were observed to have less often acute coronary syndrome events and fewer cardiovascular-related deaths were reported in the ASA group (Oz et al., 2013).

It is possible that the anatomic site of infection or the type of the pathogen could influence the potential protective role of aspirin, this is supported by the fact that urinary tract infections are not as strongly associated with subsequent cardiovascular events compared to pneumonia (Smeeth et al., 2004).

## 1.14 Other cardiovascular drugs in the context of pneumonia survival

Hydroxymethylglutaryl-CoA reductase inhibitors, better known as statins have also been proposed to be protective if administered early among pneumonia patients by enhancing neutrophil migration in patients with non-severe infection and a proposed reduction in lung inflammation (Chalmers et al., 2008; E. Sapey et al., 2017). Neutrophil function is often impaired among elderly and frail patients with pneumonia: This is observed as reduced chemotaxis of neutrophils to the site of infection and weakened neutrophil extracellular trap formation (Grudzinska et al., 2020; Wilson et al., 2020). An observational study on statins, ASA, beta-blockers and ACE inhibitors suggested an improved 30-day survival among patients on statins, and an adjusted OR of 0.63 (95% CI 0.36-1.11) was observed for ASA (Chalmers et al., 2008). A randomized double-blind, placebo-controlled trial using 80mg simvastatin for 7 days in CAP with sepsis, included 32 patients in the statin group and 30 in the control group (Elizabeth Sapey et al., 2019). The study found that patients taking statins had a more accurate migration of neutrophils than those taking placebo and had greater improvement in their SOFA scores (Elizabeth Sapey et al., 2019). The mortality at 30 days was 2 (6%) in the simvastatin group but 6 (20%) in the placebo group (p=0.14). The randomization of patients was suboptimal as can be seen in the median ages of 78 (IQR, 70-88) in the treatment group and 84 (IQR, 68-90) in the control group and the proportion of cases with 3 or more comorbidities, 25% in the treatment group and 40% in the placebo group (Elizabeth Sapey et al., 2019). This meant that the control group was older and had more comorbidities on average. Another smaller RCT (randomized

controlled trial) using 20mg simvastatin for 4 days compared to placebo on cases with a newly diagnosed CAP only included 34 patients in total and did not reveal a measurable effect of the simvastatin (Viasus et al., 2015).

Mice infected with the common gram-positive agents *S. pneumoniae,* and *Staphylococcus aureus* have shown reduced lung damage if they receive concomitant treatment with statins (Boyd & Orihuela, 2011; L. P. Tavares et al., 2021). This effect has not been observed in mice infected with the gram-negative pathogen *E. coli* (Hussein et al., 2019; L. P. Tavares et al., 2021).

## 1.15 The role of vaccinations

Influenza vaccinations have been found to decrease mortality during hospitalization following pneumonia with an adjusted OR of 0.61 (0.43-0.87) (Spaude et al., 2007). Polysaccharide pneumococcal vaccinations (PPV) among adults offer moderate protection (around 10-24%) against hospitalizations due to pneumonia (Lawrence et al., 2020; Tin Tin Htar et al., 2017). A meta-analysis found that the 23 valent PPV (PPV23) provided 50% effectiveness in preventing invasive pneumococcal disease among adults above 50 years of age but a smaller effect was provided in preventing CAP (Kraicer-Melamed et al., 2016). A second meta-analysis examining adult vaccination found an OR of 0.26 (95% CI 0.14-0.45) for protection against IPD (Moberley et al., 2013). A third meta-analysis found vaccinations to be associated with preventing pneumonia among adults 65 year or older and in those at high risk, relative risk 0.67 (95% CI 0.43-1.04) (Diao et al., 2016). The Directorate of Health in Iceland recommends PPV vaccination for all individuals 60 year or older and individuals at high risk (Embætti Landlæknis & Sóttvarnalæknir, 2014). A systematic review of the literature following the pneumococcal conjugate vaccination (PCV) of children found in general an overall decrease in invasive pneumococcal disease among adults and especially those 65 year old or older (Tsaban & Ben-Shimol, 2017), as previously mentioned.

PCV vaccination among adults provides good protection against vaccine type CAP and IPD (Theilacker et al., 2022). The efficacy of PCV-13 has been demonstrated up to 84 year of age, but was limited in that study by statistical power rather than effect among those older than 84 years (Theilacker et al., 2022). PCV targeting 7, 10 and 13 serotypes of pneumococci have been available for more than a decade now, but recently 15 and 20 valent PCVs have been authorized by the USA Food and Drug Administration and the European Medicines Agency.

PCV vaccination leads to a T-cell dependent response with accompanying memory cell production of specific antibodies while PPV leads to a T-cell-independent production of antibodies (Bonnave et al., 2019). Among adults PCV vaccination leads to similar or higher levels of IgG and similar or better opsonic activity than PPV vaccination, in studies comparing PCV7 to PPV23 (Daniel M. Musher et al., 2011).

## 1.16 COVID-19 pneumonia

The SARS-CoV-2 coronavirus emerged in the end of 2019 in the city of Wuhan, China (P. Zhou et al., 2020). It is thought to have initially spread from an animal to a human, the first cluster of infections had links to a market selling food and live wild animals in Wuhan (Velavan & Meyer, 2020; W. Wang et al., 2022; Worobey et al.; Zhai et al., 2020). Soon it was clear that human to human transmission was not only possible, but rampant in the city and not long thereafter infections were diagnosed in other countries causing a global pandemic (J. Li et al., 2020; Sohrabi et al., 2020). The mean incubation periods is 5 days (Sohrabi et al., 2020), with many patients with COVID-19 only showing mild symptoms, but a substantial portion developed a viral pneumonia which can have grave consequences (Eythorsson et al., 2020). The administration of vaccines has decreased the likelihood of a severe viral pneumonia following infection (Baden et al., 2020; Polack et al., 2020; Tian et al., 2022). Early reports on mortality reported 1.4 – 3.6% mortality (Baud et al., 2020; Guan et al., 2020).

The most common symptoms of COVID-19 disease are fever, myalgia, headache, lethargy, cough, shortness of breath, decrease in sense of smell or taste, sore throat and gastrointestinal symptoms (Eythorsson et al., 2020). The literature on COVID-19 developed quickly but reports published during the first months of COVID-19 assessing risk factors of severe COVID-19 did not adequately adjust for biases and confounding (Jordan et al., 2020). The first studies identified higher age and sex as a risk factor for severe outcome which is a trait COVID-19 shares with pneumonia prior to the pandemic (Guan et al., 2020; Marrie, 1996; Petrilli et al., 2020; Williamson et al., 2020; C. Wu et al., 2020a; Z. Wu & McGoogan, 2020). Male sex, severe obesity, cancer, DM, chronic lung disease, chronic kidney failure and heart failure were later also associated with severe COVID-19 infection (Petrilli et al., 2020; Williamson et al., 2020).

This pandemic highlights the need to monitor country-level geographic variation in pneumonia etiology and symptoms to be constantly monitored and for the data to be automatically shared globally in as close to real time as possible.

### 1.16.1 Obstructive sleep apnea and severe COVID-19

Early-on obstructive sleep apnea (OSA) was proposed as a possible risk factor for severe outcome in patients with COVID-19 (McSharry & Malhotra, 2020), however OSA in itself is associated with many of the same risk factors as COVID-19: male sex, obesity, heart failure and DM (Farrell & Richards, 2017; Garvey et al., 2015; Shahar et al., 2001). Therefore, it was of great importance to adjust for these confounders when assessing the association og OSA with COVID-19.

A large study on hospitalized patients with DM diagnosed with COVID-19, which was performed early in the COVID-19 pandemic, assessed multiple risk factors simultaneously (Cariou et al., 2020). The Cariou study found an association for OSA with mortality following COVID with an OR of 2.8 (95% CI, 1.5-5.4) but 1.2 (0.8-1.7) for tracheal intubation and or death (Cariou et al., 2020). A study by Cade et al. did not find an association with death among those with COVID-19 and OSA however, Goldstein et al found an OR of 1.8 (95% CI 0.9-3.8) for death and Maas et al. found an OR of 1.7 (95% CI 1.4-2.0) for hospitalization and Strausz et al found an OR of 2.9 (95% CI 1.0-8.4) also for hospitalizations (Cade et al., 2020; Goldstein et al., 2021; Maas et al., 2020; Strausz et al., 2021). Many of these studies lacked adjusting for important confounders, almost all were not population-based, many had a strict selection criteria for patient inclusion, some lacked PCR confirmation of cases and/or clinical sleep analysis and some did not look specifically at OSA as a risk factor for severe COVID-19 and lacked corrections for multiple testing (Cade et al., 2020; Cariou et al., 2020; Goldstein et al., 2021; Gottlieb et al., 2020; Ioannou et al., 2020; Maas et al., 2020; Kristján Godsk Rögnvaldsson et al., 2021; Strausz et al., 2021). Therefore, a population-based study was called for, adjusting for known confounders to estimate the potential role of OSA as an individual risk factor for severe COVID-19.

# 2 Aims

The original aim of this study was to improve the diagnosis of pneumonia using PCR on swabs gathered from the URT in adults recently hospitalized with CAP as well as monitor changes in rates of etiologic agents. Many prior studies have done this before, however our study also collected URT swabs from an age and sex matched control group of patients hospitalized without new respiratory tract symptoms. This makes our study unique. The proposed novelty is that a control group will provide information on the actual carriage rates of respiratory viruses and bacteria and serve as a reference point for assessing the proportional contribution of individual pathogens in patients hospitalized with pneumonia. The few studies examining CAP etiology that have included control groups, have used healthy asymptomatic controls or outpatients and often only assessed a limited number of pathogens (Self et al., 2015). By using hospitalized patients without pneumonia as controls we argue that it gives a better estimate of the carriage rate among the population that is hospitalized, beyond using age and sex matched healthy community dwelling indiviudals.

After 2-years of planning, obtaining permissions, gathering funding, recruiting, sampling, surveying, and obtaining data we were ready to get the samples analysed by PCR in the summer of 2020. However, an impasse to our current research plan occurred, in the form of a global pandemic overwhelming the laboratories that were our planned collaborators for the PCR analysis. This meant we needed to make changes to the research plan.

The study team had noted that many patients with symptoms of pneumonia who had been screened and consented did not have a clear infiltrate on chest radiography. This sparked interest in this group, particularly their prognosis and survival compared to those with a confirmed infiltrate on chest radiography and resulted in the first paper of the study.

For the second paper we had seen studies that looked at the association of aspirin use and improved survival in patients with pneumonia. This led us to evaluate if we could assess this in our prospective dataset, but the low mortality rate and the relatively low sample number precluded any meaningful analysis. Magnús Gottfreðssson suggested using a different source of information, using information on patients with bacteremic pneumococcal pneumonia from a nationwide dataset which covers all IPD in Iceland from the year 1975. This work had been initiated in collaboration with Helga Erlendsdóttir several years

ago, thereby providing a larger dataset with a single pathogen as a model organism, with a longer follow-up time and greater number of endpoints, increasing the statistical power.

The idea for the third article came from my friend and colleague Vilhjálmur Steingrímsson, as he was working on COVID-19 wards from the beginning of the pandemic, he soon noticed that many of the patients admitted to the ICU had a diagnosis of obstructive sleep apnea. We discussed this idea and found that no study had been published on this association. Therefore, we decided to embark on the journey of performing this study along with Elías Eyþórsson, Össur Ingi Emilsson, Magnús Gottfreðsson and others.

## 2.1 Paper 1

The aim of the first study/paper was to compare prognosis and clinical characteristics of patients with symptoms of pneumonia without infiltrates on chest radiography with CAP patients with a confirmed chest infiltrate, with respect to short- and long-term mortality.

## 2.2 Paper 2

The aim of the second study/paper was to assess if use of ASA in the setting of bacteremic pneumococcal pneumonia is associated with improved survival.

## 2.3 Paper 3

The aim of the third study/paper was to assess if obstructive sleep apnea is a risk factor for severe COVID-19 after adjusting for important confounders.

# 3 Materials and methods

## 3.1 Study populations and settings

### 3.1.1 Paper 1 – prospective patient recuitment

The study took place at Landspitali- The National University Hospital of Iceland (LUH) it is the only hospital serving the capital area of Iceland. Roughly 2/3 of the population in Iceland lives in the capital area. The study population was recruited by the PhD candidate over a one-year period from May 1st, 2018 (following a two-week pilot period) to April 30th (2 weeks longer for the control group). Recruitment took place at the two adult emergency wards at the time at LUH, the emergency ward and the acute cardiac portal (Hjartagátt). The latter was changed to an ambulatory ward when the recruitment period was roughly halfway through, and thus in the second half of the period recruitment only took place at the emergency ward.

Screening of possible participants 18 years or older was performed in the following way: electronic patient lists at the emergency ward and the acute heart ward were monitored multiple times each day as was the electronic reporting of admissions to the internal medicine wards. Both have very short descriptions of patients' chief complaints and/or the preliminary diagnosis made by the managing physician. For example: "high fever and coughing, probably pneumonia", another example would be: "respiratory distress and fever". Patients with symptoms or a preliminary diagnosis that could be compatible with pneumonia were screened by the researcher for exclusion criteria and/or obvious lack of inclusion criteria. Inclusion criteria for participants in the pneumonia group included the following symptoms: temperature ≥38.0°C or ≤36.0°C, sweating, shaking/chills, chest pain, a new cough, or new onset of dyspnea. All pneumonia patients were required to have an infiltrate on a radiograph (CXR or CT scan) obtained within 48-hours of admission (Kristján Godsk Rögnvaldsson et al., 2023).

Recently admitted patients (<24 hours since arrival) without new respiratory tract symptoms matching pneumonia participants in terms of age (+/- 5 years) and sex were screened for participation in the control group. For this paper, the control group of patients was not used, because the main goal was to evaluate the significance of the infiltrate on chest radiography on mortality and other prognostic factors.

Exclusion criteria for all patients were: hospitalization within the prior 2 weeks, a definite infectious focus outside of lungs, severe neutropenia (<500 cells/µL), cytotoxic cancer therapy, organ transplant recipients and advanced HIV (CD4+ T cells < 200 cells/mm3) (Kristján Godsk Rögnvaldsson et al., 2023). For Paper I, cases were grouped into CAP and SPWI groups depending on the chest radiography assessment made by the on-call radiologist (specialist in medical imaging certified by the Directorate of Health). If the assessment included: pneumonia infiltrate, infiltrate of infectious origin or another wording with a similar meaning, the patient was grouped as CAP. Sometimes the assessment had some uncertainty, e.g. described as possibly, suspecting, beginning, suggests or the first differential diagnosis mentioned was pneumonia. These cases were all included in the CAP group. In the case of multiple images being obtained within 48 hours of the admission the highest quality image was used, e.g. if the initial image was obtained on patient lying in bed and the subsequent was a CXR on the patient standing or, if the initial image was a CXR and the follow-up study was a CT scan. All included patients or their surrogate signed an informed consent (Kristján Godsk Rögnvaldsson et al., 2023).

### 3.1.2 Paper 2 – data from a nationwide dataset on IPD

All cultures of streptococci (including pneumococci) at the microbiology and virology department at LUH from 1975 in normally sterile sites have been registered and stored at -70°C. Helga Erlendsdóttir, a clinical laboratory technologist and clinical professor has maintained this registry. Samples include positive cultures from blood, cerebrospinal fluid, peritoneal and synovial fluids. Several studies have been published using this dataset and the stored strains (Brueggemann et al., 2020; Sigurdardóttir et al., 1997; Snaebjarnardóttir et al., 2013; Þórðardóttir et al., 2014). In the early noughties (2000s) Professor Magnús Gottfreðsson supervised a couple of medical students, that went through medical records of cases diagnosed in 1975-2005. In 2021 a medical student continued and expanded this work to include cases diagnosed in 2005-2020 in addition to covering previously unreviewed cases from 1975-2005.

For the study presented in paper 2, all cases 18 years of age or older with a blood culture of *S. pneumoniae* and radiography consistent with pneumonia according to the on-call radiologist were included. Cases that had received ASA prior to the admission, according to the admission medical records were classified into the ASA group and other cases were classified into the control group.

### 3.1.3 Paper 3 – two datasets: obstructive sleep apnea and COVID-19

All adults diagnosed with a SARS-CoV-2 infection with a PCR test in the year 2020 in Iceland were included in the data, if determined to have active COVID-19 by the COVID-19 ambulatory clinic at LUH. Detailed information regarding symptoms of the patients and the severity of the infection was gathered by the COVID-19 outpatient clinic at LSH, mostly through phone calls (Eythorsson et al., 2020; Gudbjartsson et al., 2020; Helgason et al., 2020). This approach has been described thoroughly in previous studies (Eythorsson et al., 2020; Helgason et al., 2020).

Sleep studies performed prior to the diagnosis of COVID-19 were assessed, as were medical records relating to the sleep studies and the diagnosis of obstructive sleep apnea (OSA). Treatment with positive airway pressure (PAP) devices was identified. The Division of Respiratory Medicine and Sleep at LUH is the single providor of PAP therapy in Iceland.

The apnea-hypopnea index (AHI) was used to categorize patients as having OSA or not, AHI≥5 times/hour was defined as a cutoff for inclusion in the OSA group and they all had symptoms consistent with OSA (Sateia, 2014).

Patients diagnosed with SARS-COV-2 when already hospitalized or those reciding in nursing homes were excluded.

## 3.2 Variables obtained

### 3.2.1 Paper 1

Data regarding demographics, symptoms, inclusion and exclusion criteria, alcohol consumption, smoking, vapeing, injection drug use, recent travel abroad, nursing home residence, prior hospitalizations, prior antibiotic therapy, underlying illnessess (also checked in medical records), FRAIL questionnaire, ECOG performance score, the Abbreviated Mental Test Score (AMTS) and number of falls in the past 1-year were gathered by the researcher at the time of recruitment. This information was collected using an online data gathering tool, REDCap, maintained at the University of Iceland (P. A. Harris et al., 2009). The AMTS was used to assess delirium as had been done in the CURB-65 score (Lim et al., 2003a; QURESHI & HODKINSON, 1974). Frailty was also measured in the same interview using translated questions from the FRAIL questionnaire and the Eastern Cooperative Group performance status (ECOG) (Jeon et al., 2017; Morley et al., 2012). An oropharyngeal swab was collected from all the patients during this bedside interview.The study was observational

and the researchers did not have control over clinical management of patients.

Data from medical records was subsequently monitored, registered, and transferred to the REDCap data management program when all patients had been recruited. Underlying illnesses registered in the admission medical records were obtained and supplemented with previous diagnostic codes that are registered in the electronic patient history in an ICD-10 format, current medication use was collected from the admission records and supplemented with the Prescription Medicines Register of the Directorate of Health. Survival was assessed 1-year after admission of each patient based on national data from Registers Iceland. Active malignancy was defined as a history of active malignancy within 5 years. Daily use of 5mg of prednisolone or other equivalent glucocorticoid for more than 1 month before admission was defined as chronic use of glucocorticoids. Pneumonia Severity Index (PSI), CRB65 and quick Sequential Organ Failure Assessment (qSOFA) scores were calculated from vital signs and test results at arrival. CURB-65 was not calculated as serum urea was only available in less than half the patients included in the pneumonia group. Missing values in the severity scores were treated as a normal value to enable the calculation for all patients.

### 3.2.2 Paper 2

Medical records were non-electronic for many of the cases prior to 2007, but after that they were almost exclusively electronic. Data was transported to the Filemaker Pro 8.0 v2 program and when data registration was completed, it was exported as a comma separated value (csv) file for statistical analyses. Data was collected on age, sex, symptoms, vital signs, comorbidities and lifestyle, Glasgow coma score (GCS), results from laboratory analysis and medical imaging, intensive care unit admissions, mechanical ventilation, pneuamonia treatment, length of admission, complications, serogroup/serotype of the pneumococcus and antimicrobial resistance test results. Active underlying illnesses listed as part of past medical history of the patient were included. APACHE II (Acute Physiology and Chronic Health Evaluation II) was calculated from values in the first 24 hours of admission. APACHE II is in incremental scoring system, higher score means more severe disease and higher mortality, the lowest possible score is 0 and the highest score is 71. Missing values for the APACHE II score were treated as a normal value, so if all values were missing that case would have had a zero overall APACHE II score of zero.

### 3.2.3 Paper 3

The presence of underlying illnesses was based on the ICD-10 codes in the hospital discharge registry, the Register of Primary Health Care and in the Private Practice Register which is handled by the Directorate of Health. This was the method for all comorbidities apart from chronic kidney disease which was defined based on two separate measurements of creatinine and calculation of glomerular filtration rate, but transient events of acute kidney injury were not included as a chronic kidney disease. The presence of the comorbidities was cross-checked if applicable using the Prescription Medicines Register of the Directorate of Health, more than 14 days but less than 1 year before the SARS-CoV-2 diagnosis. Management and collection of this information on COVID-19 patients and their comorbidities was done by Elías Eyþórsson as previously described (Eythorsson et al., 2020). The PhD candidate and Vilhjálmur Steingrímsson collected data related to OSA diagnoses from the nationwide Sleep Department Registry. This included data on weight, height, date of clinical sleep analysis, time of diagnosis of OSA, information on treatment if initiated and if waiting for treatment, halting of treatment, the presence of an application for cPAP therapy, AHI, supine AHI, Epworth sleepiness scale score, oxygen desaturation events per hour, average $SpO_2$, lowest $SpO_2$ and $SpO_2$ time below 90%.

## 3.3 Outcome measures

### 3.3.1 Paper 1

The primary outcomes of the first paper were mortality at 30-days and 1-year. The literature on pneumonia commonly uses 30-day mortality or in-hospital mortality for outcome assessment. In recent decades studies on longer term mortality have increasingly been published, especially among older adults (Grijalva, 2015; Mortensen, 2011; Nguyen et al., 2019; Marcos I. Restrepo et al., 2013; Szakmany et al., 2021; Tokgoz Akyil et al., 2018). Additionally, the risk of common comorbidities following pneumonia, e.g. cardiovascular diseases has been found to be elevated for months and even years. Therefore, 1-year mortality following pneumonia was also included as outcome.

### 3.3.2 Paper 2

The primary outcomes of the second paper were survival at 30-days, 90-days, and 1-year. The same reasons for including these endpoints apply here as in the first paper.

### 3.3.3 Paper 3

The endpoint of this study was a binary variable made from combining

hospitalizations and death. The variable was given value 1 if the case was either hospitalized or died. This outcome was chosen as it represented more severe disease and at the same time had more statistical power than only including death or intensive care admissions. Many of the previous studies included hospitalizations or death as their endpoint variable.

## 3.4 Covariates selected for adjustment

### 3.4.1 Paper 1

Variables for adjustment were selected *„a priori“* based on the literature, this was done because pneumonia mortality has been extensively studied and many risk factors have been identified (Flanders et al., 1999; Lim et al., 2003a).

There were 32 endpoints for the 30-day mortality and thus the number of covariates was limited. A general rule of thumb is that regression models can accommodate one predictor for roughly every 10 events (Peduzzi et al., 1996; Vittinghoff & McCulloch, 2007). Based on this we selected three variables for adjustment, which made the total number of variables in the analysis four (including the variable of interest: grouping of patients into the SPWI or the CAP group). Age and sex are standard parameters commonly used in pneumonia studies, thus we had only one spot left for a covariate. CURB-65 and PSI were considered, but both suffered from missing data. CCI was selected as we had complete data on it and the CCI is a well-known general mortality risk assessment tool. It has been shown to be associated with both short-term and long-term mortality following pneumonia in recent pneumonia studies (Nguyen et al., 2019; S. Song et al., 2018; Surme et al., 2021; Szakmany et al., 2021).

### 3.4.2 Paper 2

Covariates selected for inclusion in the propensity score for adjustment of groups in paper 2 were selected based on the research literature on mortality following pneumonia. When choosing covariates for use in propensity scores, it is important to select all variables which are associated with the outcome measure (in this case mortality), however, including variables which are only associated with the exposure (variable of interest) and not the outcome can increase bias (Bergstra et al., 2019; Brookhart et al., 2006). We kept this in mind when we chose the variables. Age and sex have almost always been included in previous studies. Nursing home residence, functional status, do not resuscitate order, heart failure, liver disease, neoplastic disease, chronic kidney disease, cerebrovacsular disease and current malingnacy have all been

reported to be associated with 30-day mortality (Fine et al., 1997; Flanders et al., 1999; Lim et al., 2003a; Murcia et al., 2010). Unfortunately, in this cohort we did not have information on frailty. Smoking, alcohol abuse and chronic lung disease have also been reported by others to be associated with mortality following pneumonia (Drijkoningen & Rohde, 2014; Gili-Miner et al., 2015; Gupta et al., 2019; Naucler et al., 2013). DM has in some studies also been identified (Foley et al., 2015; Kukull et al., 1994; Torres et al., 2015). Additionally immunosuppressive treatment has also been associated with mortality in some studies (D R Feikin & Jorgensen, 2000), as has dementia (Hespanhol & Bárbara, 2020). In contrast, statin use has in some studies been associated with improved survival following pneumonia (Chalmers et al., 2008; Nielsen et al., 2012).

A whole range of examination variables and laboratory tests are related to outcome (Fine et al., 1997; Flanders et al., 1999; Lim et al., 2003b), but we did not include those, because the exposure, aspirin-use prior to admission, means the drug had been used for some time before the examination. If aspirin decreases the risk of mortality following pneumonia it is possible that at the time of the examination and laboratory tests, the groups would be different because of the effects of aspirin. Adjusting for them would lead to thinning of the possible effects of aspirin on pneumonia mortality. Therefore, we did not adjust for examination and laboratory tests.

### 3.4.3 Paper 3

Covariates were chosen *a priori* based on the literature for the third paper as well. It was clear at the time that many of the known risk factors for severe COVID-19 infection were known comorbidities or complications of obstructive sleep apnea (McSharry & Malhotra, 2020; Mutti et al., 2020; Pazarlı et al., 2020). In the fully adjusted model, the following variables were included: age, sex, BMI, hypertension, heart failure, chronic kidney failure, DM, COPD and current smoking.

## 3.5 Statistical analysis

All statistical tests were performed using Rstudio (Rstudio Team 2021) and R (R core Team 2021) (R. Team, 2021a; R. C. Team, 2021b). Confidence intervals and/or p values were presented, and p values less than 0.05 were deemed significant in two tailed statistical tests.

### 3.5.1 Paper 1

#### *3.5.1.1 Mortality analysis*

In the first study the association of absence of an infiltrate (patients grouped to the SPWI group) with mortality was assessed using logistic regression and results were described using odds ratios (ORs). Data was missing on smoking in 8.5% of participants, therefore multiple imputation was performed calculating the association with 1-year mortality. We performed 20 multiple imputations by chained equations (MICE) (van Buuren et al., 2015; Zhongheng Zhang, 2016). Data sets were complete for 30-day mortality logistic regression. Results were presented with a 95% confidence intervals. Survival was measured from the time of arrival at the emergency ward or the acute heart portal and the endpoint was the time of death or the end of follow-up if the patient survived.

#### *3.5.1.2 Descriptive analysis*

Additional descriptive comparison of the groups was performed using Fisher‘s exact test and Mann-Whitney U test. However, due to the number of the planned descriptive analyses, we performed adjustment of the P-values limiting the false discovery rate (FDR), also known as the Benjamini-Hochberg method (Glickman et al., 2014). Testing for multiple associations without adjusting for multiple testing increases the risk of finding associations due to chance (Bender & Lange, 2001; Glickman et al., 2014; Jafari & Ansari-Pour, 2019). Using this method we limited the number of these findings but we did not eliminate them, and using the FDR method highlights that these are exploratory findings that need to be confirmed in larger, preferably multicenter studies (Glickman et al., 2014). Bonferroni is another popular method of limiting the number of false positive associations found when testing multiple associations, but it is much more aggressive and has the tradeoff especially in smaller samples to decrease power quite significantly (Glickman et al., 2014).

#### *3.5.1.3 Repeated admissions*

Individuals with more than one admission were excluded from the primary outcome analysis if they had been included within 30 days for the 30-day mortality analysis or within 1-year for the 1-year mortality. Due to this, 4 episodes were excluded in the 30-day mortality assessment and 49 in the 1-year mortality.

#### *3.5.1.4 Missing data*

Missing data was reported in tables 1-3, the highest rate was observed in the FRAIL questionnaire score (21.1%), then for the ECOG performance score (17.6%), alcoholism (17.0%), daily smoking (8.5%), serum-glucose at

admission (4.8%), and then several variables had missing values in 5,4,3,2, or 1 case. Of these, only smoking was planned for outcome analysis in the 1-year adjusted logistic regression of mortality. The analysis was thus performed as a complete case analysis and another analysis utilizing MICE, with 20 repetitions using the mice package in r (van Buuren et al., 2015; Zhongheng Zhang, 2016).

#### *3.5.1.5 Sensitivity analysis*

Two sensitivity analyses were performed, first excluding cases with a chest CT scan then excluding patients who did not receive antibiotics. This was done as it was hypothesized that these variables could potentially be associated with mortality. Those that received a chest CT scan probably had a more severe disease than those that did not receive a chest CT scan and the same can be said about those that received antibiotics.

### 3.5.2 Paper 2

#### *3.5.2.1 Survival analysis*

The main outcome of paper 2 was the survival at 30-days, 90-days, and 1-year. Kaplan Meier survival curves were plotted, and Cox regression was performed using propensity scores for inverse probability weighting. The reason for choosing Cox regression was that it utilizes the data better than logistic regression when dealing with survival data. Logistic regression treats deaths that occur soon or late in the follow-up the same, making Cox regression more accurate and more powerful in detecting differences (Annesi et al., 1989; Green & Symons, 1983). Additionally, it can utilize available data even if the patient didn't finish the follow-up, with the censoring at the time of loss of follow-up, which is not possible with a traditional logistic regression. In our study we also used censoring for individuals with repeated participation, censoring the prior admission at the start time of the second admission. This makes it possible to utilize the full follow-up period of the patient without counting the survival twice of this single individual. Using traditional logistic regression, we would have to exclude the latter admission from the analysis and thus loose valuable data.

We decided to use propensity score weighting, inverse probability weighting rather than a logistic regression model, due to the many known risk factors of pneumonia and the fact that we expected patients on aspirin to differ substantially from those not on the drug. Propensity score methods are known to be good at decreasing confounding if done properly (Austin, 2011; Austin &

Stuart, 2015). Another important factor as has been previously mentioned is the limited number of adjustment variables regression models can accommodate, when the number of endpoints is relatively low (Peduzzi et al., 1996; van Smeden et al., 2018; Vittinghoff & McCulloch, 2007).

The time of blood culture collection marked the start for the survival analysis and the endpoint was death. Survival was measured in days, death within one day was reported as a fraction of a day. Censoring was done at the end of follow-up and if the patient had another infection that qualified for inclusion in the study, then the survival for the first admission was censored and the survival follow-up for the second infection started. Another infection was deemed eligible if it occurred more than 14 days after the inclusion of the prior one or if the two infections were caused by different serotypes of pneumococci. Cox regression with clustering of individual cases was done to account for the individuals with repeated inclusion. We tested if the hazards were proportional using the cox.zph() function from the Survival package in R (Therneau & Lumley, 2015). If the hazards were not proportional, we splitted the survival time depending on the hazard slope using the survSplit function from the Survival package (Zhongheng Zhang et al., 2018). Average hazard ratios were also presented when the assumption was violated (Lau et al., 2009).

#### *3.5.2.2 Propensity score weighting – inverse probability weighting*

When performing propensity score analysis, it is important to select covariates related or thought to be related to the outcome, even those being unrelated to the exposure (Adelson et al., 2017; Austin & Stuart, 2015; Bergstra et al., 2019; Brookhart et al., 2006). Including variables only associated with the exposure variable but not the outcome variables can increase the bias of the study (Adelson et al., 2017). Additionally, it is of great importance that there is overlap of the propensity score values of patients in the exposure and control groups (DuGoff et al., 2014).

When perfoming inverse probability weighting it is important to assess the balance of covariates before and after propensity score adjustment, the standard mean difference is recommended as is a graphical observation of the difference before and after adjustment (Austin & Stuart, 2015).

#### *3.5.2.3 Treatment effect*

When doing propensity score weighting one has to choose if calculations

should be done to estimate the average treatment effect overall (ATE) or the average treatment effect of the treated (ATT). In this paper we chose the ATT.

When performing a randomized controlled trial ATE and ATT are the same. However, in many observational studies ATT and ATE can differ quite significantly. ATT is the effect found if patients already receiving the drug would not have received the drug, but the ATE is the effect if all patients in the study (both in the control and treatment group) would have received the exposure compared to the scenario if none of the patients had received the drug (Austin, 2011).

When choosing between ATE and ATT one should evaluate if the target group of the possible treatment/exposure would be the whole study population, in this context all patients diagnosed with a bacteremic pneumococcal pneumonia. We could not be sure of this as according to the literature the possibility of aspirin reducing mortality is highest among patients with certain cardiovascular risk factors. It is likely it would not be offered to all patients with invasive bacteremic pneumonia, but rather to a selected group of pneumonia patients with an elevated cardiovascular risk, but not already receiving cardiovascular therapy. Aspirin has also important contraindications and complications that would limit the use in a substantial part of the population. Patients under 30 years of age without any cardiovascular risk factors would be very unlikely to have any benefit of the agent if we believe the potential effects of ASA on pneumonia mortality are through cardiovascular risk decrease. Contraindications for the use of this drug include severe kidney or liver failure which were covariates used in the propensity score. Other contraindications for the drug inlude allergy, active bleeding, very low platelet levels, use of methotrexate more than 15 mg per week, and recent thrombolytic therapy (Association, 2004; Lyfjastofnun Icelandic Medicines Agency, 2021; Petersen et al., 2012).

Another consideration was the fact that the ATE requires a stricter positivity assumption than the ATT. Using the ATE the distribution of the propensity scores in both groups should be overlapping, but for the ATT it is important that the distribution of the propensity scores for the treated/exposed group are within the distribution of the propensity scores of the control group (Petersen et al., 2012; Pirracchio et al., 2016).

Choosing the ATT means that the effect that we get of the main outcome analysis is the survival effect among the group on ASA compared to if the same group had not received ASA, after adjustment for the covariates of the control group (Pirracchio et al., 2016).

#### *3.5.2.4 Missing data*

Information on the survival of 14 cases that moved abroad during the follow-up were missing. Because the exact timing of their loss to follow-op was unknown they were excluded from the analysis. Information was most frequently missing for the active smoking variable, in 33.5% (273/815) of episodes. The smoking variable was included in two sensitivity analyses – a complete case analysis and a multiple imputation analysis. Muliple imputations (20 imputations) were performed using the MICE package in R, as previously described (van Buuren et al., 2015).

Multiple imputation and propensity score weighting were combined using the „within“ method (Granger et al., 2019), this was done using the MatchThem package in R (Pishgar et al., 2021). Combination and pooling of imputations and outcome analysis was performed using pooling according to Rubin‘s rules (Granger et al., 2019).

#### *3.5.2.5 Sensitivity analyses*

Several sensitivity analyses were planned, Cox regressions with a traditional direct covariate adjustment, Cox regression using IPW on the associations of beta blockers, statins, proton pump inhibitors and macrolides with mortality.

### 3.5.3 Paper 3

#### *3.5.3.1 Outcome analysis*

The main outcome was the combination of hospital admission and mortality. Models with increasing number of adjustment variables were assessed. The first model included no adjustment, the next only age and sex, the third included BMI and the fourth was a fully adjusted model. Logistic regression was used in the main analysis of the different models. In addition, inverse probability weighting was done. Multiple imputation of missing information was done and outcome analyses using all the variables. The outcome analysis were performed on imputed datasets, following 100 imputations. Odds ratios (ORs) were calculated with 95% confidence intervals (CI). The logistic regression was performed using the rms package and combining of the propensity score and the imputations was performed using the MatchThem package in R (Harrell Jr et al., 2017; Pishgar et al., 2021). When performing the logistic regression, restricted cubic spline was used to model age, using 4 knots. Pooling of the results following the imputations was done according to Rubin‘s rules, as has been stated previously. Here we estimated the average treatment effect since the people with obstructive sleep apnea were not given

a certain treatment or drug, this is a chronic disease which was the chosen variable of interest and importantly it is not possible to remove the variable of interest (OSA) in isolation without other covariates changing (Thor Aspelund, 2021). The difference in outcome if all cases had OSA compared to if none of the patients had OSA, is the prefereable outcome in this case. On top of previously mentioned requirements for ATE to be valid a stable unit treatment value is required, which means that there should be no “spillover effect” between cases and each case should have only one outcome and the same treatment/exposure as other cases (Sävje et al., 2021). There is no evidence in the literature to suggest that this assumption is substantially violated in our study settings.

#### *3.5.3.2 Missing data*

Data was missing for BMI. Missing data was imputed using the rms package in R, multiple imputations by chained equations were performed.

#### *3.5.3.3 Sensitivity analysis*

A sensitivity analysis was done that used only individuals with complete information, often called a complete case analysis. This was done to observe if the results of the outcome analyses changed markedly when excluding cases with missing information, this would have led us to re-evaluate the imputations or to re-examine the groups with missing and available information

## 3.6 Ethics statement

We obtained permits for the research required by the Icelandic law and according to the Helsinki Declaration. The Chief Medical Executive and the Health Research Ethics Committeee at LUH (application number 19/2018) granted the group permits for the study utilized in the first article. All patients in the prospective study or their surrogate signed an informed consent. Permission was obtained from the National Bioethics Committee (VSNb2015020023/03.01) and an extension was granted from the same institution in 2021 (VSN15-039 V3 and V4) for the study which data was used in the second paper. For the third study on COVID-19 and obstructive sleep apnea the work was based on a permit granted from the National Bioethics Committee (VSN20-078).

# 4 Results

## 4.1 Paper 1

### 4.1.1 Basic characteristics, symptoms, vital signs, and laboratory results

625 episodes met the final inclusion requirements, of those 409 had an infiltrate on CXR and were thus placed in the CAP group, 216 did not and were categorized as SPWI. Median age at inclusion was 75 years (Interquartile Range (IQR) 64-84), 315 of the episodes were among females and 310 among males. The CCI was higher among patients with SPWI than CAP, but with the same median of 2 (IQR 1-4 vs. 1-3, p=0.007). All patients in the SPWI group had at least one of the listed underlying illnesses (Table 1 – Paper 1) but 15 (3.9%) in the CAP group did not have any of the listed underlying illnesses.

The symptom profile on admission was similar for both groups, apart from fever (≥38.0°C) which was more frequently reported by patients and measured in the CAP group (75.6% vs. 65.3% p=0.038 and 66.9% vs. 49.3% p<0.001, respectively). No major difference in vital signs on admission was observed between the groups. However, inflammatory indicators were higher in the CAP group, both CRP (median 103mg/L (IQR 34-205) vs. 55 (IQR 17-103), p<0.001) and white blood cell (WBC) counts (median $13x10^9$ (IQR 10-17) vs. 11 (IQR 8-14), p=0.002).

While median severity scores were slightly higher in the CAP group this difference was not statistically significant, qSOFA (median 2 (IQR 1-2) vs. 1.5 (IQR 1-2)), CRB65 (median 1 (IQR 1-2) vs. 1 (IQR 1-2)) or the PSI (median 102 (IQR 74-125) vs. 99 (IQR 79-123)), (p=0.64, 0.95 and 0.97, respectively).

### 4.1.2 Etiology, treatment, and prognosis

There were some differences in rates of etiologic testing between the groups. Pneumococcal antigen testing from urinary samples was more commonly performed among the CAP patients than the SPWI patients (52.6% vs. 30.2%, p<0.001), the same was true for blood cultures (67.2% vs. 49.5%, p<0.001). Among tested participants, respiratory viruses were more commonly found among the SPWI group (51.2% vs. 25.4%, p<0.001) and conversely *S. pneumoniae* was more commonly found when tested for among the CAP group (18.0% vs. 6.3%, p=0.002).

Antibiotics were administered to all but two patients (99.5%) in the CAP group, but to 87.5% in the SPWI group (p<0.001). Length of stay was similar (median of 5 days in both groups). The proportion admitted to the intensive care unit (ICU) was 5.6% in the CAP goup and 1.9% in the SPWI group (p=0.125). Non-invasive (BiPAP/cPAP) ventilation was used in 11.0% of CAP patients and 13.4% of SPWI patients (p=0.629). Readmission rates were 15.4% and 19.9% respectively for the CAP and SPWI groups (p=0.381). A significant difference in antimicrobial choice was noted, treatment included coverage for atypical pneumonia pathogens in 52.6% among CAP vs. 39.8% among SPWI (p=0.013).

### 4.1.3 Outcome analyses

Unadjusted mortality at 30 days in the CAP and SPWI groups were 5.2% and 5.1% respectively, and 17.4% and 25.0% at 1 year, respectively. Logistic regression adjusting for age, sex and CCI, showed an adjusted odds ratio (aOR) for death of 0.86 (95% CI, 0.40-2.42) for SPWI compared to CAP at 30 days. An analysis excluding cases with missing information for the 1-year mortality had an aOR for mortality of SPWI compared to CAP of 1.50 (95% CI, 0.93-2.42) and an analysis following multiple imputation of the missing data showed an aOR of 1.46 (95% CI, 0.92 -2.32). Age, sex, CCI, do not resuscitate directive, smoking, and nursing home residence were adjusted for in the 1-year outcome analyses.

### 4.1.4 Supplementary and sensitivity analyses

Within 48 hours of admission 55% of patients in the CAP group and 65% of patients in the SPWI group had one CXR and no other radiograph (CXR or CT) performed, 58% overall. All patients included in the study received at least one lung radiograph within 48 hours of admission. Of those with more than one radiograph, 33 cases with an initially negative study had an infiltrate on a subsequent study performed within 2 days. Conversely, 10 patients´ first image showed an infiltrate which was not visible on later radiography. To change the diagnosis the later image was required to be of better quality than the first one e.g., standing or sitting CXR was considered of better quality than a bedside CXR; likewise, a CT scan trumped a CXR. Within 48 hours 22% of SPWI patients and 30% of CAP patients underwent a CT study, 27% overall.

Sensitivity analysis excluding patients with a CT scan showed an aOR 0.99 (95% CI, 0.34-2.90) for the 30-day mortality of the SPWI group and at 1-year the aOR was 1.22 (95% CI, 0.68-2.19). A sensitivity analysis excluding patients who did not receive antibiotics gave an aOR of 0.78 (95% CI, 0.34 – 1.78) at

30-days and 1.50 (95% CI, 0.93-2.42) at 1-year following multiple imputation.

## 4.2 Paper 2

### 4.2.1 Patient characteristics

1505 positive blood cultures were registered in the Icelandic pneumococcal registry from 1975-2020. In 48 of these cases no medical records could be obtained. Only adults with a confirmed pneumonia were included in the study, thus the final dataset was comprised of 815 bacteremic episodes in 795 individuals.

The burden of underlying disease was greater among patients receiving ASA at admission (Table 1 – Paper 2). Patients taking ASA were older and had more frequently been diagnosed with DM, hypertension, ischemic heart disease, cerebrovascular disease and heart failure. Other cardiovascular drugs (statins and beta blockers) were also more commonly used by patients in the ASA group, the same was true for proton pump inhibitors (PPIs). However, current smoking and alcoholism rates were lower among patients using ASA compared to those not using the drug (smoking 34.5% vs. 53.5%, and alcoholism 3.1% vs. 10.9%). Information on smoking was missing for similar proportions in both groups (34.4% among ASA and 33.3% among those not on ASA). Patients taking ASA had a higher median APACHE II score (13 [IQR 10-16] vs.12 [IQR 8-16]) but admission rates to the ICU were similar (20.3% vs. 20.2%).

### 4.2.2 Outcome analyses

The unadjusted mortality rate at 30-days was 14.8% for the ASA group and 13.3% for the control group. At 90-days it was 18.0% vs. 18.2% and at 1-year it was 22.7% vs. 25.7%. Unadjusted survival curves show a slightly lower mortality in the first 14 days for patients taking ASA compared to those not taking the drug, albeit nonsignificant (Paper 2, Figure 2a) (Kristján G. Rögnvaldsson et al., 2022).

A notable difference between survival curves is seen after adjustment with IPW (Paper 2, Figure 2b), with a higher survival rate among those taking ASA. The fastest separation between the lines occurs in the first few days and the separation continues to grow until 1-year following the infection when the curves start to converge. Inverse probability weighting is commonly used to control for confounding. It works by estimating how likely each case was of having received the exposure/treatment, the inverse of this probability is then used as a weight.

The main outcomes using Cox regression with IPW were a hazard ratio for those on ASA (HR) of 0.42 (95% CI 0.19-0.92) for days 0-6 and 1.08 (95% CI 0.46-2.55) for days 7-30. The average HR for the 90-day mortality was 0.53 (95% CI 0.32-0.87) and 0.48 (95% CI 0.31-0.75) for the 1-year mortality. Because of the non-proportional hazards within 30-days, splitting of the survival period was done before and after day 7, guided by the hazard slope.

### 4.2.3 Causes of death analysis 1975-2015

Cardiovascular disease was registered as the primary underlying cause of 30-day mortality in 1.9% of all patients in the ASA group and 2.3% of all patients in the non aspirin group. Pneumonia or sepsis was registered in 5.6% and 5.4%, respectively and malignancy in 2.8% and 3.3%. However, at 1-year 4.6% of patients in the ASA group had cardiovascular disease as their primary underlying cause of death and 3.9% of those in the non-ASA group. Malignancy was coded as a primary cause of death among 4.6% of patients in the ASA group and 10.2% of patients not in the ASA group.

### 4.2.4 Sensitivity and supplementary analyses

A traditional multivariable Cox-regression was performed. For 30-day survival the average HR was 0.66 (95% CI 0.39-1.09) and for 1-year survival it was 0.54 (95% CI 0.35-0.82).

The main outcome analysis lacked the smoking variable, when it was added to the IPW model in a complete case analysis (excluding cases that did not have information on smoking) the average HR for the 30-day mortality was 0.70 (95% 0.29-1.66) and for the 1-year mortality it was 0.47 (95% CI 0.27-0.85). Imputation of the missing information however lead to an average HR of 0.60 (95% CI 0.34-1.07) for the 30-day survival and 0.49 (95% CI 0.31–0.78) for the 1-year survival.

Exchanging our main variable of interest (ASA) with other common drugs (including medications commonly used in heart diseases) did not lead to any significant associations. The other drugs tested were beta blockers, PPIs, statins and macrolides. Statin use did show a nonsignificant trend towards protection, however.

Splitting the dataset into decades showed similar HRs. However, a post-hoc analysis prompted by a reviewer, splitting the dataset into two by cases diagnosed during typical influenza period or outside typical influenza period, showed a significant protective effect for ASA only among cases diagnosed during the influenza period but not during other periods.

Regarding antimicrobial therapy, 94.6% of patients in the not on-ASA group received beta-lactams and 95.3% in the ASA group. Information on penicillin susceptibility was available in 75.7% of all cases. 7.1% of ASA cases had reduced susceptibility to penicillins and 7.3% of the non-ASA group. Only 1 patient had a penicillin-resistant strain and 44 had intermediate penicillin-resistance according to results of disc screening or E-tests. After reviewing susceptibility data and the treatment regimes provided it was estimated that therapy was inadequate in only 1 case which was in the non-ASA group. Additionally, therapy of uncertain clinical efficacy was provided in 7 cases (1 in the ASA group and 6 in the non-ASA group).

## 4.3 Paper 3

### 4.3.1 Basic characteristics

The overall sample included 4756 individuals with a COVID-19 diagnosis by PCR and evaluation by the outpatient COVID-19 ward at LUH, of those 185 (3.9%) had a prior OSA diagnosis. The median age of cases diagnosed with OSA was 59 (IQR 50-67) vs. 39 (IQR 28-53) in the non-OSA group. BMI was also higher in the OSA group (median of 32 [IQR 29-36] compared to 26 [IQR 23-29]). Patients in the OSA group also had a higher prevalence of hypertension, DM, heart failure, chronic kidney disease, COPD but not smoking. At the time of COVID-19 diagnosis 49% of the OSA group were using PAP therapy, 13% had stopped using PAP, 8% were on a waiting list and the rest (30%) had not been prescribed PAP therapy.

### 4.3.2 Main outcome analysis

The unadjusted rates of the combined endpoint (death or hospitalization due to COVID-19) were 4% (200/4571) in the non-OSA group and 21% (38/185) in the OSA group. This translates to an odds ratio of 5.6 (95% CI 3.8-8.3) using logistic regression (Figure 3). The OR for the association of OSA with the combined endpoint was 2.0 (95% CI 1.2-3.2) when correction with all the included covariates had been applied using the logistic regression. The inverse probability weighting analysis showed an OR of 2.0 (95% CI 1.1-3.6) (Figure 1).

| Model | Odds ratio (95% CI) |
|---|---|
| **Raw numbers** | 5.6 (3.8–8.3) |
| **Sex and age** | 2.9 (1.9–4.4) |
| **Sex, age and BMI** | 2.2 (1.4–3.5) |

| | |
|---|---|
| **All covariates*** | 2.0 (1.2–3.2) |
| **Inverse probability weighting*** | 2.0 (1.1–3.6) |

*Age, sex, BMI, hypertension, diabetes mellitus, heart failure, chronic kidney disease, COPD, smoking status, and BMI

Figure 1 Outcome analysis from paper 3, displaying different OR depending on covariates included in the analysis.

### 4.3.3 Supplementary and sensitivity analyses

An analysis limited to the subgroup of patients with a confirmed OSA diagnosis prior to COVID-19 infection (n=185) comparing those that received PAP treatment (n=90) with those that did not showed an unadjusted OR of 2.1 (95% CI 1.0-4.4) and the fully adjusted model resulted in an OR of 1.9 (95% CI 0.6-6.0) for the risk of severe COVID-19 (hospitalization or death). Using the same subgroup another analysis was performed, where OSA patients not receiving PAP therapy were the reference group patients treated with PAP for less than 4 years had a fully adjusted OR of 4.1 (95% CI 0.9–18.6) but those that had received PAP therapy for more than 4 years had an aOR of 1.4 (95% CI 0.4-5.5).

Sensitivity analysis including only cases with no missing information (complete case analysis) showed similar ORs to main outcome analysis.

# 5 Discussion

The results presented here contribute to the literature on „classic pneumonia“ (CAP) and „non-classic“ pneumonia among hospitalized adults. Papers 1 and 3 targeted two different non-classic pneumonia: SPWI and a viral pandemic pneumonia (COVID-19). Paper 2 assessed the assocation between use of ASA and mortality among those with a bacteremic pneumococcal pneumonia, the archetype of pneumonia from the early 20th century (Daniel M Musher et al., 2017).

The incidence of hospitalization due to SPWI turned out to be significant. Even though vital signs and inflammatory markers indicate less severe disease and pneumococci were less frequently detected among patients in the SPWI group, mortality was similar to CAP at 30-days and 1-year following hospitalization. The results of this study reinforce both the size and disease severity within this understudied group of patients. Use of ASA on admission was associated with decreased mortality following bacteremic pneumococcal pneumonia, after rigorous adjustment. However, further work needs to be done to establish if the association is causal. Lastly, obstructive sleep apnea is associated with a more severe COVID-19 after adjusting for known confounders.

## 5.1 Paper 1 SPWI and CAP – Searching for similar previous studies

Prior studies on CAP among hospitalized patients almost always require radiological confirmation and therefore exclude cases without infiltrates. The few studies that include patients with SPWI very rarely compare this group of patients to those with documented infiltrates. The study by Basi et al. published in 2004 is the only prior study we have found that does exactly this. Basi et al. report a 2:1 ratio between CAP and SPWI incidence requiring hospitalization. Another more recent study performed in Malawi showed a ratio of 3:1 of CAP vs. SPWI incidence of hospital admissions (Aston et al., 2019; Basi et al., 2004). The Malawi study did however not compare the CAP and SPWI groups directly and the patients were much younger than in our group. In the study by Basi et al. the comorbidity rate was similar in both patient groups, however the mortality was 8% in the SPWI group but 10% in the CAP group (p=0.09). The

study by Basi et al. provided a novel insight into this area but it lacked detailed information on comorbidities, vital signs, PCR and antigen-based diagnostics and on treatment, ICU admissions, ventilation (non-invasive and invasive), length of hospital stay and longer-term mortality. Some of these limitations can be explained by the fact that the study was performed more than two decades ago.

Interestingly, some studies have been published comparing patients with a negative CXR but a positive CT scan (red circle in figure 2) to patients

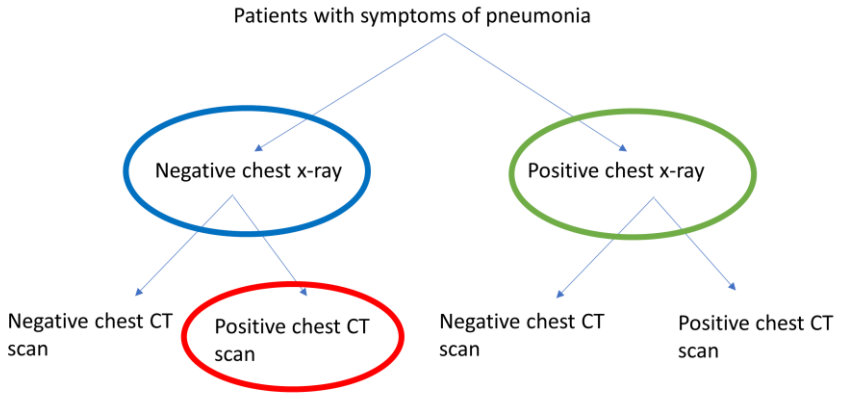


Figure 2 Patients admitted to hospital suspected of having pneumonia commonly have a chest x-ray done, some of those patients also have a chest CT scan done. The results of each of these radiographies can be positive for new infiltrates, confirming the diagnosis of pneumonia.

diagnosed with a CXR (green circle). In a study by Upchurch et al. around 3% of those diagnosed with pneumonia had a negative CXR but a pneumonia infiltrate on chest CT scan (Upchurch et al., 2017), and around 5% in the study by Seo et al. (Seo et al., 2019). However, these studies were also limited by the fact that they were not population-based and not all included patients received a CT scan. These studies are not directly comparable to our study, as they are comparing different groups. Those with a negative CXR and positive CT scan would have been categorized as CAP in our study. In our study 33 patients (8.1% of CAP) first had a negative CXR but a later (within 48 hours) better quality image showed an infiltrate.

A small retrospective observational study found 205 adults had presented to the emergency ward of a hospital in South-Korea January 2012- May 2012 with a suspected acute LRTI and had a CXR and a chest CT scan performed.

Imaging identified pneumonia in 128 cases but did not in 77, representing an approximate CAP:SPWI ratio of 2:1 (Park et al., 2016). However, this study is at risk of bias as patients who underwent both CXR and CT scan imaging studies, did so for a reason that sets them apart from those that did not receive both these radiographs.

A randomized trial on procalcitonin levels among adults presenting to emergency wards with ALRI had a CAP:SPWI ratio of 1:3 (Huang et al., 2018). That is a much higher rate of SPWI than we found in our study but can perhaps be explained by less severity as reflected by the fact that only 47% were admitted to the hospital.

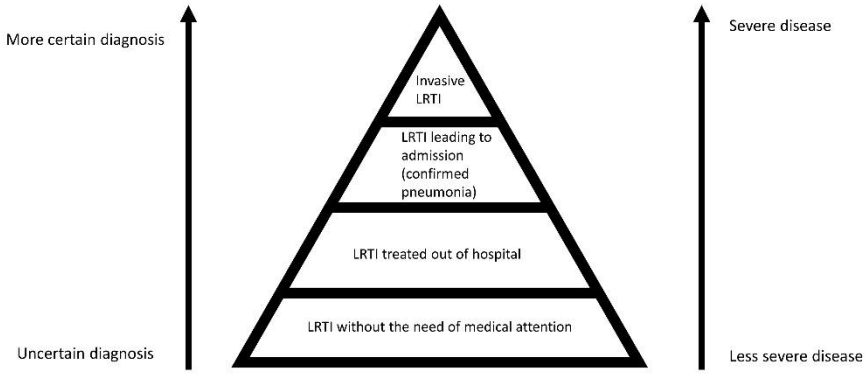


Figure 3 Certainty of diagnosis of lower respiratory tract infections generally increases with the severity of the illness, however, the certainty of lower respiratory tract infection (LRTI) among older adults is often lower due to fewer and less specific symptoms reported and due to a higher frequency of a low quality CXR (e.g. bedside CXR) and because of chronic or concomittant CXR abnormalities that can make CXRs more complicated to interpret, like heart failure (Nicolas Garin et al., 2019).

The literature on LRTI in the outpatient setting more commonly includes patients without radiological confirmation of pneumonia. Unfortunately, the lack of radiological chest imaging in the outpatient population with LRTI makes all comparisons very difficult. Only 6% of patients diagnosed with pneumonia according to diagnostic codes in general practice in Denmark had a CXR performed (Hansen et al., 2020). A small study (n=246) from 2003 on

pneumonia among patients with LRT symptoms visiting general practitioners found an infiltrate on CXR in 21 (8.5%) of the participants (Hopstaken et al., 2003).

### 5.1.1 Patient characteristics, symptoms, vital signs, and laboratory results

When each underlying illness was compared between the groups, no major difference was noted, apart from COPD and CKD which were more frequently noted in the SPWI group (Kristján Godsk Rögnvaldsson et al., 2023). However, more subtle differences were noted, generally indicating a slightly higher proportion of comorbidities in the SPWI group. This was reflected in the Charlson comorbidity index which was higher within the SPWI group and the portion of patients with no underlying illness was lower within the SPWI group. This highlights that in small samples, the lack of statistically significant differences does not mean there is no difference, it only makes major differences between samples unlikely. In their comparable study, Basi et al. found that patients in the SPWI group were older and had a higher PSI score (CCI score was not presented), HF and COPD was more frequently observed within the SPWI group (Basi et al., 2004).

Presenting symptoms of patients with SPWI were very similar to those among patients with CAP, apart from patient reported fever which was more commonly reported in patients with CAP. Of special interest was that pleuritic chest pain was observed in 39% in CAP and in 40% in SPWI. Likewise, both patient- reported sputum production as well as obtained sputum samples were similar in both groups. Perhaps unsurprisingly, flu-like symptoms were 50% more commonly reported among patients in the SPWI group. In the study by Basi et al. fever was reported among 44% and 43% of patients in the CAP and SPWI groups, respectively. Contrary to our study the rate was lower and similar in both groups. However, Basi et al. did not describe how information regarding fever was obtained or the precise threshold denoting fever (Basi et al., 2004). In our study measured temperature above 38°C was more frequently observed in CAP than SPWI, coinciding with patient reported fever. In the study by Basi et al. dyspnea and sputum production were more commonly reported among the SPWI patients but hemoptysis and pleurisy were more commonly observed among patients with CAP (Basi et al., 2004).

The study by Basi et al. lacked information on heart rate, blood pressure and oxygen saturation but included information on the partial pressure of oxygen and $CO_2$. In our study, white blood cells and neutrophils were higher in patients with CAP as was in the study by Basi et al (Basi et al., 2004).

Additionally in our study CRP levels were higher in the CAP group than the SPWI group.

Taken together, this could indicate that the infection was more severe at presentation among patients with CAP compared to SPWI. Despite symptoms being surprisingly similar between the groups, the overall clinical picture of the CAP syndrome has a more typical presentation in keeping with acute bacterial infection compared with the SPWI syndrome.

### 5.1.2 Etiology and treatment

The etiological diagnosis in the study by Basi et al. were based on blood and sputum cultures. Our study also included urine antigen tests for pneumococci and *Legionella pneumophila* and PCR detection of respiratory viruses and atypical bacteria, however these were tests ordered by the treating physicians and thus not obtained from all patients. Blood cultures were obtained in a higher percentage of CAP patients than SPWI patients, both in our study and the study by Basi et al.

A very similar rate of pneumococcal bacteremia among those with blood cultures performed was observed in both studies (5.1% CAP vs. 0.9% SPWI in Basi et al. and 4.0% CAP and 0.9% SPWI in our study). Sputum cultures were collected in 40% of CAP and 30% of SPWI patients in the Basi et al. study compared to 45% in both groups in our study. However, we found that a larger percentage of patients in the CAP group vs. the SPWI group provided sputum of an acceptable quality (53.8% vs. 36.1%), of those that provided sputum.

Respiratory viruses were more commonly detected among cases in the SPWI group than in the CAP group in our study, although most patients in both groups did not receive a respiratory viral test. This does not come as a surprise, as LRTI without infiltrates comprise e.g. bronchitis which is considered to be more commonly caused by viruses than bacteria (Clark et al., 2014). However, studies from the last decade indicate that viruses may play a larger role in CAP requiring hospital admission than previously thought (Cilloniz et al., 2016; J. C. Holter et al., 2015; Huijskens et al., 2013; Jain et al., 2015; Lupisan et al., 2019; Palmu et al., 2014; Rhedin et al., 2014; Self et al., 2015).

All but 2 patients in the CAP group received antibiotics but 12.5% (27/216) did not receive antibiotics in the SPWI group in our study. The study by Basi et al. did not report on treatment. Length of stay and biPAP/ciPAP use were similar in both groups, but ICU admission was observed in 5.6% of the CAP group but 1.9% of the SPWI group. Rates of ceftriaxone and amoxicillin/clavulanate administration were similar between the groups but

coverage for „atypical bacteria“ was much higher in the CAP group than in the SPWI group. Perhaps this is due to an observed higher severity among the CAP cases and the inevitable effect of a radiographic infiltrate on the treatment decision vs. the lack of an infiltrate. Furthermore, the hospital CAP guidelines recommend a broader antibiotic coverage for patients with a more severe CAP. The hospital guidelines do not include specific treatment recommendations for SPWI (Kristjánsson, 2017). It seems unlikely that radiographic differences have influenced the choice of coverage for an atypical bacteria as older studies on CXRs did not find significant differences in the radiographic features of atypical pneumonia compared to typical (Macfarlane et al., 1984; M. A. Woodhead & Macfarlane, 1987). Studies using CT scans have been able to find some differences between mycoplasma and pneumococcal pneumonia, but these are not very reliable (N. Miyashita et al., 2011; Naoyuki Miyashita et al., 2009).

Our study adds information from urinary antigen tests and respiratory viral tests as well as on treatment and length of stay. The results support older knowledge that CAP more commonly has bacteria identified as a cause than SPWI. Despite this, length of stay and non invasive ventilation rates were similar.

### 5.1.3 Prognosis

Unadjusted in-house mortality in the study by Basi et al. was 10% and 8% among CAP and SPWI patients, respectively. In our study we reported on 30-day mortality, 5.2% in the CAP group and 5.1% in the SPWI group. The difference in the unadjusted mortality rates could reflect differences in settings of the studies, the two decades between them and/or endpoints (in-hospital vs 30-day mortality). In the study by Basi et al, the adjusted OR for in-hospital mortality of CAP compared to SPWI was 1.4 (95% CI, 0.95-2.1). We presented the aOR of 30-day mortality for SPWI compared to CAP as 0.86 (95% CI, 0.40-1.86) which translates to aOR of 1.16 (95% CI, 0.54-2.5) for CAP compared to SPWI. This result is in line with the result of the study by Basi et al. which shows that despite more severe disease and a higher rate of pneumococci, patients in the CAP group do not have a much higher mortality rate than patients in the SPWI group.

However, the aOR for 1 year mortality of SPWI compared to CAP following multiple imputation was 1.46 (95% CI 0.92-2.32). The adjusted OR at 1-year may reflect that the SPWI group has more underlying comorbidity than we were able to adjust for and/or perhaps that this patient group is not able to fully recover following the infection. The infection could be hypothesized to lead to

a shift in the baseline performance status of patients, despite a seemingly lighter infection compared to CAP. The SPWI group consisted of older and more frail patients than the CAP group. Previous studies have shown that the higher the frailty the lower the likelihood of full recovery to the pre-infection performance (Lees et al., 2020; Townsend et al., 2021).

The SPWI group has an incredibly high 25% absolute 1-year mortality. To put this in context, a recent study on adults ≥60 year old diagnosed with gastrointestinal malignancy reported 28% 1-year mortality (Williams et al., 2022). It is remarkable that there are not more studies on this subgroup of patients presenting with symptoms of pneumonia and how often this group is excluded from studies, making comparisons to other studies difficult.

### 5.1.4 Sensitivity and supplementary analyses

The majority of patients in our study were diagnosed by a single CXR with no other radiograph performed during the first 48 hours of admission. A higher percentage of patients in the study by Basi et al had a second radiography obtained (overall 98% of cases compared to the 58% overall percentage in our study), although they used a wider cutoff of 72 hours. No information was provided by Basi et al. on the number of chest CT scans. One in four of patients in our study underwent a CT scan within 48 hours of admission.

Post-hoc sensitivity analyses were performed to assess if the same trends were observed if patients that did not receive antibiotics were removed and if patients with a chest CT scan were removed from the sample. Similar trends were indeed observed.

## 5.2 Paper 2

The interest in ASA as an agent which possibly could decrease mortality from pneumonia resurfaced in response to the SARS-CoV-2 pandemic. Some prior in vitro studies had shown that the drug demonstrated antiviral effects e.g. on influenza virus and human rhinovirus (Glatthaar-Saalmüller et al., 2017). The RECOVERY study, a large multi-arm RCT on various treatments for COVID-19, did not show mortality benefit among COVID-19 patients who received ASA (rate ratio 0.96, 95% CI 0.90-1.04). However, treatment shortened the duration of hospitalization from 9 to 8 days and it was associated with a 0.6% absolute risk decrease in thrombotic events. Unfortunately, it increased the absolute risk of major bleedings by the same margin, 0.6% (RECOVERY

Collaborative Group, 2022).

Protective effects of ASA may be mediated by platelet inhibition or inhibition of other inflammatory pathways (Collins et al., 1997; Desborough & Keeling, 2017; Glatthaar-Saalmüller et al., 2017; Layne et al., 2016; Oz et al., 2013). Alternatively direct pathogen effects are not impossible (Glatthaar-Saalmüller et al., 2017). Roughly a quarter of patients hospitalized due to CAP experience a heart or vascular complication in the first 30 days, half of these occurring within the first day (V. F. Corrales-Medina et al., 2012). An increased risk of cardiovascular disease has been observed among patients with severe pneumonia up to 10 years following the infection, compared to adults of same age and sex (V. F. Corrales-Medina et al., 2015). More severe infections are associated with a greater increase in subsequent risk for cardiovascular disease than seen in less severe infections (Daniel M. Musher et al., 2019). The pathogenesis of cardiovascular complications associated with pneumonia are thought to be a mix of different factors: tissue hypoxemia, direct damage to cardiac muscle, inflammation, activation and aggregation of platelets and subsequently decreased blood flow through coronary arteries (Roberto Cangemi et al., 2014a; Rae et al., 2016; M. I. Restrepo & Reyes, 2018). Pneumonia cases with an etiological diagnosis of *S. pneumoniae* have been associated with cardiovascular events (Daniel M Musher et al., 2017; M. I. Restrepo & Reyes, 2018; Shenoy et al., 2018). One recent study showed a 20-fold increased risk of myocardial infarction and 26 times increased risk of stroke in the first 3 days following invasive pneumococcal infection, compared to the same individuals over a disease free period (Ohland et al., 2020).

Our study is the first study assessing the effect of treatment with ASA in the setting of culture-proven invasive pneumococcal pneumonia. The study was population-based and adjusted for multiple comorbidities using inverse probability weighting.

### 5.2.1 Difference in covariates between the groups and the possibility of a healthy user bias

The study examined patients with bacteremic pneumococcal pneumonia, comparing patients on ASA with those who were not taking the drug. It was clear before the study was performed that there was a risk of confounding due to differences between the groups in terms of comorbidities. To address this problem, we attempted to adjust for differences using propensity score weighting instead of a direct covariate adjustment. The latter option would have limited the possible number of comorbidities that could be included in the adjustment. In general, the group using ASA was older and had more

comorbidities, this was true for almost all the assessed chronic illnesses. However, smoking and alcoholism were an exception.

Perhaps this can be partially explained by the older age in the ASA group (median of 75 [68-82]) and the fact that daily smoking is lower among the oldest age groups compared to younger adults in many countries in the last decades (Kleykamp & Heishman, 2011). For example 22% of those younger than 65 year old in the USA smoked in 2007 but only 8% of those older than 65 years (Kleykamp & Heishman, 2011). The same trend has been noted in Iceland, but this difference has been decreasing in the last few years in parallel with a dramatic overall decrease in smoking in the country (Directorate of Health Iceland, 2022).

We defined alcoholism as the listing of alcoholism in the patient's medical history. According to a relatively recent European summary of alcohol consumption among elderly, 60-70 year olds drink more and have more complications due to alcohol than those older than 70 years (Hallgren et al., 2009). This could at least partly explain why the alcoholism rate was higher in the non-ASA group compared to the ASA group. Other possible explanations could be that those who have alcoholism are less likely to reach this age and those that are started on aspirin are more likely to stop drinking because of the diagnosis of a cardiovascular disease that is often the reason of the initiation of aspirin.

The possibility of a heatlhy user bias is important to note. A healthy user effect is due to the fact that someone who seeks preventive therapies (like ASA) is more likely to also pursue healthy lifestyle choices, seek timely therapy of chronic illnesses and be more adherent of long-term treatments (Shrank et al., 2011). Similarly, patients who adhere to preventive therapies like ASA are also more likely to stop smoking. Some RCTs have even shown that patients who adhere to placebo have lower mortality rates than those who do not adhere to placebo (Shrank et al., 2011).

To tackle this potential bias we included statin use and alcoholism in the adjustment of covariates using the propensity score in the main analysis. Statin use has been associated with a healthy user bias in prior studies and alcoholism is one of the variables that could be affected by the bias (Shrank et al., 2011). Smoking was not included in the main analysis due to the high rate of missing data; however, it was included in two supplementary analyses which yielded similar results to the main outcome analysis. Even though the smoking rate itself was different between the groups, reassuringly, the rate of missing information on smoking was similar in both groups. To tackle the potential

healthy user bias, we also performed sensitivity analyses assessing if other cardiovascular drugs and PPI improved survival. These analyses did not show significant protective effects, apart from a slight nonsignificant trend in the case of statin drugs. Interestingly, of the 34 patients that received both statin and aspirin, only one patient (2.9%) died within 30-days. Even though this number of patients is far to low for any conclusions to be drawn, it raised our interest on the protective effects of statin combined with aspirin. However, it could also just be a marker of a double healthy user effect.

A previous study on the association of ASA with mortality among pneumonia patients also reported patients in the ASA group to be older and more likely to have underlying illnesses than those not receiving the drug (Falcone et al., 2019a). This previous study did not report on smoking and alcoholism and did not adjust for these variables in their outcome analysis.

### 5.2.2 Outcome analyses

#### *5.2.2.1 Survival*

Our results indicate a potential protective effect of ASA on mortality on average over the 1-year follow-up. The association was not proportional for the entire follow-up period. The same was true for the analysis limited to the first 30-days. It must however be noted that biologicially there was no reason to assume a proportional hazard over the entire 1-year follow-up period of invasive pneumococcal pneumonia, an acute infection with the highest mortality in the first few days. To solve this problem, we split the survival period guided by the hazard curve. Using this approach, a protective trend was noted for days 0-6 (including day 6) but not for days 7-30. We had exact information on time of death of patients in our study and when the death occurred on the same day as hospital admission, we calculated the time from admission to death based on timing registered in the medical records. In our study the mortality was by far highest in the first few days after which the mortality slope decreases. In the study by Falcone et al. the mortality slopes seem to be almost constant over the first 30 days (Falcone et al., 2019a), as previously mentioned this is curious because mortality is the highest in the first couple of days following pneumonia (Dupuis et al., 2021).

If we extend our view to sepsis in general and ASA, more studies come into focus. A long-term double blind, placebo-controlled randomized study on primary prevention in general by using ASA among the elderly, did not find an association between use of this agent and improved survival following sepsis (Eisen et al., 2020). The study was a substudy of a larger trial on ASA among

older adults. The primary endpoint was disease and disability free survival (Eisen et al., 2020). The study was performed in USA and Australia but the sepsis substudy was only performed among the Australian participants. The study included 16703 healthy participants and excluded patients with “major illnesses”, cardiovascular disease, atrial fibrillation, dementia or a mental exam result below a certain threshold (Eisen et al., 2020). The primary endpoint of the study was death due to sepsis. Data on deaths was retrospectively analysed using hospital records and/or Causes of Death Registers. Therefore, the study relied fully on a retrospective analysis of hospital records made by treating physicians and death certificates. This method did not allow for the assessment of all-cause mortality following sepsis which is a major limitation. Previous studies on the quality of death certificates in diagnosing pneumonia have shown low quality of the data (Brown et al., 2020), a Japanese study using autopsy diagnosed pneumonia as the reference found the sensitivity of death certificates to be 46% in diagnosing pneumonia (Mieno et al., 2016).

In the study by Eisen et al. 99 deaths were observed in the placebo group and 104 in the aspirin group. The authors of the study had expected 133 deaths due to sepsis in the placebo group, accounting for expected dropouts (Eisen et al., 2020). The observed number in the study by Eisen was 26% below expectations, which means it is possible that the study missed some cases. In the study by Eisen et al. 144 of the 203 sepsis related deaths were registered as pneumonia, however, only 11/144 had an identified causative organism and not a single *S. pneumoniae* was diagnosed among those categorized as having had pneumonia with sepsis. That is strange considering *S. pneumoniae* is one of - if not the most common cause of - severe pneumonia worldwide (A Bjarnason et al., 2018c; Eisen et al., 2020; J. C. Holter et al., 2015; Huijskens et al., 2013; Jain et al., 2015). Additionally, the study did not explain if an acute cardiovascular event following sepsis would have been registered as a sepsis related death, or for how long following sepsis a death would have been regarded as sepsis related, and it did not report on the median/mean time from sepsis to death (Eisen et al., 2020).

Even though this randomized study decreases the likelihood of a protective effect of ASA among sepsis patients, we do not think it rules out the possibility that treatment with this agent could decrease the risk of all-cause mortality following invasive pneumococcal pneumonia.

One randomized trial on cardiovascular events and mortality following pneumonia has been published; however, it was small, non-blinded and lacked a placebo arm; it showed protective effects from ASA on cardiovascular events

and cardiovascular related mortality among pneumonia patients (Oz et al., 2013).

Lower quality observational studies have shown mixed results in terms of the effects of ASA in reducing mortality following pneumonia. Some have shown improved short-term survival (Falcone et al., 2015; Falcone et al., 2019a) and others have not (Roberto Cangemi et al., 2014a; Chalmers et al., 2008). One study showed reduced mortality following acute respiratory distress syndrome among patients receiving this agent (W. Chen et al., 2015). Another study associated improved survival with the drug following invasive *Staphylococcus aureus* infection but not following invasive *Escherichia coli* infection (Osthoff et al., 2016). The last study could mean that the effects of ASA could somehow be pathogen- or organ-specific. This means also that the randomized trial by Eisen et al. on sepsis death would perhaps not be able to find an overall protective effect if the protective effect is limited to certain pathogens or organs.

In our study, ASA treatment was defined as any dosage of the drug, according to admission records. An important limitation to our study is that we do not have information on dosages, duration nor if ASA was continued during or following hospitalization. The drug starts to work within 60 minutes and the effects following discontinuation are only slowly reduced and can take up to 10 days to be reversed (Awtry & Loscalzo, 2000).

#### *5.2.2.2 Causes of death analysis 1975-2015*

Data for the causes of death analysis was gathered for cases in the period of 1975-2015 but not to 2019 like the overall sample. This is an important limitation of this analysis. This decreased the sample size and due to the fact that only those that died, a fraction of the overall sample, are available for this analysis hinders statistical analysis. Therefore, descriptive statistics are provided but no statistical adjustments were performed. While no large differences were noted between the groups for the different categories of causes of death, one difference stood out at one year follow-up: 4.6% (5/108) of deaths in the ASA group were attributed to malignancies but 10.2% (58/567) in the non-aspirin group. It is hard to interpret this difference, due to the previously mentioned limitations, but one might have expected higher rates of deaths attributed to malignancies among the older and frailer recipients of ASA. Possible explanations include: that patients were perhaps less likely to receive this drug if they had a more severe malignancy or a metastatic malignancy? Or could it be that those older and frailer less frequently have malignancy registered as the primary underlying cause of death? When

patients have many severe underlying illnesses, it can be hard to choose which one is the primary underlying cause of death. To explore these speculations, a supplementary analysis was performed excluding patients with a history of malignancy. However HRs remained similar to the overall model (unpublished data by Kristján and Magnús).

Focusing on the period following ICD-10 introduction in 1996, we found that 23% of cases of invasive pneumococcal pneumonia that died within 30-days did not have infection or respiratory disease registered as the cause of death or as a contributing cause of death (unpublished data by Kristján and Magnús). This suggests that relying on Causes of death Registries to find cases that have died due to sepsis or infection may underestimate the true number of cases that died due to sepsis.

### 5.2.3 Sensitivity and supplementary analyses

The Cox regression with the direct covariate adjustment supported the main results. The same can be said about analyses including the smoking variable (complete case and multiple imputation analyses). The assessment of the effects of PPI, beta blockers, statins and macrolides did not show any significant protective effects. Splitting the results by decades was done, but with some compromises to the propensity score due to the reduced sample sizes within each decade. Nevertheless, a similar protective trend for ASA use was observed within all decades. Surprisingly, following a reviewer request we grouped cases by occurring within months of a typical influenza period or not, and found that the protective effect was only observed within the influenza period. The influenza period was defined as the period from December to May and could perhaps more accurately be named the period of respiratory pathogens. This needs further evaluation and confirmation in other studies. This could be caused by chance as dividing the dataset into two decreases power and increases uncertainty. However, it could be hypothesized that the risk of myocardial infarction would be greater if cases are infected by both influenza and pneumococci. In a recent study, those with a bacterial and viral coinfection (most commonly pneumococci and influenza) had a more severe disease (Abelenda-Alonso et al., 2020). Additionally, the lethality of the 1918 influenza pandemic has in part been attributed to the high level of pneumococcal coinfection (Morens et al., 2008; Walters et al., 2016).

One additional factor that might lead to a difference in prognosis would be if the treatment was different between the groups, therefore we included macrolide treatment in the adjustment of all the analyses.

On request by a reviewer, we assessed penicillin susceptibility and the antimicrobial therapy given. As outlined in chapter 4.2.4. a very low number of patients in both groups did not clearly receive adequate initial antimicrobial therapy indicating that this did not influence the results.

We propose a large multicenter observational study on the possible protective effects of ASA on mortality following pneumonia before an RCT is conducted. This proposed study would have to include socioeconomic factors, known modifiers of overall mortality and cardiovascular health to try to minimize the risk of a healthy user and healthy adherer bias. Finding and locating the bias could prove valuable in identifying studies lacking proper adjustment.

## 5.3 Paper 3

The prepations for this study were initiated in April 2020, when SARS-CoV-2 had just recently emerged in Iceland. At the time, no studies had been published examining the association between OSA and severe COVID-19. This study provides important insights into this relationship due to its nationwide coverage of cases, widespread testing for SARS-CoV-2 in society and due to the accounting for important confounders of OSA and severe COVID-19.

### 5.3.1 Increased risk of severe COVID-19 among cases with OSA

This study strengthens previously published evidence linking OSA independently to increased risk of severe COVID-19 infection. The uniqueness of this study includes the COVID-19 outpatient service that evaluated (mostly by telehealth) all who had a SARS-CoV-2 positive PCR result for symptoms, underlying illnesses and other comorbities, and the centralised center for diagnosis and treatment of OSA at LUH (Arnardottir et al., 2016; Helgason et al., 2020). Another important factor was the widespread testing and tracing performed systematically by healthcare providers.

The result of our study is in accordance with several other published studies (Maas et al., 2020; McSharry & Malhotra, 2020; Mutti et al., 2020; Pazarlı et al., 2020; Voncken et al., 2022). However, a prior study only found an association with mortality in unadjusted models (Mashaqi et al., 2021). That study was not population-based, and included patients according to ICD-10 codes and OSA diagnosis was not directly based on sleep study analysis;

moreover it did not adjust for smoking and excluded patients lacking information on BMI (Mashaqi et al., 2021).

A review of prior studies was published when the statistical analysis of the third paper had been performed (Hariyanto & Kurniawan, 2021). The paper included a meta-analysis which found an OR of 1.7 (95% CI 1.4-2.2) for short term mortality and OR of 1.8 (95% CI, 1.5-2.1) for intensive care unit admissions (Hariyanto & Kurniawan, 2021).

### 5.3.2 Supplementary and sensitivity analyses

We reported an association of PAP therapy among the subgroup of OSA patients (n=185) with severe COVID-19 adjusting for age, sex and AHI but not when adjusting for AHI, BMI and all the other comorbities (age, sex, HTN, DM, HF, CKF, COPD and smoking). Despite the lack of association in the fully adjusted model, it raised the question if there were some unobserved confounding present or if the PAP therapy in itself could increase the likelihood of a more severe COVID-19 disease. Theoretically, it is possible that PAP therapy could help spread SARS-CoV-2 viral particles from a localized upper respiratory tract infection further down into the lungs. This is interesting because patients on PAP treatment would be expected to be less likely to have a severe COVID-19 due to better controlled OSA, a disease known to have systemic detrimental effects e.g. on cardiovascular and neurologic system (Arnardottir et al., 2016; Barceló et al., 2001; Bradley & Floras, 2009; Dewan et al., 2015; Sánchez-de-la-Torre et al., 2013). This particular analysis was done on a small subgroup and therefore needs confirmation in larger cohorts and settings, and possibly in other viral diseases. Two small studies have reported on an association of pneumonia with PAP therapy compared with other OSA patients (Mercieca et al., 2017; Su et al., 2014). Furthermore, these kind of secondary observations have to be interpreted with the utmost caution as they could be due to a bias that was not accounted for, this is especially important as the group receiving PAP therapy is more likely to have a more severe disease than those not receiving PAP. Patients who stopped using the treatment are perhaps individuals that were not as severely affected to begin with and or got better. In addition, it is known that AHI is not perfectly correlated with self reported disease severity (Arnardottir et al., 2016).

The treatment effect of PAP on OSA was possibly reflected in our study by the fact that aOR of patients that had received PAP therapy for less than 4 years was 4.1 (95% CI 0.9–18.6), whereas it was 1.4 (95% CI 0.4-5.5) among

those who had received PAP therapy for more than 4 years, compared to patients without OSA.

Sensitivity analysis including only cases with no missing information showed similar ORs as the main outcome analysis.

## 5.4 Overall limitations

The papers presented here are based on three different studies with three different datasets, patient cohorts and study designs. Therefore they have different strengths and limitations, as specifically outlined in the previous paper specific discussion subchapters.

The main strength of our studies is their population-based nature. Studies 2 and 3 were nationwide and the first study was population-based in the capital area of Iceland. They were performed in a real-world setting with minimal exclusion criteria. Data was gathered prospectively in the first study.

The PhD candidate recruited participants for the study presented in paper 1, data was gathered using a questionnaire by a bedside interview with participants and from medical records. The PhD candidate gathered some of the patient data for papers 2 and 3. This helped identify some additional limitations of both prospective and retrospective observational study designs. Many of these limitations are inherent to the designs but some limitations can be somewhat adjusted for by certain methods.

One of the challenges with prospective studies is the fact that you can never know what the future will bring. In our case the COVID-19 pandemic which overwhelmed the capacity to perform PCR for the study and delayed the etiological PCR analysis of our newly gathered samples. This meant the original thesis plan needed change and adaption, resulting in the diverse papers presented here.

Recruiting participants into the prospective study opened the eyes of the student to the inherent problem of prospective studies in regards to recruiting severely ill individuals who are often not capable of providing informed consent. Next of kin are sometimes not available or reluctant to consent to participation on behalf of their severely ill relative (perhaps even more reluctant than they would be providing an informed consent for themselves).

Recruitment of control group participants also needs special consideration, as these participants do not have the same motivation as those with

pneumonia. “Why do you want me to participate in a pneumonia study when I do not have pneumonia?”. This reaction by potential participants in the control group was a recurring theme. We found that the key to recruiting control group participants was to motivate them, this included providing information on the importance of control cases without pneumonia for pneumonia research. In hindsight, the name of the study could have been more open and perhaps included something like “and control group without pneumonia”. Recruiting severely ill participants in the control group was especially demanding. Because of this, we risked recruiting fewer severely ill participants in the control group than in the pneumonia group and therefore covariate adjustment will need to be performed when comparing the control group to the other groups. None of our currently published studies have included the control group that we recruited. However, a study utilizing the control group is underway, comparing the microbial etiology of CAP, SPWI and the control participants. It was the centerpiece in the original PhD study plan which was delayed due to the COVID-19 pandemic.

Nevertheless, our study had a very high participation rate compared to previous studies with 93% of patients with suspected of pneumonia (SPWI and CAP) signing an informed consent and 90% in the control group.

However, it is possible that cases may have been missed if they were admitted directly to the intensive care unit from the emergency ward without a preliminary diagnosis of pneumonia. This is especially true if the patient was severely ill with non-specific symptoms and later turned out to have sepsis due to pneumonia. How could the risk of this be minimized in future prospective studies? The PhD candidate could screen the ICU more frequently. Identifying the ratio of severely ill patients in these groups at screening and comparing this ratio to the final samples could perhaps help identify if this is a potential source of bias. This potential bias might lead to an overall underestimation of severe outcomes. In contrast, retrospective observational studies almost never require informed consent and therefore all patients meeting the inclusion criteria can be studied, potentially making mortality and disease severity calculations more accurate.

A clear advantage of the prospective observational design is that information can be gathered directly from participants in a standardized way and robust inclusion criterion can be assigned to all patients. Retrospective observational studies are based on information that has already been gathered by multiple different health care professionals and information is commonly missing or not entered correctly. Even when using diagnostic codes, the overall

sensitivity and specificity of diagnostic codes for diagnosing pneumonia is only around 70-80% (chapter 1.2.1)). Another part of the problem with pneumonia diagnosis is the lack of a universal diagnostic criterion of pneumonia among adults.

A common limitation to all non-randomized observational studies is that groups within the study do not neccessarily have an identical baseline risk of reaching the study endpoint. This means that some adjustment must be performed, and it can only be performed on variables that have been recorded or gathered. Even though adjustments are made for all known confounders and biases, we do not know if there are still some unmeasured and unaccounted factors. That is why RCTs are the only type of study that can confirm the causal link between treatment and outcome. They are expensive, complicated and can cause more direct adverse effects to participants than observational studies.

Therefore, observational studies have an important role, but must be interpreted with their limitations in mind. Observational studies cannot identify causal links, only associations which are sometimes explained by non-causal factors such as study settings, biases or confounders (M. T. M. Wang et al., 2015). However, observational studies often find the same results as RCT, but tend to overestimate treatment effects. Regardless of study design, differences between individual studies are often large and require close examination (Hannan, 2008). However, inadequately designed studies (both observational and RCTs) can harm future recipients of treatment. According to Hannan, the roles of observational studies are to come up with hypothesis for RCT to test, extend results of RCTs to real world settings, explore what study sizes would be appropriate for future studies and to study effects among subpopulations (Hannan, 2008). With the increasing population of older adults it is interesting that even the recent COVID-19 RCTs had a very low inclusion rate of older adults (Veronese et al., 2021).

In retrospect it would have been useful to include several socioeconomic variables in our studies. Socioeconomic factors such as income and education are associated with incidence and mortality of infectious diseases such as pneumonia (Burton et al., 2010; Flory et al., 2009; F. K. Ho et al., 2020; Stelianides et al., 1999; Wiemken et al., 2020). Even though Iceland scores high regarding equality and access to healthcare there are important differences that could have been adjusted for, especially in relation to the healthy user effects.

Additional biases include publication bias and “p value fishing” when

performing multiple tests. To avoid this, we formulated clear research questions prior to performing the analysis. Due to the number of tests performed in paper 1 we presented false discovery rate adjusted p-values to minimize the likelihood of reporting on false associations.

## 5.5 Opportunities in pneumonia research

Pneumonia research is a competetive field, searching the pubmed.org database with the word “pneumonia“, and limiting the results to humans aged 18 or older, leads to 134000 results. Nevertheless, there is an urgent need for a single universal diagnostic criterion for the diagnosis of pneumonia, especially for use in research. This would allow to better comparison of the plethora of different studies. More work comparing different diagnostic criteria is needed.

One of the major problems regarding adult CAP research in general is the lack of studies done in poorer countries, an excellent recent paper by Aston on pneumonia etiology in Malawi is an exception to this (Aston et al., 2019). There are great opportunities in studying pneumonia in poorer countries, with both local and international relevance.

It is important to continue studying the group of patients admitted to hospitals with SPWI as this appears to be a large group of patients with mortality similar to CAP. Due to an extremely high incidence among older adults, studying SPWI among the oldest age groups may be even more important. The effects of influenza, COVID-19 and pneumococcal vaccinations in the SPWI group is also an area of interest. Comparing microbial etiology in detail among patients in the SPWI and the CAP group could also provide additional information on potential differences in disease presentations and clinical course.

Additionally, we believe there is space for RCTs assessing the benefit of ASA among patients with severe pneumonia, as it is possible that patients with high levels of inflammatory activity could benefit from an early intervention with platelet inhibition and/or immunomodulation.

Further work on the association between pneumonia and other respiratory tract infections and subsequent cardiovascular disease is of great importance, searching for possible preventive modalities continues to be important.

The constant evolution of pneumonia pathogens means that constant surveillance of pneumonia etiology is important as is the surveillance of antimicrobial resistance among these pathogens (Chow et al., 2023).

# 6 Conclusions

Our work explores different aspects of pneumonia and lower respiratory tract infections, including risk factors for severe disease and mortality, and possible protective factors. Special focus is placed on patients frequently excluded from studies on hospitalized CAP due to lack of radiological confirmation.

A large number, half the number of CAP, of patients with symptoms of pneumonia without infiltrate on chest radiograph (SPWI) are hospitalized with a similar mortality to those with a radiographically confirmed pneumonia, despite being less often diagnosed with pneumococci and having lower objective measures of inflammation. This group has been absent from many prior studies of pneumonia. With the ageing population the number of SPWIs requiring hospitalization is likely to increase rapidly and therefore should be studied in greater detail.

Use of ASA is associated with improved survival following bacteremic pneumococcal pneumonia, especially in the first few days following diagnosis. To determine whether this association is due to a healthy user effect or not, larger future studies will be required, preferably large multi-center studies followed by a randomized controlled trial. The protective effects of ASA remained in multiple sensitivity analyses in our study.

Finally, obstructive sleep apnea is associated with more severe COVID-19 according to our nationwide study where previous clinical sleep analysis among those diagnosed with COVID-19 were reviewed.

Studying pneumonia is like doing a puzzle where many pieces have already been laid out, but many are still missing leaving holes while the puzzle itself is constantly growing with pieces being added to the edges. In general, new research questions are constantly being formed during the research but the remarkable thing about infectious diseases is that pathogens are also constantly evolving, emerging, or re-emerging, supercharging the problems at hand and making the task a perpetual challenge.

# References

Abelenda-Alonso, G., Rombauts, A., Gudiol, C., Meije, Y., Ortega, L., Clemente, M., Ardanuy, C., Niubó, J., & Carratalà, J. (2020). Influenza and Bacterial Coinfection in Adults With Community-Acquired Pneumonia Admitted to Conventional Wards: Risk Factors, Clinical Features, and Outcomes. *Open Forum Infectious Diseases, 7*(3). doi:10.1093/ofid/ofaa066

Adelson, J. L., McCoach, D. B., Rogers, H. J., Adelson, J. A., & Sauer, T. M. (2017). Developing and Applying the Propensity Score to Make Causal Inferences: Variable Selection and Stratification. *Frontiers in Psychology, 8*, 1413. Retrieved from https://www.frontiersin.org/article/10.3389/fpsyg.2017.01413

Aliberti, S., Bellelli, G., Belotti, M., Morandi, A., Messinesi, G., Annoni, G., & Pesci, A. (2015). Delirium symptoms during hospitalization predict long-term mortality in patients with severe pneumonia. *Aging Clinical and Experimental Research, 27*(4), 523-531. doi:10.1007/s40520-014-0297-9

Alimi, Y., Lim, W. S., Lansbury, L., Leonardi-Bee, J., & Nguyen-Van-Tam, J. S. (2017). Systematic review of respiratory viral pathogens identified in adults with community-acquired pneumonia in Europe. *J Clin Virol, 95*, 26-35. doi:10.1016/j.jcv.2017.07.019

Almirall, J., Bolíbar, I., Serra-Prat, M., Roig, J., Hospital, I., Carandell, E., Agustí, M., Ayuso, P., Estela, A., Torres, A., & the Community-Acquired Pneumonia in Catalan Countries Study, G. (2008). New evidence of risk factors for community-acquired pneumonia: a population-based study. *European Respiratory Journal, 31*(6), 1274. doi:10.1183/09031936.00095807

Altuna-Venegas, S., Aliaga-Vega, R., Maguiña, J. L., Parodi, J. F., & Runzer-Colmenares, F. M. (2019). Risk of community-acquired pneumonia in older adults with sarcopenia of a hospital from Callao, Peru 2010–2015. *Archives of Gerontology and Geriatrics, 82*, 100-105. doi:https://doi.org/10.1016/j.archger.2019.01.008

Annesi, I., Moreau, T., & Lellouch, J. (1989). Efficiency of the logistic regression and cox proportional hazards models in longitudinal studies. *Statistics in medicine, 8*(12), 1515-1521. doi:https://doi.org/10.1002/sim.4780081211

Antithrombotic Trialists' Collaboration. (2002). Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high

risk patients. *BMJ, 324*(7329), 71-86. doi:10.1136/bmj.324.7329.71

Arnardottir, E. S., Bjornsdottir, E., Olafsdottir, K. A., Benediktsdottir, B., & Gislason, T. (2016). Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms. *Eur Respir J, 47*(1), 194. doi:10.1183/13993003.01148-2015

Arnold, F. W., & Fuqua, J. L. (2020). Viral respiratory infections: a cause of community-acquired pneumonia or a predisposing factor? *Current opinion in pulmonary medicine, 26*(3), 208-214. doi:10.1097/mcp.0000000000000666

Association, A. D. (2004). Aspirin Therapy in Diabetes. *Diabetes Care, 27*(suppl_1), s72-s73. doi:10.2337/diacare.27.2007.S72

Aston, S. J. (2017). Pneumonia in the developing world: Characteristic features and approach to management. *Respirology, 22*(7), 1276-1287. doi:https://doi.org/10.1111/resp.13112

Aston, S. J., Ho, A., Jary, H., Huwa, J., Mitchell, T., Ibitoye, S., Greenwood, S., Joekes, E., Daire, A., Mallewa, J., Everett, D., Nyirenda, M., Faragher, B., Mwandumba, H. C., Heyderman, R. S., & Gordon, S. B. (2019). Etiology and Risk Factors for Mortality in an Adult Community-acquired Pneumonia Cohort in Malawi. *American Journal of Respiratory and Critical Care Medicine, 200*(3), 359-369. doi:10.1164/rccm.201807-1333OC

Austin, P. C. (2011). An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research, 46*(3), 399-424. doi:10.1080/00273171.2011.568786

Austin, P. C., & Stuart, E. A. (2015). Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Statistics in medicine, 34*(28), 3661-3679. doi:10.1002/sim.6607

Awtry, E. H., & Loscalzo, J. (2000). Aspirin. *Circulation, 101*(10), 1206-1218. doi:doi:10.1161/01.CIR.101.10.1206

Azmi, S., Aljunid, S. M., Maimaiti, N., Ali, A.-A., Muhammad Nur, A., De Rosas-Valera, M., Encluna, J., Mohamed, R., Wibowo, B., Komaryani, K., & Roberts, C. (2016). Assessing the burden of pneumonia using administrative data from Malaysia, Indonesia, and the Philippines. *International Journal of Infectious Diseases, 49*, 87-93. doi:https://doi.org/10.1016/j.ijid.2016.05.021

Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S. A., Rouphael, N., Creech, C. B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., . . . Zaks, T. (2020). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine, 384*(5), 403-416. doi:10.1056/NEJMoa2035389

Baggett, H. C., Watson, N. L., Deloria Knoll, M., Brooks, W. A., Feikin, D. R., Hammitt, L. L., Howie, S. R. C., Kotloff, K. L., Levine, O. S., Madhi, S. A., Murdoch, D. R., Scott, J. A. G., Thea, D. M., Antonio, M., Awori, J. O., Baillie, V. L., DeLuca, A. N., Driscoll, A. J., Duncan, J., . . . Group, P. S. (2017). Density of Upper Respiratory Colonization With Streptococcus pneumoniae and Its Role in the Diagnosis of Pneumococcal Pneumonia Among Children Aged <5 Years in the PERCH Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 64*(suppl_3), S317-S327. doi:10.1093/cid/cix100

Bal, A., Pichon, M., Picard, C., Casalegno, J. S., Valette, M., Schuffenecker, I., Billard, L., Vallet, S., Vilchez, G., Cheynet, V., Oriol, G., Trouillet-Assant, S., Gillet, Y., Lina, B., Brengel-Pesce, K., Morfin, F., & Josset, L. (2018). Quality control implementation for universal characterization of DNA and RNA viruses in clinical respiratory samples using single metagenomic next-generation sequencing workflow. *BMC Infectious Diseases, 18*. doi:ARTN 537 10.1186/s12879-018-3446-5

Barceló, A., Elorza, M. A., Barbé, F., Santos, C., Mayoralas, L. R., & Agusti, A. G. (2001). Angiotensin converting enzyme in patients with sleep apnoea syndrome: plasma activity and gene polymorphisms. *Eur Respir J, 17*(4), 728-732. doi:10.1183/09031936.01.17407280

Basi, S. K., Marrie, T. J., Huang, J. Q., & Majumdar, S. R. (2004). Patients admitted to hospital with suspected pneumonia and normal chest radiographs: Epidemiology, microbiology, and outcomes. *The American Journal of Medicine, 117*(5), 305-311. doi:https://doi.org/10.1016/j.amjmed.2004.03.029

Baud, D., Qi, X., Nielsen-Saines, K., Musso, D., Pomar, L., & Favre, G. (2020). Real estimates of mortality following COVID-19 infection. *The Lancet Infectious Diseases, 20*(7), 773. doi:10.1016/S1473-3099(20)30195-X

Bender, R., & Lange, S. (2001). Adjusting for multiple testing—when and how? *Journal of Clinical Epidemiology, 54*(4), 343-349. doi:https://doi.org/10.1016/S0895-4356(00)00314-0

Bergstra, S. A., Sepriano, A., Ramiro, S., & Landewé, R. (2019). Three handy tips and a practical guide to improve your propensity score models. *RMD Open, 5*(1), e000953. doi:10.1136/rmdopen-2019-000953

Berk, S. L. (1984). Bacterial Pneumonia in the Elderly: The Observations of Sir William Osler in Retrospect. *Journal of the American Geriatrics Society, 32*(9), 683-685. doi:https://doi.org/10.1111/j.1532-5415.1984.tb02261.x

Bjarnason, A., Westin, J., Lindh, M., Andersson, L.-M., Kristinsson, K. G., Löve, A., Baldursson, O., & Gottfredsson, M. (2018a). Incidence, Etiology, and Outcomes of Community-Acquired Pneumonia: A Population-Based Study. *Open Forum Infectious Diseases, 5*(2). doi:10.1093/ofid/ofy010

Bjarnason, A., Westin, J., Lindh, M., Andersson, L., Kristinsson, K., Löve, A., Baldursson, O., & Gottfredsson, M. (2018b). Incidence, Etiology, and Outcomes of Community-Acquired Pneumonia: A Population-Based Study. *Open Forum Infectious Diseases, 5*(2), ofy010-ofy010. doi:10.1093/ofid/ofy010

Bjarnason, A., Westin, J., Lindh, M., Andersson, L., Kristinsson, K., Löve, A., Baldursson, O., & Gottfredsson, M. (2018c). Incidence, Etiology, and Outcomes of Community-Acquired Pneumonia: A Population-Based Study. *Open Forum Infect. Dis., 5*(2), ofy010-ofy010. doi:10.1093/ofid/ofy010

Boelsen, L. K., Dunne, E. M., Gould, K. A., Ratu, F. T., Vidal, J. E., Russell, F. M., Mulholland, E. K., Hinds, J., Satzke, C., & Gales, A. C. (2020). The Challenges of Using Oropharyngeal Samples To Measure Pneumococcal Carriage in Adults. *mSphere, 5*(4), e00478-00420. doi:doi:10.1128/mSphere.00478-20

Bonnave, C., Mertens, D., Peetermans, W., Cobbaert, K., Ghesquiere, B., Deschodt, M., & Flamaing, J. (2019). Adult vaccination for pneumococcal disease: a comparison of the national guidelines in Europe. *European Journal of Clinical Microbiology & Infectious Diseases, 38*(4), 785-791. doi:10.1007/s10096-019-03485-3

Bourcier, J.-E., Paquet, J., Seinger, M., Gallard, E., Redonnet, J.-P., Cheddadi, F., Garnier, D., Bourgeois, J.-M., & Geeraerts, T. (2014). Performance comparison of lung ultrasound and chest x-ray for the diagnosis of pneumonia in the ED. *The American Journal of Emergency Medicine, 32*(2), 115-118. doi:https://doi.org/10.1016/j.ajem.2013.10.003

Boyd, A. R., & Orihuela, C. J. (2011). Dysregulated inflammation as a risk factor for pneumonia in the elderly. *Aging Dis, 2*(6), 487-

500. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22288022

Bradley, T. D., & Floras, J. S. (2009). Obstructive sleep apnoea and its cardiovascular consequences. *The Lancet, 373*(9657), 82-93. doi:https://doi.org/10.1016/S0140-6736(08)61622-0

Braveman, P. (2013). Health in Europe 2014 - a view from across the Atlantic. *The Lancet, 381*(9874), 1257-1259. doi:10.1016/S0140-6736(13)60587-5

Brookhart, M. A., Schneeweiss, S., Rothman, K. J., Glynn, R. J., Avorn, J., & Stürmer, T. (2006). Variable Selection for Propensity Score Models. *American Journal of Epidemiology, 163*(12), 1149-1156. doi:10.1093/aje/kwj149

Brown, T. S., Dubowski, K., Plitt, M., Falci, L., Lee, E., Huynh, M., Furuya, Y., & Vora, N. M. (2020). Erroneous Reporting of Deaths Attributed to Pneumonia and Influenza at 2 New York City Teaching Hospitals, 2013-2014. *Public health reports (Washington, D.C. : 1974), 135*(6), 796-804. doi:10.1177/0033354920953209

Brueggemann, A. B., van Rensburg, M. J. J., Shaw, D., McCarthy, N., Jolley, K. A., Maiden, M. C. J., van der Linden, M. P. G., Amin-Chowdhury, Z., Bennett, D. E., Borrow, R., Brandileone, M.-C. C., Broughton, K., Campbell, R., Cao, B., Casanova, C., Choi, E. H., Chu, Y. W., Clark, S. A., Claus, H., . . . Zhou, F. (2020). The Invasive Respiratory Infection Surveillance (IRIS) Initiative reveals significant reductions in invasive bacterial infections during the COVID-19 pandemic. *medRxiv*, 2020.2011.2018.20225029. doi:10.1101/2020.11.18.20225029

Bruns, A. H., Oosterheert, J. J., Cucciolillo, M. C., El Moussaoui, R., Groenwold, R. H., Prins, J. M., & Hoepelman, A. I. (2011). Cause-specific long-term mortality rates in patients recovered from community-acquired pneumonia as compared with the general Dutch population. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 17*(5), 763-768. doi:10.1111/j.1469-0691.2010.03296.x

Burk, M., El-Kersh, K., Saad, M., Wiemken, T., Ramirez, J., & Cavallazzi, R. (2016). Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. *Eur Respir Rev, 25*(140), 178-188. doi:10.1183/16000617.0076-2015

Burton, D. C., Flannery, B., Bennett, N. M., Farley, M. M., Gershman, K., Harrison, L. H., Lynfield, R., Petit, S., Reingold, A. L., Schaffner, W., Thomas, A., Plikaytis, B. D., Charles E. Rose, J.,

Whitney, C. G., Schuchat, A., & Network, f. t. A. B. C. S. E. I. P. (2010). Socioeconomic and Racial/Ethnic Disparities in the Incidence of Bacteremic Pneumonia Among US Adults. *American Journal of Public Health, 100*(10), 1904-1911. doi:10.2105/ajph.2009.181313

Cade, B. E., Dashti, H. S., Hassan, S. M., Redline, S., & Karlson, E. W. (2020). Sleep Apnea and COVID-19 Mortality and Hospitalization. *Am J Respir Crit Care Med, 202*(10), 1462-1464. doi:10.1164/rccm.202006-2252LE

Caliendo, A. M. (2011). Multiplex PCR and emerging technologies for the detection of respiratory pathogens. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 52 Suppl 4*, S326-330. doi:10.1093/cid/cir047

Cangemi, R., Casciaro, M., Rossi, E., Calvieri, C., Bucci, T., Calabrese, C. M., Taliani, G., Falcone, M., Palange, P., Bertazzoni, G., Farcomeni, A., Grieco, S., Pignatelli, P., Violi, F., Albanese, F., Biliotti, E., Carnevale, R., Catasca, E., Celestini, A., . . . Ullo, I. (2014a). Platelet Activation Is Associated With Myocardial Infarction in Patients With Pneumonia. *Journal of the American College of Cardiology, 64*(18), 1917-1925. doi:https://doi.org/10.1016/j.jacc.2014.07.985

Cangemi, R., Casciaro, M., Rossi, E., Calvieri, C., Bucci, T., Calabrese, C. M., Taliani, G., Falcone, M., Palange, P., Bertazzoni, G., Farcomeni, A., Grieco, S., Pignatelli, P., Violi, F., & Grp, C. S. S. (2014b). Platelet Activation Is Associated With Myocardial Infarction in Patients With Pneumonia. *Journal of the American College of Cardiology, 64*(18), 1917-1925. doi:10.1016/j.jacc.2014.07.985

Cariou, B., Hadjadj, S., Wargny, M., Pichelin, M., Al-Salameh, A., Allix, I., Amadou, C., Arnault, G., Baudoux, F., Bauduceau, B., Borot, S., Bourgeon-Ghittori, M., Bourron, O., Boutoille, D., Cazenave-Roblot, F., Chaumeil, C., Cosson, E., Coudol, S., Darmon, P., . . . Gourdy, P. (2020). Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia, 63*(8), 1500-1515. doi:10.1007/s00125-020-05180-x

Chalmers, J. D., Rother, C., Salih, W., & Ewig, S. (2013). Healthcare-Associated Pneumonia Does Not Accurately Identify Potentially Resistant Pathogens: A Systematic Review and Meta-Analysis. *Clinical Infectious Diseases, 58*(3), 330-339. doi:10.1093/cid/cit734

Chalmers, J. D., Singanayagam, A., Murray, M. P., & Hill, A. T. (2008). Prior Statin Use Is Associated with Improved Outcomes in Community-acquired Pneumonia. *The American Journal of Medicine, 121*(11), 1002-1007.e1001. doi:https://doi.org/10.1016/j.amjmed.2008.06.030

Charalampous, T., Kay, G. L., Richardson, H., Aydin, A., Baldan, R., Jeanes, C., Rae, D., Grundy, S., Turner, D. J., Wain, J., Leggett, R. M., Livermore, D. M., & O'Grady, J. (2019). Nanopore metagenomics enables rapid clinical diagnosis of bacterial lower respiratory infection. *Nature Biotechnology, 37*(7), 783-792. doi:10.1038/s41587-019-0156-5

Chen, J., Zhao, Y., Shang, Y., Lin, Z., Xu, G., Bai, B., Zheng, J., Li, P., Mao, Y., Deng, Q., & Yu, Z. (2021). The clinical significance of simultaneous detection of pathogens from bronchoalveolar lavage fluid and blood samples by metagenomic next-generation sequencing in patients with severe pneumonia. *Journal of Medical Microbiology, 70*(1). doi:https://doi.org/10.1099/jmm.0.001259

Chen, W., Janz, D. R., Bastarache, J. A., May, A. K., O'Neal, H. R., Bernard, G. R., & Ware, L. B. (2015). Prehospital Aspirin Use Is Associated With Reduced Risk of Acute Respiratory Distress Syndrome in Critically Ill Patients: A Propensity-Adjusted Analysis. *Critical Care Medicine, 43*(4), 801-807. doi:10.1097/Ccm.0000000000000789

Chiotan, R., & Chiotan, M. (2014). Pneumonias - a dynamic relationship between the human organism and the etiologic agent. *Journal of medicine and life, 7*(2), 192-201. Retrieved from https://pubmed.ncbi.nlm.nih.gov/25408724

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4197495/

Chow, E. J., Uyeki, T. M., & Chu, H. Y. (2023). The effects of the COVID-19 pandemic on community respiratory virus activity. *Nature Reviews Microbiology, 21*(3), 195-210. doi:10.1038/s41579-022-00807-9

Christensen, K., Doblhammer, G., Rau, R., & Vaupel, J. W. (2009). Ageing populations: the challenges ahead. *The Lancet, 374*(9696), 1196-1208. doi:https://doi.org/10.1016/S0140-6736(09)61460-4

Cillóniz, C., Ewig, S., Polverino, E., Muñoz-Almagro, C., Marco, F., Gabarrús, A., Menéndez, R., Mensa, J., & Torres, A. (2012). Pulmonary complications of pneumococcal community-acquired pneumonia: incidence, predictors, and outcomes.

*Clinical Microbiology and Infection, 18*(11), 1134-1142. doi:https://doi.org/10.1111/j.1469-0691.2011.03692.x

Cillóniz, C., Liapikou, A., Martin-Loeches, I., García-Vidal, C., Gabarrús, A., Ceccato, A., Magdaleno, D., Mensa, J., Marco, F., & Torres, A. (2018). Twenty-year trend in mortality among hospitalized patients with pneumococcal community-acquired pneumonia. *PLOS ONE, 13*(7), e0200504. doi:10.1371/journal.pone.0200504

Cilloniz, C., Martin-Loeches, I., Garcia-Vidal, C., San Jose, A., & Torres, A. (2016). Microbial Etiology of Pneumonia: Epidemiology, Diagnosis and Resistance Patterns. *Int J Mol Sci, 17*(12). doi:10.3390/ijms17122120

Claessens, Y. E., Debray, M. P., Tubach, F., Brun, A. L., Rammaert, B., Hausfater, P., Naccache, J. M., Ray, P., Choquet, C., Carette, M. F., Mayaud, C., Leport, C., & Duval, X. (2015). Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia. *American Journal of Respiratory and Critical Care Medicine, 192*(8), 974-982. doi:10.1164/rccm.201501-0017OC

Clark, T. W., Medina, M.-j., Batham, S., Curran, M. D., Parmar, S., & Nicholson, K. G. (2014). Adults hospitalised with acute respiratory illness rarely have detectable bacteria in the absence of COPD or pneumonia; viral infection predominates in a large prospective UK sample. *Journal of Infection, 69*(5), 507-515. doi:https://doi.org/10.1016/j.jinf.2014.07.023

Collins, R., Peto, R., Baigent, C., & Sleight, P. (1997). Aspirin, Heparin, and Fibrinolytic Therapy in Suspected Acute Myocardial Infarction. *New England Journal of Medicine, 336*(12), 847-860. doi:10.1056/nejm199703203361207

Corrado, R. E., Lee, D., Lucero, D. E., Varma, J. K., & Vora, N. M. (2017). Burden of Adult Community-acquired, Health-care-Associated, Hospital-Acquired, and Ventilator-Associated Pneumonia: New York City, 2010 to 2014. *Chest, 152*(5), 930-942. doi:https://doi.org/10.1016/j.chest.2017.04.162

Corrales-Medina, V. F., Alvarez, K. N., Weissfeld, L. A., Angus, D. C., Chirinos, J. A., Chang, C. C. H., Newman, A., Loehr, L., Folsom, A. R., Elkind, M. S., Lyles, M. F., Kronmal, R. A., & Yende, S. (2015). Association Between Hospitalization for Pneumonia and Subsequent Risk of Cardiovascular Disease (vol 313, pg 264, 2015). *Jama-Journal of the American Medical Association, 313*(3), 264-264. Retrieved from <Go to ISI>://WOS:000348145000032

Corrales-Medina, V. F., deKemp, R. A., Chirinos, J. A., Zeng, W., Wang, J., Waterer, G., Beanlands, R. S. B., & Dwivedi, G. (2021). Persistent Lung Inflammation After Clinical Resolution of Community-Acquired Pneumonia as Measured by 18FDG-PET/CT Imaging. *Chest*, *160*(2), 446-453. doi:https://doi.org/10.1016/j.chest.2021.02.048

Corrales-Medina, V. F., Musher, D. M., Wells, G. A., Chirinos, J. A., Chen, L., & Fine, M. J. (2012). Cardiac Complications in Patients With Community-Acquired Pneumonia Incidence, Timing, Risk Factors, and Association With Short-Term Mortality. *Circulation*, *125*(6), 773-U792. doi:10.1161/Circulationaha.111.040766

Croxen, M. A., Lee, T. D., Azana, R., & Hoang, L. M. (2018). Use of genomics to design a diagnostic assay to discriminate between Streptococcus pneumoniae and Streptococcus pseudopneumoniae. *Microbial Genomics*, *4*(7). doi:ARTN 000175 10.1099/mgen.0.000175

Cutts, F. T., Zaman, S. M. A., Enwere, G., Jaffar, S., Levine, O. S., Okoko, J. B., Oluwalana, C., Vaughan, A., Obaro, S. K., Leach, A., McAdam, K. P., Biney, E., Saaka, M., Onwuchekwa, U., Yallop, F., Pierce, N. F., Greenwood, B. M., & Adegbola, R. A. (2005). Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *The Lancet*, *365*(9465), 1139-1146. doi:https://doi.org/10.1016/S0140-6736(05)71876-6

D R Feikin, A. S., M Kolczak, N L Barrett, L H Harrison, L Lefkowitz, A McGeer, M M Farley, D J Vugia, C Lexau, K R Stefonek, J E Patterson,, & Jorgensen, J. H. (2000). Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997. *American Journal of Public Health*, *90*(2), 223-229. doi:10.2105/ajph.90.2.223

Daniel, P., Woodhead, M., Welham, S., Mckeever, T. M., & Lim, W. S. (2016). Mortality reduction in adult community-acquired pneumonia in the UK (2009–2014): results from the British Thoracic Society audit programme. *Thorax*, *71*(11), 1061-1063. doi:10.1136/thoraxjnl-2016-208937

Davies, E. C., Green, C. F., Taylor, S., Williamson, P. R., Mottram, D. R., & Pirmohamed, M. (2009). Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLOS ONE*, *4*(2), e4439. doi:10.1371/journal.pone.0004439

de Miguel-Díez, J., Jiménez-García, R., Hernández-Barrera, V., Jiménez-Trujillo, I., de Miguel-Yanes, J. M., Méndez-Bailón, M., & López-de-Andrés, A. (2017). Trends in hospitalizations for community-acquired pneumonia in Spain: 2004 to 2013. *European Journal of Internal Medicine, 40*, 64-71. doi:https://doi.org/10.1016/j.ejim.2016.12.010

Desborough, M. J. R., & Keeling, D. M. (2017). The aspirin story – from willow to wonder drug. *British Journal of Haematology, 177*(5), 674-683. doi:10.1111/bjh.14520

Dewan, N. A., Nieto, F. J., & Somers, V. K. (2015). Intermittent Hypoxemia and OSA: Implications for Comorbidities. *Chest, 147*(1), 266-274. doi:https://doi.org/10.1378/chest.14-0500

Dherani, M., Pope, D., Mascarenhas, M., Smith, K. R., Weber, M., & Bruce, N. (2008). Indoor air pollution from unprocessed solid fuel use and pneumonia risk in children aged under five years: a systematic review and meta-analysis. *Bulletin of the World Health Organization, 86*(5), 390-398. doi:10.2471/Blt.07.044529

Diao, W.-q., Shen, N., Yu, P.-x., Liu, B.-b., & He, B. (2016). Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: A systematic review and meta-analysis of randomized trials. *Vaccine, 34*(13), 1496-1503. doi:https://doi.org/10.1016/j.vaccine.2016.02.023

Directorate of Health Iceland. (2022). Tóbaksnotkun - tölur. Retrieved from https://www.landlaeknir.is/tolfraedi-og-rannsoknir/tolfraedi/heilsa-og-lidan/tobaksnotkun/. from Directorate of Health https://www.landlaeknir.is/tolfraedi-og-rannsoknir/tolfraedi/heilsa-og-lidan/tobaksnotkun/

Doyle, R., Sadlier, D. M., & Godson, C. (2018). Pro-resolving lipid mediators: Agents of anti-ageing? *Seminars in Immunology, 40*, 36-48. doi:https://doi.org/10.1016/j.smim.2018.09.002

Drijkoningen, J. J. C., & Rohde, G. G. U. (2014). Pneumococcal infection in adults: burden of disease. *Clinical Microbiology and Infection, 20*(s5), 45-51. doi:https://doi.org/10.1111/1469-0691.12461

DuGoff, E. H., Schuler, M., & Stuart, E. A. (2014). Generalizing Observational Study Results: Applying Propensity Score Methods to Complex Surveys. *Health Services Research, 49*(1), 284-303. doi:https://doi.org/10.1111/1475-6773.12090

Dupuis, C., Sabra, A., Patrier, J., Chaize, G., Saighi, A., Féger, C., Vainchtock, A., Gaillat, J., & Timsit, J.-F. (2021). Burden of

pneumococcal pneumonia requiring ICU admission in France: 1-year prognosis, resources use, and costs. *Critical Care, 25*(1), 24. doi:10.1186/s13054-020-03442-z

Ebell, M. H., Chupp, H., Cai, X., Bentivegna, M., & Kearney, M. (2020). Accuracy of Signs and Symptoms for the Diagnosis of Community-acquired Pneumonia: A Meta-analysis. *Academic Emergency Medicine, 27*(7), 541-553. doi:https://doi.org/10.1111/acem.13965

Eccles, S., Pincus, C., Higgins, B., Woodhead, M., & Guideline Development, G. (2014). Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. *BMJ, 349*, g6722. doi:10.1136/bmj.g6722

Eisen, D. P., Leder, K., Woods, R. L., Lockery, J. E., McGuinness, S. L., Wolfe, R., Pilcher, D., Moore, E. M., Shastry, A., Nelson, M. R., Reid, C. M., McNeil, J. J., & McBryde, E. S. (2020). Effect of aspirin on deaths associated with sepsis in healthy older people (ANTISEPSIS): a randomised, double-blind, placebo-controlled primary prevention trial. *Lancet Respir. Med.* doi:10.1016/s2213-2600(20)30411-2

Eljaaly, K., Alshehri, S., Aljabri, A., Abraham, I., Al Mohajer, M., Kalil, A. C., & Nix, D. E. (2017). Clinical failure with and without empiric atypical bacteria coverage in hospitalized adults with community-acquired pneumonia: a systematic review and meta-analysis. *BMC Infect Dis, 17*(1), 385. doi:10.1186/s12879-017-2495-5

Elston, J. W. T., Santaniello-Newton, A., Meigh, J. A., Harmer, D., Allgar, V., Allison, T., Richardson, G., Meigh, R., Palmer, S. R., & Barlow, G. (2012). Increasing incidence of invasive pneumococcal disease and pneumonia despite improved vaccination uptake: surveillance in Hull and East Yorkshire, UK, 2002–2009. *Epidemiology and Infection, 140*(7), 1252-1266. doi:10.1017/S0950268811001907

Embætti Landlæknis, & Sóttvarnalæknir. (2014). *Leiðbeiningar um bólusetningu gegn pneumókokkum*. Embætti Landlæknis, Sóttvarnalæknir Retrieved from https://www.landlaeknir.is/servlet/file/store93/item23265/Lei%C3%B0beiningar%20um%20notkun_b%C3%B3luefna_gegn_pneum%C3%B3kokkum-final.pdf

Esayag, Y., Nikitin, I., Bar-Ziv, J., Cytter, R., Hadas-Halpern, I., Zalut, T., & Yinnon, A. M. (2010). Diagnostic Value of Chest Radiographs in Bedridden Patients Suspected of Having Pneumonia. *The American Journal of Medicine, 123*(1), 88.e81-88.e85. doi:https://doi.org/10.1016/j.amjmed.2009.09.012

Eythorsson, E., Ásgeirsdóttir, T. L., Erlendsdóttir, H., Hrafnkelsson, B., Kristinsson, K. G., & Haraldsson, Á. (2021). The impact and cost-effectiveness of introducing the 10-valent pneumococcal conjugate vaccine into the paediatric immunisation programme in Iceland—A population-based time series analysis. *PLOS ONE, 16*(4), e0249497. doi:10.1371/journal.pone.0249497

Eythorsson, E., Helgason, D., Ingvarsson, R. F., Bjornsson, H. K., Olafsdottir, L. B., Bjarnadottir, V., Runolfsdottir, H. L., Bjarnadottir, S., Agustsson, A. S., Oskarsdottir, K., Thorvaldsson, H. H., Kristjansdottir, G., Armannsdottir, B., Bjarnason, A., Johannsson, B., Gudlaugsson, O., Gottfredsson, M., Sigurdsson, M. I., Indridason, O. S., . . . Palsson, R. (2020). Clinical spectrum of coronavirus disease 2019 in Iceland: population based cohort study. *BMJ, 371*, m4529. doi:10.1136/bmj.m4529

Falcone, M., Russo, A., Cangemi, R., Farcomeni, A., Calvieri, C., Barilla, F., Scarpellini, M. G., Bertazzoni, G., Palange, P., Taliani, G., Venditti, M., & Violi, F. (2015). Lower mortality rate in elderly patients with community-onset pneumonia on treatment with aspirin. *J Am Heart Assoc, 4*(1), e001595. doi:10.1161/jaha.114.001595

Falcone, M., Russo, A., Shindo, Y., Farcomeni, A., Pieralli, F., Cangemi, R., Liu, J., Xia, J., Okumura, J., Sano, M., Jones, C., Vannucchi, V., Mancone, M., Micek, S., Xu, F., Violi, F., & Kollef, M. (2019a). A Hypothesis-Generating Study of the Combination of Aspirin plus Macrolides in Patients with Severe Community-Acquired Pneumonia. *Antimicrob Agents Chemother, 63*(2). doi:10.1128/aac.01556-18

Falcone, M., Russo, A., Shindo, Y., Farcomeni, A., Pieralli, F., Cangemi, R., Liu, J. L., Xia, J. Y., Okumura, J., Sano, M., Jones, C., Vannucchi, V., Mancone, M., Micek, S., Xu, F., Violi, F., & Kollef, M. (2019b). A Hypothesis-Generating Study of the Combination of Aspirin plus Macrolides in Patients with Severe Community-Acquired Pneumonia. *Antimicrobial Agents and Chemotherapy, 63*(2). doi:ARTN e01556-18 10.1128/AAC.01556-18

Fally, M., Israelsen, S., Anhøj, J., Benfield, T., Tarp, B., Kolte, L., & Ravn, P. (2021). The increasing importance of Haemophilus influenzae in community-acquired pneumonia: results from a Danish cohort study. *Infectious Diseases, 53*(2), 122-130. doi:10.1080/23744235.2020.1846776

Farrell, P. C., & Richards, G. (2017). Recognition and treatment of sleep-disordered breathing: an important component of chronic

disease management. *J Transl Med, 15*(1), 114. doi:10.1186/s12967-017-1211-y

Feldman, C., & Anderson, R. (2020). Platelets and Their Role in the Pathogenesis of Cardiovascular Events in Patients With Community-Acquired Pneumonia. *Frontiers in Immunology, 11*, 2304. Retrieved from https://www.frontiersin.org/article/10.3389/fimmu.2020.577303

Feldman, C., Normark, S., Henriques-Normark, B., & Anderson, R. (2019). Pathogenesis and prevention of risk of cardiovascular events in patients with pneumococcal community-acquired pneumonia. *Journal of Internal Medicine, 285*(6), 635-652. doi:https://doi.org/10.1111/joim.12875

Fine, M. J., Auble, T. E., Yealy, D. M., Hanusa, B. H., Weissfeld, L. A., Singer, D. E., Coley, C. M., Marrie, T. J., & Kapoor, W. N. (1997). A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med, 336*(4), 243-250. doi:10.1056/nejm199701233360402

Flanders, W. D., Tucker, G., Krishnadasan, A., Martin, D., Honig, E., & McClellan, W. M. (1999). Validation of the pneumonia severity index. Importance of study-specific recalibration. *Journal of General Internal Medicine, 14*(6), 333-340. doi:10.1046/j.1525-1497.1999.00351.x

Flory, J. H., Joffe, M., Fishman, N. O., Edelstein, P. H., & Metlay, J. P. (2009). Socioeconomic risk factors for bacteraemic pneumococcal pneumonia in adults. *Epidemiology & Infection, 137*(5), 717-726. doi:10.1017/S0950268808001489

Foley, N. C., Affoo, R. H., & Martin, R. E. (2015). A Systematic Review and Meta-Analysis Examining Pneumonia-Associated Mortality in Dementia. *Dementia and Geriatric Cognitive Disorders, 39*(1-2), 52-67. doi:10.1159/000367783

Foster, D., Walker, A. S., Paul, J., Griffiths, D., Knox, K., Peto, T. E., Crook, D. W., & Group, o. b. o. t. O. I. P. S. (2011). Reduction in invasive pneumococcal disease following implementation of the conjugate vaccine in the Oxfordshire region, England. *Journal of Medical Microbiology, 60*(1), 91-97. doi:https://doi.org/10.1099/jmm.0.023135-0

Gadsby, N. J., Russell, C. D., McHugh, M. P., Mark, H., Conway Morris, A., Laurenson, I. F., Hill, A. T., & Templeton, K. E. (2016). Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia. *Clinical infectious diseases : an official publication of the Infectious*

*Diseases Society of America, 62*(7), 817-823. doi:10.1093/cid/civ1214

Galanis, I., Lindstrand, A., Darenberg, J., Browall, S., Nannapaneni, P., Sjöström, K., Morfeldt, E., Naucler, P., Blennow, M., Örtqvist, Å., & Henriques-Normark, B. (2016). Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm, Sweden. *European Respiratory Journal, 47*(4), 1208-1218. doi:10.1183/13993003.01451-2015

Garin, N., Genne, D., Carballo, S., Chuard, C., Eich, G., Hugli, O., Lamy, O., Nendaz, M., Petignat, P. A., Perneger, T., Rutschmann, O., Seravalli, L., Harbarth, S., & Perrier, A. (2014). beta-Lactam monotherapy vs beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med, 174*(12), 1894-1901. doi:10.1001/jamainternmed.2014.4887

Garin, N., Marti, C., Scheffler, M., Stirnemann, J., & Prendki, V. (2019). Computed tomography scan contribution to the diagnosis of community-acquired pneumonia. *Current opinion in pulmonary medicine, 25*(3), 242-248. doi:10.1097/mcp.0000000000000567

Garvey, J. F., Pengo, M. F., Drakatos, P., & Kent, B. D. (2015). Epidemiological aspects of obstructive sleep apnea. *J Thorac Dis, 7*(5), 920-929. doi:10.3978/j.issn.2072-1439.2015.04.52

Gili-Miner, M., López-Méndez, J., Béjar-Prado, L., Ramírez-Ramírez, G., Vilches-Arenas, Á., & Sala-Turrens, J. (2015). Alcohol Use Disorders and Community-Acquired Pneumococcal Pneumonia: Associated Mortality, Prolonged Hospital Stay and Increased Hospital Spending. *Archivos de Bronconeumología (English Edition), 51*(11), 564-570. doi:https://doi.org/10.1016/j.arbr.2015.09.014

Glatthaar-Saalmüller, B., Mair, K. H., & Saalmüller, A. (2017). Antiviral activity of aspirin against RNA viruses of the respiratory tract—an in vitro study. *Influenza and Other Respiratory Viruses, 11*(1), 85-92. doi:https://doi.org/10.1111/irv.12421

Glickman, M. E., Rao, S. R., & Schultz, M. R. (2014). False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *Journal of Clinical Epidemiology, 67*(8), 850-857. doi:10.1016/j.jclinepi.2014.03.012

Goldstein, C., A., Rizvydeen, M., Conroy Deirdre, A., O'Brien Louise, M., Gupta, G., Somers Emily, C., Sharma, P., Golob Jonathan, L., Troost Jonathan, P., & Burgess Helen, J. (2021). The

prevalence and impact of pre-existing sleep disorder diagnoses and objective sleep parameters in patients hospitalized for COVID-19. *J Clin Sleep Med 0*(0), jcsm.9100. doi:10.5664/jcsm.9132

Gottlieb, M., Sansom, S., Frankenberger, C., Ward, E., & Hota, B. (2020). Clinical Course and Factors Associated With Hospitalization and Critical Illness Among COVID-19 Patients in Chicago, Illinois. *Acad Emerg Med*. doi:10.1111/acem.14104

Graf, E. H., Simmon, K. E., Tardif, K. D., Hymas, W., Flygare, S., Eilbeck, K., Yandell, M., & Schlaberg, R. (2016). Unbiased Detection of Respiratory Viruses by Use of RNA Sequencing-Based Metagenomics: a Systematic Comparison to a Commercial PCR Panel. *Journal of Clinical Microbiology, 54*(4), 1000-1007. doi:10.1128/Jcm.03060-15

Granger, E., Sergeant, J. C., & Lunt, M. (2019). Avoiding pitfalls when combining multiple imputation and propensity scores. *Stat Med., 38*(26), 5120-5132. doi:10.1002/sim.8355

Green, M. S., & Symons, M. J. (1983). A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. *Journal of Chronic Diseases, 36*(10), 715-723. doi:https://doi.org/10.1016/0021-9681(83)90165-0

Greiner, O., Day, P. J. R., Bosshard, P. P., Imeri, F., Altwegg, M., & Nadal, D. (2001). Quantitative Detection of <em>Streptococcus pneumoniae</em> in Nasopharyngeal Secretions by Real-Time PCR. *Journal of Clinical Microbiology, 39*(9), 3129. doi:10.1128/jcm.39.9.3129-3134.2001

Griffin, M. R., Zhu, Y., Moore, M. R., Whitney, C. G., & Grijalva, C. G. (2013). U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med, 369*(2), 155-163. doi:10.1056/NEJMoa1209165

Grijalva, C. G. (2015). Is Pneumonia a Risk Factor or a Risk Marker for Long-Term Mortality? *American Journal of Respiratory and Critical Care Medicine, 192*(5), 532-534. doi:10.1164/rccm.201506-1171ED

Grijalva, C. G., Nuorti, J. P., Arbogast, P. G., Martin, S. W., Edwards, K. M., & Griffin, M. R. (2007). Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *The Lancet, 369*(9568), 1179-1186. doi:https://doi.org/10.1016/S0140-6736(07)60564-9

Grudzinska, F. S., Brodlie, M., Scholefield, B. R., Jackson, T., Scott, A., Thickett, D. R., & Sapey, E. (2020). Neutrophils in community-acquired pneumonia: parallels in dysfunction at the extremes of age. *Thorax, 75*(2), 164-171. doi:10.1136/thoraxjnl-2018-212826

Guan, W.-j., Ni, Z.-y., Hu, Y., Liang, W.-h., Ou, C.-q., He, J.-x., Liu, L., Shan, H., Lei, C.-l., Hui, D. S. C., Du, B., Li, L.-j., Zeng, G., Yuen, K.-Y., Chen, R.-c., Tang, C.-l., Wang, T., Chen, P.-y., Xiang, J., . . . Zhong, N.-s. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine, 382*(18), 1708-1720. doi:10.1056/NEJMoa2002032

Gudbjartsson, D. F., Helgason, A., Jonsson, H., Magnusson, O. T., Melsted, P., Norddahl, G. L., Saemundsdottir, J., Sigurdsson, A., Sulem, P., Agustsdottir, A. B., Eiriksdottir, B., Fridriksdottir, R., Gardarsdottir, E. E., Georgsson, G., Gretarsdottir, O. S., Gudmundsson, K. R., Gunnarsdottir, T. R., Gylfason, A., Holm, H., . . . Stefansson, K. (2020). Spread of SARS-CoV-2 in the Icelandic Population. *New England Journal of Medicine, 382*(24), 2302-2315. doi:10.1056/NEJMoa2006100

Gupta, N. M., Lindenauer, P. K., Yu, P.-C., Imrey, P. B., Haessler, S., Deshpande, A., Higgins, T. L., & Rothberg, M. B. (2019). Association Between Alcohol Use Disorders and Outcomes of Patients Hospitalized With Community-Acquired Pneumonia. *JAMA Network Open, 2*(6), e195172-e195172. doi:10.1001/jamanetworkopen.2019.5172

Hallgren, M., Högberg, P., & Andréasson, S. (2009). Alcohol consumption among elderly European Union citizens. *Health effects, consumption trends and related issues. Stockholm: Swedish National Institute of Public Health*.

Hamaguchi, S., Suzuki, M., Sasaki, K., Abe, M., Wakabayashi, T., Sando, E., Yaegashi, M., Morimoto, S., Asoh, N., Hamashige, N., Aoshima, M., Ariyoshi, K., Morimoto, K., Dhoubhadel, B. G., Furumoto, A., Ishida, M., Ishifuji, T., Kakiuchi, S., Katoh, S., . . . on behalf of The Adult Pneumonia Study Group –, J. (2018). Six underlying health conditions strongly influence mortality based on pneumonia severity in an ageing population of Japan: a prospective cohort study. *BMC Pulmonary Medicine, 18*(1), 88. doi:10.1186/s12890-018-0648-y

Hamilton, F., Arnold, D., Henley, W., & Payne, R. A. (2021). Aspirin reduces cardiovascular events in patients with pneumonia: a prior event rate ratio analysis in a large primary care database. *European Respiratory Journal, 57*(2), 2002795. doi:10.1183/13993003.02795-2020

Hannah Ritchie, E. M., Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, DIana Beltekian, Max Roser, . (2020). Coronavirus Pandemic (COVID-19). Retrieved from https://ourworldindata.org/covid-cases. Retrieved 22.08.2022, from OurWorldInData https://ourworldindata.org/covid-cases

Hannan, E. L. (2008). Randomized Clinical Trials and Observational Studies. *JACC: Cardiovascular Interventions, 1*(3), 211-217. doi:doi:10.1016/j.jcin.2008.01.008

Hanquet, G., Krizova, P., Valentiner-Branth, P., Ladhani, S. N., Nuorti, J. P., Lepoutre, A., Mereckiene, J., Knol, M., Winje, B. A., Ciruela, P., Ordobas, M., Guevara, M., McDonald, E., Morfeldt, E., Kozakova, J., Slotved, H.-C., Fry, N. K., Rinta-Kokko, H., Varon, E., . . . Savulescu, C. (2019). Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. *Thorax, 74*(5), 473-482. doi:10.1136/thoraxjnl-2018-211767

Hansen, L. S., Lykkegaard, J., Thomsen, J. L., & Hansen, M. P. (2020). Acute lower respiratory tract infections: Symptoms, findings and management in Danish general practice. *European Journal of General Practice, 26*(1), 14-20. doi:10.1080/13814788.2019.1674279

Harboe, Z. B., Valentiner-Branth, P., Ingels, H., Rasmussen, J. N., Andersen, P. H. S., Bjerre, C. C., Goldblatt, D., Ashton, L., Haston, M., Konradsen, H. B., Lambertsen, L., & on behalf of the Danish Pneumococcal Surveillance Collaborating, G. (2013). Pediatric Invasive Pneumococcal Disease Caused by Vaccine Serotypes following the Introduction of Conjugate Vaccination in Denmark. *PLOS ONE, 8*(1), e51460. doi:10.1371/journal.pone.0051460

Hariyanto, T. I., & Kurniawan, A. (2021). Obstructive sleep apnea (OSA) and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: a systematic review and meta-analysis. *Sleep Med., 82*, 47-53. doi:https://doi.org/10.1016/j.sleep.2021.03.029

Harrell Jr, F. E., Harrell Jr, M. F. E., & Hmisc, D. (2017). Package 'rms'. *Vanderbilt University, 229*, Q8.

Harris, A. M., Bramley, A. M., Jain, S., Arnold, S. R., Ampofo, K., Self, W. H., Williams, D. J., Anderson, E. J., Grijalva, C. G., McCullers, J. A., Pavia, A. T., Wunderink, R. G., Edwards, K. M., Winchell, J. M., & Hicks, L. A. (2017). Influence of Antibiotics on the Detection of Bacteria by Culture-Based and Culture-Independent Diagnostic Tests in Patients Hospitalized

With Community-Acquired Pneumonia. *Open Forum Infect Dis, 4*(1), ofx014. doi:10.1093/ofid/ofx014

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics, 42*(2), 377-381. doi:10.1016/j.jbi.2008.08.010

Hayes, B. H., Haberling, D. L., Kennedy, J. L., Varma, J. K., Fry, A. M., & Vora, N. M. (2018). Burden of Pneumonia-Associated Hospitalizations: United States, 2001-2014. *Chest, 153*(2), 427-437. doi:https://doi.org/10.1016/j.chest.2017.09.041

Helgason, D., Eythorsson, E., Olafsdottir, L. B., Agustsson, T., Ingvarsdottir, S., Sverrisdottir, S., Ragnarsdottir, E. D., Gottfredsson, M., Gudlaugsson, O., Palsson, R., & Ingvarsson, R. F. (2020). Beating the odds with systematic individualized care: Nationwide prospective follow-up of all patients with COVID-19 in Iceland. *J Intern Med*. doi:10.1111/joim.13135

Henriksen, D. P., Nielsen, S. L., Laursen, C. B., Hallas, J., Pedersen, C., & Lassen, A. T. (2014). How Well Do Discharge Diagnoses Identify Hospitalised Patients with Community-Acquired Infections? – A Validation Study. *PLOS ONE, 9*(3), e92891. doi:10.1371/journal.pone.0092891

Hespanhol, V., & Bárbara, C. (2020). Pneumonia mortality, comorbidities matter? *Pulmonology, 26*(3), 123-129. doi:https://doi.org/10.1016/j.pulmoe.2019.10.003

Higgins, T. L., Deshpande, A., Zilberberg, M. D., Lindenauer, P. K., Imrey, P. B., Yu, P.-C., Haessler, S. D., Richter, S. S., & Rothberg, M. B. (2020). Assessment of the Accuracy of Using ICD-9 Diagnosis Codes to Identify Pneumonia Etiology in Patients Hospitalized With Pneumonia. *JAMA Network Open, 3*(7), e207750-e207750. doi:10.1001/jamanetworkopen.2020.7750

Hill, A. T., Gold, P. M., El Solh, A. A., Metlay, J. P., Ireland, B., Irwin, R. S., Adams, T. M., Altman, K. W., Azoulay, E., Barker, A. F., Birring, S. S., Blackhall, F., Bolser, D. C., Boulet, L.-P., Braman, S. S., Brightling, C., Callahan-Lyon, P., Chang, A. B., Cowley, T., . . . Weinberger, M. (2019). Adult Outpatients With Acute Cough Due to Suspected Pneumonia or Influenza: CHEST Guideline and Expert Panel Report. *Chest, 155*(1), 155-167. doi:https://doi.org/10.1016/j.chest.2018.09.016

Hippenstiel, S., Opitz, B., Schmeck, B., & Suttorp, N. (2006). Lung epithelium as a sentinel and effector system in pneumonia – molecular mechanisms of pathogen recognition and signal transduction. *Respiratory Research, 7*(1), 97. doi:10.1186/1465-9921-7-97

Ho, F. K., Celis-Morales, C. A., Gray, S. R., Katikireddi, S. V., Niedzwiedz, C. L., Hastie, C., Ferguson, L. D., Berry, C., Mackay, D. F., Gill, J. M., Pell, J. P., Sattar, N., & Welsh, P. (2020). Modifiable and non-modifiable risk factors for COVID-19, and comparison to risk factors for influenza and pneumonia: results from a UK Biobank prospective cohort study. *BMJ Open, 10*(11), e040402. doi:10.1136/bmjopen-2020-040402

Ho, J. Y., & Hendi, A. S. (2018). Recent trends in life expectancy across high income countries: retrospective observational study. *BMJ, 362*, k2562. doi:10.1136/bmj.k2562

Holter, J. C., Muller, F., Bjorang, O., Samdal, H. H., Marthinsen, J. B., Jenum, P. A., Ueland, T., Froland, S. S., Aukrust, P., Husebye, E., & Heggelund, L. (2015). Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. *BMC Infect Dis, 15*, 64. doi:10.1186/s12879-015-0803-5

Holter, J. C., Ueland, T., Jenum, P. A., Müller, F., Brunborg, C., Frøland, S. S., Aukrust, P., Husebye, E., & Heggelund, L. (2016). Risk Factors for Long-Term Mortality after Hospitalization for Community-Acquired Pneumonia: A 5-Year Prospective Follow-Up Study. *PLOS ONE, 11*(2), e0148741. doi:10.1371/journal.pone.0148741

Hopstaken, R. M., Muris, J. W., Knottnerus, J. A., Kester, A. D., Rinkens, P. E., & Dinant, G. J. (2003). Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *Br J Gen Pract, 53*(490), 358-364. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12830562

Horita, N., Otsuka, T., Haranaga, S., Namkoong, H., Miki, M., Miyashita, N., Higa, F., Takahashi, H., Yoshida, M., Kohno, S., & Kaneko, T. (2016). Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: A systematic review and meta-analysis. *Respirology, 21*(7), 1193-1200. doi:10.1111/resp.12835

Houck, P. M., Bratzler, D. W., Nsa, W., Ma, A., & Bartlett, J. G. (2004). Timing of Antibiotic Administration and Outcomes for Medicare Patients Hospitalized With Community-Acquired

Pneumonia. *Archives of Internal Medicine, 164*(6), 637-644. doi:10.1001/archinte.164.6.637

Huang, D. T., Yealy, D. M., Filbin, M. R., Brown, A. M., Chang, C.-C. H., Doi, Y., Donnino, M. W., Fine, J., Fine, M. J., Fischer, M. A., Holst, J. M., Hou, P. C., Kellum, J. A., Khan, F., Kurz, M. C., Lotfipour, S., LoVecchio, F., Peck-Palmer, O. M., Pike, F., . . . Angus, D. C. (2018). Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. *New England Journal of Medicine, 379*(3), 236-249. doi:10.1056/NEJMoa1802670

Huijskens, E. G., Rossen, J. W., Kluytmans, J. A., van der Zanden, A. G., & Koopmans, M. (2014). Evaluation of yield of currently available diagnostics by sample type to optimize detection of respiratory pathogens in patients with a community-acquired pneumonia. *Influenza Other Respir Viruses, 8*(2), 243-249. doi:10.1111/irv.12153

Huijskens, E. G., van Erkel, A. J., Palmen, F. M., Buiting, A. G., Kluytmans, J. A., & Rossen, J. W. (2013). Viral and bacterial aetiology of community-acquired pneumonia in adults. *Influenza Other Respir Viruses, 7*(4), 567-573. doi:10.1111/j.1750-2659.2012.00425.x

Hussein, H. M., Al-Khoury, D. K., Abdelnoor, A. M., & Rahal, E. A. (2019). Atorvastatin increases the production of proinflammatory cytokines and decreases the survival of Escherichia coli-infected mice. *Scientific Reports, 9*(1), 11717. doi:10.1038/s41598-019-48282-2

Iceland, S. (2008). *Mannfjöldi 1. janúar 2008*. Retrieved from https://hagstofa.is/utgafur/nanar-um-utgafu?id=54621

Iceland, S. (2020). Mannfjöldi eftir kyni og aldri 1841 -2020. Retrieved from https://px.hagstofa.is/pxis/pxweb/is/Ibuar/Ibuar__mannfjoldi__1_yfirlit__Yfirlit_mannfjolda/MAN00101.px. Retrieved 07.05.2020, from Hagstofa Íslands https://px.hagstofa.is/pxis/pxweb/is/Ibuar/Ibuar__mannfjoldi__1_yfirlit__Yfirlit_mannfjolda/MAN00101.px

Ioannou, G. N., Locke, E., Green, P., Berry, K., O'Hare, A. M., Shah, J. A., Crothers, K., Eastment, M. C., Dominitz, J. A., & Fan, V. S. (2020). Risk Factors for Hospitalization, Mechanical Ventilation, or Death Among 10 131 US Veterans With SARS-CoV-2 Infection. *JAMA Netw. Open, 3*(9), e2022310-e2022310. doi:10.1001/jamanetworkopen.2020.22310

Iroezindu, M. O., Chima, E. I., Isiguzo, G. C., Mbata, G. C., Onyedum, C. C., Onyedibe, K. I., & Okoli, L. E. (2014). Sputum

bacteriology and antibiotic sensitivity patterns of community-acquired pneumonia in hospitalized adult patients in Nigeria: a 5-year multicentre retrospective study. *Scandinavian Journal of Infectious Diseases, 46*(12), 875-887. doi:10.3109/00365548.2014.954263

Jackson, M. L., Neuzil, K. M., Thompson, W. W., Shay, D. K., Yu, O., Hanson, C. A., & Jackson, L. A. (2004). The burden of community-acquired pneumonia in seniors: results of a population-based study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 39*(11), 1642-1650. doi:10.1086/425615

Jafari, M., & Ansari-Pour, N. (2019). Why, When and How to Adjust Your P Values? *Cell journal, 20*(4), 604-607. doi:10.22074/cellj.2019.5992

Jain, S., Self, W. H., Wunderink, R. G., Fakhran, S., Balk, R., Bramley, A. M., Reed, C., Grijalva, C. G., Anderson, E. J., Courtney, D. M., Chappell, J. D., Qi, C., Hart, E. M., Carroll, F., Trabue, C., Donnelly, H. K., Williams, D. J., Zhu, Y., Arnold, S. R., . . . Finelli, L. (2015). Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *New England Journal of Medicine, 373*(5), 415-427. doi:10.1056/NEJMoa1500245

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., Accrombessi, M. M. K., . . . Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet, 392*(10159), 1789-1858. doi:https://doi.org/10.1016/S0140-6736(18)32279-7

Jennings, L. C., Anderson, T. P., Beynon, K. A., Chua, A., Laing, R. T. R., Werno, A. M., Young, S. A., Chambers, S. T., & Murdoch, D. R. (2008). Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax, 63*(1), 42-48. doi:10.1136/thx.2006.075077

Jeon, K., Yoo, H., Jeong, B. H., Park, H. Y., Koh, W. J., Suh, G. Y., & Guallar, E. (2017). Functional status and mortality prediction in community-acquired pneumonia. *Respirology, 22*(7), 1400-1406. doi:10.1111/resp.13072

Jones, B. E., Jones, M. M., Huttner, B., Stoddard, G., Brown, K. A., Stevens, V. W., Greene, T., Sauer, B., Madaras-Kelly, K., Rubin,

M., Goetz, M. B., & Samore, M. (2015). Trends in Antibiotic Use and Nosocomial Pathogens in Hospitalized Veterans With Pneumonia at 128 Medical Centers, 2006–2010. *Clinical Infectious Diseases, 61*(9), 1403-1410. doi:10.1093/cid/civ629

Jordan, R. E., Adab, P., & Cheng, K. K. (2020). Covid-19: risk factors for severe disease and death. *BMJ, 368*, m1198. doi:10.1136/bmj.m1198

Josephson, K. L., Gerba, C. P., & Pepper, I. L. (1993). Polymerase chain reaction detection of nonviable bacterial pathogens. *Appl Environ Microbiol, 59*(10), 3513-3515. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8250575

Jump, R. L. (2013). Clostridium difficile infection in older adults. *Aging health, 9*(4), 403-414. doi:10.2217/ahe.13.37

Karimi, E. (2019). Comparing Sensitivity of Ultrasonography and Plain Chest Radiography in Detection of Pneumonia; a Diagnostic Value Study. *Archives of academic emergency medicine, 7*(1), e8-e8. Retrieved from https://pubmed.ncbi.nlm.nih.gov/30847443

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6377225/

Kinkade, S., & Long, N. A. (2016). Acute Bronchitis. *Am Fam Physician, 94*(7), 560-565. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27929206

Kleykamp, B. A., & Heishman, S. J. (2011). The Older Smoker. *JAMA, 306*(8), 876-877. doi:10.1001/jama.2011.1221

Koivula, I., Sten, M., & Makela, P. H. (1994). Risk factors for pneumonia in the elderly. *The American Journal of Medicine, 96*(4), 313-320. doi:https://doi.org/10.1016/0002-9343(94)90060-4

Koskela, H. O., Salonen, P. H., Romppanen, J., & Niskanen, L. (2014). Long-term mortality after community-acquired pneumonia—impacts of diabetes and newly discovered hyperglycaemia: a prospective, observational cohort study. *BMJ Open, 4*(8), e005715. doi:10.1136/bmjopen-2014-005715

Kraicer-Melamed, H., O'Donnell, S., & Quach, C. (2016). The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. *Vaccine, 34*(13), 1540-1550. doi:https://doi.org/10.1016/j.vaccine.2016.02.024

Kristjánsson, M. (2017). Samfélagslungnabólga Verkferill. In Landspítali (Ed.). Reykjavík: Landspítali.

Kukull, W. A., Brenner De Fau - Speck, C. E., Speck Ce Fau - Nochlin, D., Nochlin D Fau - Bowen, J., Bowen J Fau - McCormick, W., McCormick W Fau - Teri, L., Teri L Fau - Pfanschmidt, M. L., Pfanschmidt Ml Fau - Larson, E. B., & Larson, E. B. (1994). Causes of death associated with Alzheimer disease: variation by level of cognitive impairment before death. *Journal of the American Geriatrics Society, Jul;42(7)*(0002-8614 (Print)), 723-726. doi:10.1111/j.1532-5415.1994.tb06531.x

Kunz, W. G., Patzig, M., Crispin, A., Stahl, R., Reiser, M. F., & Notohamiprodjo, M. (2018). The Value of Supine Chest X-Ray in the Diagnosis of Pneumonia in the Basal Lung Zones. *Academic Radiology, 25*(10), 1252-1256. doi:https://doi.org/10.1016/j.acra.2018.01.027

Landes, U., Bental, T., Orvin, K., Vaknin-Assa, H., Rechavia, E., Iakobishvili, Z., Lev, E., Assali, A., & Kornowski, R. (2016). Type 2 myocardial infarction: A descriptive analysis and comparison with type 1 myocardial infarction. *Journal of Cardiology, 67*(1), 51-56. doi:https://doi.org/10.1016/j.jjcc.2015.04.001

Lau, B., Cole, S. R., & Gange, S. J. (2009). Competing Risk Regression Models for Epidemiologic Data. *American Journal of Epidemiology, 170*(2), 244-256. doi:10.1093/aje/kwp107

Lawrence, H., Pick, H., Baskaran, V., Daniel, P., Rodrigo, C., Ashton, D., Edwards-Pritchard, R. C., Sheppard, C., Eletu, S. D., Litt, D., Fry, N. K., Rose, S., Trotter, C., McKeever, T. M., & Lim, W. S. (2020). Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: A case-control test-negative design study. *PLOS Medicine, 17*(10), e1003326. doi:10.1371/journal.pmed.1003326

Layne, K., Di Giosia, P., Ferro, A., & Passacquale, G. (2016). Anti-platelet drugs attenuate the expansion of circulating CD14highCD16+ monocytes under pro-inflammatory conditions. *Cardiovascular Research, 111*(1), 26-33. doi:10.1093/cvr/cvw089

Lee, S. H., Ruan, S.-Y., Pan, S.-C., Lee, T.-F., Chien, J.-Y., & Hsueh, P.-R. (2019). Performance of a multiplex PCR pneumonia panel for the identification of respiratory pathogens and the main determinants of resistance from the lower respiratory tract specimens of adult patients in intensive care units. *Journal of Microbiology, Immunology and Infection, 52*(6), 920-928. doi:https://doi.org/10.1016/j.jmii.2019.10.009

Lees, C., Godin, J., McElhaney, J. E., McNeil, S. A., Loeb, M., Hatchette, T. F., LeBlanc, J., Bowie, W., Boivin, G., McGeer, A., Poirier, A., Powis, J., Semret, M., Webster, D., & Andrew, M. K. (2020). Frailty Hinders Recovery From Influenza and Acute Respiratory Illness in Older Adults. *The Journal of Infectious Diseases, 222*(3), 428-437. doi:10.1093/infdis/jiaa092

Li, J., Huang, D. Q., Zou, B., Yang, H., Hui, W. Z., Rui, F., Yee, N. T. S., Liu, C., Nerurkar, S. N., Kai, J. C. Y., Teng, M. L. P., Li, X., Zeng, H., Borghi, J. A., Henry, L., Cheung, R., & Nguyen, M. H. (2020). Epidemiology of COVID-19: A Systematic Review and Meta-analysis of Clinical Characteristics, Risk factors and Outcomes. *J Med Virol*. doi:10.1002/jmv.26424

Li, N., Ma, X., Zhou, J., Deng, J., Gu, C., Fei, C., Cao, L., Zhang, Q., & Tao, F. (2022). Clinical application of metagenomic next-generation sequencing technology in the diagnosis and treatment of pulmonary infection pathogens: A prospective single-center study of 138 patients. *Journal of Clinical Laboratory Analysis, 36*(7), e24498. doi:https://doi.org/10.1002/jcla.24498

Lim, W. S., Baudouin, S. V., George, R. C., Hill, A. T., Jamieson, C., Le Jeune, I., Macfarlane, J. T., Read, R. C., Roberts, H. J., Levy, M. L., Wani, M., Woodhead, M. A., & Pneumonia Guidelines Committee of the, B. T. S. S. o. C. C. (2009). BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax, 64 Suppl 3*, iii1-55. doi:10.1136/thx.2009.121434

Lim, W. S., van der Eerden, M. M., Laing, R., Boersma, W. G., Karalus, N., Town, G. I., Lewis, S. A., & Macfarlane, J. T. (2003a). Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax, 58*(5), 377. doi:10.1136/thorax.58.5.377

Lim, W. S., van der Eerden, M. M., Laing, R., Boersma, W. G., Karalus, N., Town, G. I., Lewis, S. A., & Macfarlane, J. T. (2003b). Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax, 58*(5), 377-382. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12728155

Lindenauer, P. K., Lagu, T., Shieh, M.-S., Pekow, P. S., & Rothberg, M. B. (2012). Association of Diagnostic Coding With Trends in Hospitalizations and Mortality of Patients With Pneumonia, 2003-2009. *JAMA, 307*(13), 1405-1413. doi:10.1001/jama.2012.384

Loeb, M., McGeer, A., McArthur, M., Walter, S., & Simor, A. E. (1999). Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch Intern Med, 159*(17), 2058-2064. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10510992

Lupisan, S., Suzuki, A., Macalalad, N., Egos, R., Sombrero, L., Okamoto, M., Dapat, C., Mondoy, M., Galang, H., Zeta, V. F. F., de la Pena, F., Romano, V., Olveda, R., & Oshitani, H. (2019). Etiology and epidemiology of community-acquired pneumonia in adults requiring hospital admission: A prospective study in rural Central Philippines. *International Journal of Infectious Diseases, 80*, 46-53. doi:https://doi.org/10.1016/j.ijid.2018.12.005

Lv, M., Zhu, C., Zhu, C., Yao, J., Xie, L., Zhang, C., Huang, J., Du, X., & Feng, G. (2023). Clinical values of metagenomic next-generation sequencing in patients with severe pneumonia: a systematic review and meta-analysis. *Front Cell Infect Microbiol, 13*, 1106859. doi:10.3389/fcimb.2023.1106859

Lyfjastofnun Icelandic Medicines Agency. (2021). Hjartamagnýl (Drug information). Retrieved from https://www.serlyfjaskra.is/FileRepos/d65a6a44-7838-eb11-80fe-00155d15460a/Hjartamagnyl_SmPC.pdf. from Lyfjastofnun Icelandic Medicines Agency, https://www.serlyfjaskra.is/FileRepos/d65a6a44-7838-eb11-80fe-00155d15460a/Hjartamagnyl_SmPC.pdf

Ma, H. M., Tang, W. H., & Woo, J. (2011). Predictors of in-hospital mortality of older patients admitted for community-acquired pneumonia. *Age Ageing, 40*(6), 736-741. doi:10.1093/ageing/afr087

Maas, M. B., Kim, M., Malkani, R. G., Abbott, S. M., & Zee, P. C. (2020). Obstructive Sleep Apnea and Risk of COVID-19 Infection, Hospitalization and Respiratory Failure. *Sleep Breath*. doi:10.1007/s11325-020-02203-0

Macfarlane, J. T., Miller, A. C., Roderick Smith, W. H., Morris, A. H., & Rose, D. H. (1984). Comparative radiographic features of community acquired Legionnaires' disease, pneumococcal pneumonia, mycoplasma pneumonia, and psittacosis. *Thorax, 39*(1), 28-33. doi:10.1136/thx.39.1.28

Mackenzie, G. (2016). The definition and classification of pneumonia. *Pneumonia, 8*(1), 14. doi:10.1186/s41479-016-0012-z

Mandell, L. A., Wunderink, R. G., Anzueto, A., Bartlett, J. G., Campbell, G. D., Dean, N. C., Dowell, S. F., File, T. M., Jr.,

Musher, D. M., Niederman, M. S., Torres, A., Whitney, C. G., Infectious Diseases Society of, A., & American Thoracic, S. (2007). Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 44 Suppl 2*, S27-72. doi:10.1086/511159

Marrie, T. J. (1996). Pneumonia in the elderly. *Current opinion in pulmonary medicine, 2*(3), 192-197. doi:10.1097/00063198-199605000-00006

Marrie, T. J. (2000). Community-acquired pneumonia in the elderly. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 31*(4), 1066-1078. doi:10.1086/318124

Marshall, D. C., Goodson, R. J., Xu, Y., Komorowski, M., Shalhoub, J., Maruthappu, M., & Salciccioli, J. D. (2018). Trends in mortality from pneumonia in the Europe union: a temporal analysis of the European detailed mortality database between 2001 and 2014. *Respiratory Research, 19*(1), 81. doi:10.1186/s12931-018-0781-4

Mashaqi, S., Lee-Iannotti, J., Rangan, P., Celaya, M. P., Gozal, D., Quan, S. F., & Parthasarathy, S. (2021). Obstructive sleep apnea and COVID-19 clinical outcomes during hospitalization: a cohort study. *Journal of Clinical Sleep Medicine, 17*(11), 2197-2204. doi:doi:10.5664/jcsm.9424

McCabe, C., Kirchner, C., Zhang, H., Daley, J., & Fisman, D. N. (2009). Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med, 169*(16), 1525-1531. doi:10.1001/archinternmed.2009.259

McSharry, D., & Malhotra, A. (2020). Potential influences of obstructive sleep apnea and obesity on COVID-19 severity. *J Clin Sleep Med, 16*(9), 1645. doi:10.5664/jcsm.8538

Meehan, T. P., Fine, M. J., Krumholz, H. M., Scinto, J. D., Galusha, D. H., Mockalis, J. T., Weber, G. F., Petrillo, M. K., Houck, P. M., & Fine, J. M. (1997). Quality of Care, Process, and Outcomes in Elderly Patients With Pneumonia. *JAMA, 278*(23), 2080-2084. doi:10.1001/jama.1997.03550230056037

Mercieca, L., Pullicino, R., Camilleri, K., Abela, R., Mangion, S. A., Cassar, J., Zammit, M., Gatt, C., Deguara, C., Barbara, C., Fsadni, P., & Montefort, S. (2017). Continuous Positive Airway Pressure: Is it a route for infection in those with Obstructive

Sleep Apnoea? *Sleep Sci*, *10*(1), 28-34. doi:10.5935/1984-0063.20170005

Metlay, J. P., Kapoor, W. N., & Fine, M. J. (1997a). Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA*, *278*(17), 1440-1445. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9356004

Metlay, J. P., Schulz, R., Li, Y. H., Singer, D. E., Marrie, T. J., Coley, C. M., Hough, L. J., Obrosky, D. S., Kapoor, W. N., & Fine, M. J. (1997b). Influence of age on symptoms at presentation in patients with community-acquired pneumonia. *Arch Intern Med*, *157*(13), 1453-1459. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9224224

Metlay, J. P., Waterer, G. W., Long, A. C., Anzueto, A., Brozek, J., Crothers, K., Cooley, L. A., Dean, N. C., Fine, M. J., Flanders, S. A., Griffin, M. R., Metersky, M. L., Musher, D. M., Restrepo, M. I., & Whitney, C. G. (2019). Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *American Journal of Respiratory and Critical Care Medicine*, *200*(7), e45-e67. doi:10.1164/rccm.201908-1581ST

Miao, Q., Ma, Y., Wang, Q., Pan, J., Zhang, Y., Jin, W., Yao, Y., Su, Y., Huang, Y., Wang, M., Li, B., Li, H., Zhou, C., Li, C., Ye, M., Xu, X., Li, Y., & Hu, B. (2018). Microbiological Diagnostic Performance of Metagenomic Next-generation Sequencing When Applied to Clinical Practice. *Clinical Infectious Diseases*, *67*(suppl_2), S231-S240. doi:10.1093/cid/ciy693

Mieno, M. N., Tanaka, N., Arai, T., Kawahara, T., Kuchiba, A., Ishikawa, S., & Sawabe, M. (2016). Accuracy of Death Certificates and Assessment of Factors for Misclassification of Underlying Cause of Death. *J Epidemiol*, *26*(4), 191-198. doi:10.2188/jea.JE20150010

Miyashita, N., Kawai, Y., Yamaguchi, T., Ouchi, K., Oka, M., & Atypical Pathogen Study, G. (2011). Clinical potential of diagnostic methods for the rapid diagnosis of Mycoplasma pneumoniae pneumonia in adults. *European Journal of Clinical Microbiology & Infectious Diseases*, *30*(3), 439-446. doi:10.1007/s10096-010-1107-8

Miyashita, N., Sugiu, T., Kawai, Y., Oda, K., Yamaguchi, T., Ouchi, K., Kobashi, Y., & Oka, M. (2009). Radiographic features of Mycoplasma pneumoniaepneumonia: differential diagnosis and

performance timing. *BMC Medical Imaging, 9*(1), 7. doi:10.1186/1471-2342-9-7

Moberley, S., Holden, J., Tatham, D. P., & Andrews, R. M. (2013). Vaccines for preventing pneumococcal infection in adults. *Cochrane Database of Systematic Reviews*(1). doi:10.1002/14651858.CD000422.pub3

Moore, C. E., Paul, J., Foster, D., Mahar, S. A., Griffiths, D., Knox, K., Peto, T. E., Walker, A. S., & Crook, D. W. (2014). Reduction of Invasive Pneumococcal Disease 3 Years After the Introduction of the 13-Valent Conjugate Vaccine in the Oxfordshire Region of England. *The Journal of Infectious Diseases, 210*(7), 1001-1011. doi:10.1093/infdis/jiu213

Morens, D. M., Taubenberger, J. K., & Fauci, A. S. (2008). Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness. *The Journal of Infectious Diseases, 198*(7), 962-970. doi:10.1086/591708

Morley, J. E., Malmstrom, T. K., & Miller, D. K. (2012). A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *Journal of Nutrition Health & Aging, 16*(7), 601-608. doi:10.1007/s12603-012-0084-2

Mortensen, E. M. (2011). Potential causes of increased long-term mortality after pneumonia. *European Respiratory Journal, 37*(6), 1306-1307. doi:10.1183/09031936.00194110

Murcia, J., Llorens, P., Sanchez-Paya, J., Reus, S., Boix, V., Merino, E., Laghzaoui, F., & Portilla, J. (2010). Functional status determined by Barthel Index predicts community acquired pneumonia mortality in general population. *The Journal of infection, 61*(6), 458-464. doi:10.1016/j.jinf.2010.08.006

Musher, D. M., Abers, M. S., & Bartlett, J. G. (2017). Evolving Understanding of the Causes of Pneumonia in Adults, With Special Attention to the Role of Pneumococcus. *Clinical Infectious Diseases, 65*(10), 1736-1744. doi:10.1093/cid/cix549

Musher, D. M., Abers, M. S., & Corrales-Medina, V. F. (2019). Acute Infection and Myocardial Infarction. *New England Journal of Medicine, 380*(2), 171-176. doi:10.1056/NEJMra1808137

Musher, D. M., Roig, I. L., Cazares, G., Stager, C. E., Logan, N., & Safar, H. (2013). Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: Results of a one-year study. *Journal of Infection, 67*(1), 11-18. doi:10.1016/j.jinf.2013.03.003

Musher, D. M., Sampath, R., & Rodriguez-Barradas, M. C. (2011). The Potential Role for Protein-Conjugate Pneumococcal Vaccine in Adults: What Is the Supporting Evidence? *Clinical Infectious Diseases, 52*(5), 633-640. doi:10.1093/cid/ciq207

Mutti, C., Azzi, N., Soglia, M., Pollara, I., Alessandrini, F., & Parrino, L. (2020). Obstructive sleep apnea, cpap and COVID-19: a brief review. *Acta Biomed, 91*(4), e2020196. doi:10.23750/abm.v91i4.10941. (Accession No. 33525235)

Naucler, P., Darenberg, J., Morfeldt, E., Örtqvist, Å., & Henriques Normark, B. (2013). Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia. *Thorax, 68*(6), 571. doi:10.1136/thoraxjnl-2012-203106

Neill, A. M., Martin, I. R., Weir, R., Anderson, R., Chereshsky, A., Epton, M. J., Jackson, R., Schousboe, M., Frampton, C., Hutton, S., Chambers, S. T., & Town, G. I. (1996). Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. *Thorax, 51*(10), 1010-1016. doi:10.1136/thx.51.10.1010

Nguyen, M. T. N., Saito, N., & Wagatsuma, Y. (2019). The effect of comorbidities for the prognosis of community-acquired pneumonia: an epidemiologic study using a hospital surveillance in Japan. *BMC Research Notes, 12*(1), 817. doi:10.1186/s13104-019-4848-1

NICE. (2019). Pneumonia (community-acquired): antimicrobial prescribing. Retrieved from https://www.nice.org.uk/guidance/ng138

Nielsen, A. G., Nielsen, R. B., Riis, A. H., Johnsen, S. P., Sørensen, H. T., & Thomsen, R. W. (2012). The impact of statin use on pneumonia risk and outcome: a combined population-based case-control and cohort study. *Critical Care, 16*(4), R122. doi:10.1186/cc11418

Novack, V., Avnon, L. S., Smolyakov, A., Barnea, R., Jotkowitz, A., & Schlaeffer, F. (2006). Disagreement in the interpretation of chest radiographs among specialists and clinical outcomes of patients hospitalized with suspected pneumonia. *European Journal of Internal Medicine, 17*(1), 43-47. doi:https://doi.org/10.1016/j.ejim.2005.07.008

Ohland, J., Warren-Gash, C., Blackburn, R., Mølbak, K., Valentiner-Branth, P., Nielsen, J., & Emborg, H.-D. (2020). Acute myocardial infarctions and stroke triggered by laboratory-confirmed respiratory infections in Denmark, 2010 to 2016.

*Eurosurveillance*, *25*(17), 1900199. doi:doi:https://doi.org/10.2807/1560-7917.ES.2020.25.17.1900199

Okazaki, T., Ebihara, S., Mori, T., Izumi, S., & Ebihara, T. (2020). Association between sarcopenia and pneumonia in older people. *Geriatrics & Gerontology International, 20*(1), 7-13. doi:https://doi.org/10.1111/ggi.13839

Okazaki, T., Suzukamo, Y., Miyatake, M., Komatsu, R., Yaekashiwa, M., Nihei, M., Izumi, S., & Ebihara, T. (2021). Respiratory Muscle Weakness as a Risk Factor for Pneumonia in Older People. *Gerontology, 67*(5), 581-590. doi:10.1159/000514007

Olofsson, S., Brittain-Long, R., Andersson, L. M., Westin, J., & Lindh, M. (2011). PCR for detection of respiratory viruses: seasonal variations of virus infections. *Expert Rev Anti Infect Ther, 9*(8), 615-626. doi:10.1586/eri.11.75

Organization, W. H. (2020). *Medical certification, ICD mortality coding, and reporting mortality associated with COVID-19: technical note, 7 June 2020*. Retrieved from

Osthoff, M., Sidler, J. A., Lakatos, B., Frei, R., Dangel, M., Weisser, M., Battegay, M., & Widmer, A. F. (2016). Low-Dose Acetylsalicylic Acid Treatment and Impact on Short-Term Mortality in Staphylococcus aureus Bloodstream Infection: A Propensity Score–Matched Cohort Study. *Critical Care Medicine, 44*(4). Retrieved from https://journals.lww.com/ccmjournal/Fulltext/2016/04000/Low_Dose_Acetylsalicylic_Acid_Treatment_and_Impact.15.aspx

Oz, F., Gul, S., Kaya, M. G., Yazici, M., Bulut, I., Elitok, A., Ersin, G., Abakay, O., Akkoyun, C. D., Oncul, A., Cetinkaya, E., Gibson, M. C., & Oflaz, H. (2013). Does aspirin use prevent acute coronary syndrome in patients with pneumonia: multicenter prospective randomized trial. *Coronary Artery Disease, 24*(3), 231-237. doi:10.1097/MCA.0b013e32835d7610

Palmu, A. A., Saukkoriipi, A., Snellman, M., Jokinen, J., Torkko, P., Ziegler, T., Kaijalainen, T., Hausdorff, W. P., Verlant, V., & Kilpi, T. M. (2014). Incidence and etiology of community-acquired pneumonia in the elderly in a prospective population-based study. *Scand J Infect Dis, 46*(4), 250-259. doi:10.3109/00365548.2013.876509

Park, J. E., Kim, Y., Lee, S. W., Shim, S. S., Lee, J. K., & Lee, J. H. (2016). The usefulness of low-dose CT scan in elderly patients with suspected acute lower respiratory infection in the

emergency room. *The British Journal of Radiology*, *89*(1060), 20150654. doi:10.1259/bjr.20150654

Pazarlı, A. C., Ekiz, T., & İlik, F. (2020). Coronavirus disease 2019 and obstructive sleep apnea syndrome. *Sleep and Breathing*. doi:10.1007/s11325-020-02087-0

Peduzzi, P., Concato, J., Kemper, E., Holford, T. R., & Feinstein, A. R. (1996). A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology*, *49*(12), 1373-1379. doi:https://doi.org/10.1016/S0895-4356(96)00236-3

Peltan, I. D., Brown, S. M., Bledsoe, J. R., Sorensen, J., Samore, M. H., Allen, T. L., & Hough, C. L. (2019). ED Door-to-Antibiotic Time and Long-term Mortality in Sepsis. *Chest*, *155*(5), 938-946. doi:https://doi.org/10.1016/j.chest.2019.02.008

Pérez-Trallero, E., Marimon, J. M., Ercibengoa, M., Vicente, D., & Pérez-Yarza, E. G. (2009). Invasive Streptococcus pneumoniae infections in children and older adults in the north of Spain before and after the introduction of the heptavalent pneumococcal conjugate vaccine. *European Journal of Clinical Microbiology & Infectious Diseases*, *28*(7), 731-738. doi:10.1007/s10096-008-0693-1

Petersen, M. L., Porter, K. E., Gruber, S., Wang, Y., & van der Laan, M. J. (2012). Diagnosing and responding to violations in the positivity assumption. *Statistical Methods in Medical Research, 21*(1), 31-54. doi:10.1177/0962280210386207

Petrilli, C. M., Jones, S. A., Yang, J., Rajagopalan, H., O'Donnell, L., Chernyak, Y., Tobin, K. A., Cerfolio, R. J., Francois, F., & Horwitz, L. I. (2020). Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ, 369*, m1966. doi:10.1136/bmj.m1966

Pieralli, F., Vannucchi, V., De Marzi, G., Mancini, A., Bacci, F., Para, O., Nozzoli, C., & Falcone, M. (2018). Performance status and in-hospital mortality of elderly patients with community acquired pneumonia. *Internal and Emergency Medicine, 13*(4), 501-507. doi:10.1007/s11739-018-1822-1

Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A. K., Walley, T. J., Farrar, K., Park, B. K., & Breckenridge, A. M. (2004). Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ, 329*(7456), 15-19. doi:10.1136/bmj.329.7456.15

Pirozzi, C. S., Jones, B. E., VanDerslice, J. A., Zhang, Y., Paine, R., 3rd, & Dean, N. C. (2017). Short-Term Air Pollution and Incident Pneumonia: A Case-Crossover Study. *Ann Am Thorac Soc*. doi:10.1513/AnnalsATS.201706-495OC

Pirracchio, R., Carone, M., Rigon, M. R., Caruana, E., Mebazaa, A., & Chevret, S. (2016). Propensity score estimators for the average treatment effect and the average treatment effect on the treated may yield very different estimates. *Statistical Methods in Medical Research, 25*(5), 1938-1954. doi:10.1177/0962280213507034

Pishgar, F., Greifer, N., Leyrat, C., & Stuart, E. (2021). MatchThem:: Matching and Weighting after Multiple Imputation. *The R Journal, 13/2*. doi:10.32614/RJ-2021-073

Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., Pérez Marc, G., Moreira, E. D., Zerbini, C., Bailey, R., Swanson, K. A., Roychoudhury, S., Koury, K., Li, P., Kalina, W. V., Cooper, D., Frenck, R. W., Hammitt, L. L., . . . Gruber, W. C. (2020). Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine, 383*(27), 2603-2615. doi:10.1056/NEJMoa2034577

Postma, D. F., van Werkhoven, C. H., van Elden, L. J., Thijsen, S. F., Hoepelman, A. I., Kluytmans, J. A., Boersma, W. G., Compaijen, C. J., van der Wall, E., Prins, J. M., Oosterheert, J. J., Bonten, M. J., & Group, C.-S. S. (2015). Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med, 372*(14), 1312-1323. doi:10.1056/NEJMoa1406330

Prendki, V., Scheffler, M., Huttner, B., Garin, N., Herrmann, F., Janssens, J. P., Marti, C., Carballo, S., Roux, X., Serratrice, C., Serratrice, J., Agoritsas, T., Becker, C. D., Kaiser, L., Rosset-Zufferey, S., Soulier, V., Perrier, A., Reny, J. L., Montet, X., . . . Stirnemann, J. (2018). Low-dose computed tomography for the diagnosis of pneumonia in elderly patients: a prospective, interventional cohort study. *Eur Respir J, 51*(5). doi:10.1183/13993003.02375-2017

Quan, T. P., Fawcett, N. J., Wrightson, J. M., Finney, J., Wyllie, D., Jeffery, K., Jones, N., Shine, B., Clarke, L., Crook, D., Walker, A. S., & Peto, T. E. A. (2016). Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998–2014. *Thorax, 71*(6), 535-542. doi:10.1136/thoraxjnl-2015-207688

Quinton, L. J., Walkey, A. J., & Mizgerd, J. P. (2018). Integrative Physiology of Pneumonia. *Physiological Reviews, 98*(3), 1417-1464. doi:10.1152/physrev.00032.2017

QURESHI, K. N., & HODKINSON, H. M. (1974). EVALUATION OF A TEN-QUESTION MENTAL TEST IN THE INSTITUTIONALIZED ELDERLY. *Age and Ageing, 3*(3), 152-157. doi:10.1093/ageing/3.3.152

Rae, N., Finch, S., & Chalmers, J. D. (2016). Cardiovascular disease as a complication of community-acquired pneumonia. *Current opinion in pulmonary medicine, 22*(3), 212-218. doi:10.1097/mcp.0000000000000261

Ramirez, J. A., Wiemken, T. L., Peyrani, P., Arnold, F. W., Kelley, R., Mattingly, W. A., Nakamatsu, R., Pena, S., Guinn, B. E., Furmanek, S. P., Persaud, A. K., Raghuram, A., Fernandez, F., Beavin, L., Bosson, R., Fernandez-Botran, R., Cavallazzi, R., Bordon, J., Valdivieso, C., . . . Group, f. t. U. o. L. P. S. (2017). Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. *Clinical Infectious Diseases, 65*(11), 1806-1812. doi:10.1093/cid/cix647

RECOVERY Collaborative Group. (2022). Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet, 399*(10320), 143-151. doi:https://doi.org/10.1016/S0140-6736(21)01825-0

Restrepo, M. I., Faverio, P., & Anzueto, A. (2013). Long-term prognosis in community-acquired pneumonia. *Current opinion in infectious diseases, 26*(2), 151-158. doi:10.1097/QCO.0b013e32835ebc6d

Restrepo, M. I., Mortensen, E. M., Rello, J., Brody, J., & Anzueto, A. (2010). Late Admission to the ICU in Patients With Community-Acquired Pneumonia Is Associated With Higher Mortality. *Chest, 137*(3), 552-557. doi:https://doi.org/10.1378/chest.09-1547

Restrepo, M. I., & Reyes, L. F. (2018). Pneumonia as a cardiovascular disease. *Respirology, 23*(3), 250-259. doi:10.1111/resp.13233

Rhedin, S., Lindstrand, A., Rotzen-Ostlund, M., Tolfvenstam, T., Ohrmalm, L., Rinder, M. R., Zweygberg-Wirgart, B., Ortqvist, A., Henriques-Normark, B., Broliden, K., & Naucler, P. (2014). Clinical utility of PCR for common viruses in acute respiratory illness. *Pediatrics, 133*(3), e538-545. doi:10.1542/peds.2013-3042

Rivero-Calle, I., Pardo-Seco, J., Aldaz, P., Vargas, D. A., Mascaros, E., Redondo, E., Diaz-Maroto, J. L., Linares-Rufo, M., Fierro-Alacio, M. J., Gil, A., Molina, J., Ocana, D., Martinon-Torres, F., & Grp, N. (2017). Incidence and risk factor prevalence of community-acquired pneumonia in adults in primary care in

Spain (NEUMO-ES-RISK project) (vol 16, 645, 2016). *BMC Infectious Diseases, 17*. doi:ARTN 64 10.1186/s12879-016-2134-6

Rodenburg, G. D., de Greeff, S. C., Jansen, A. G., de Melker, H. E., Schouls, L. M., Hak, E., Spanjaard, L., Sanders, E. A., & van der Ende, A. (2010). Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. *Emerg Infect Dis, 16*(5), 816-823. doi:10.3201/eid1605.091223

Rögnvaldsson, K. G., Bjarnason, A., Kristinsson, K., Bragason, H. T., Erlendsdóttir, H., Þorgeirsson, G., & Gottfreðsson, M. (2022). Acetylsalicylic acid use is associated with improved survival in bacteremic pneumococcal pneumonia: A long-term nationwide study. *Journal of Internal Medicine, 292*(2), 321-332. doi:https://doi.org/10.1111/joim.13485

Rögnvaldsson, K. G., Bjarnason, A., Ólafsdóttir, I. S., Helgason, K. O., Guðmundsson, A., & Gottfreðsson, M. (2023). Adults with symptoms of pneumonia: a prospective comparison of patients with and without infiltrates on chest radiography. *Clinical Microbiology and Infection, 29*(1), 108.e101-108.e106. doi:https://doi.org/10.1016/j.cmi.2022.07.013

Rögnvaldsson, K. G., Eyþórsson, E. S., Emilsson, Ö. I., Eysteinsdóttir, B., Pálsson, R., Gottfreðsson, M., Guðmundsson, G., & Steingrímsson, V. (2021). Obstructive sleep apnea is an independent risk factor for severe COVID-19: a population-based study. *Sleep, 45*(3). doi:10.1093/sleep/zsab272

Rothberg, M. B. (2022). Community-Acquired Pneumonia. *Annals of Internal Medicine, 175*(4), ITC49-ITC64. doi:10.7326/aitc202204190 %m 35404672

Ruhnke, G. W., Coca-Perraillon, M., Kitch, B. T., & Cutler, D. M. (2010). Trends in mortality and medical spending in patients hospitalized for community-acquired pneumonia: 1993-2005. *Medical care, 48*(12), 1111-1116. doi:10.1097/MLR.0b013e3181f38006

Ruhnke, G. W., Coca-Perraillon, M., Kitch, B. T., & Cutler, D. M. (2011). Marked Reduction in 30-Day Mortality Among Elderly Patients with Community-acquired Pneumonia. *The American Journal of Medicine, 124*(2), 171-178.e171. doi:https://doi.org/10.1016/j.amjmed.2010.08.019

Ruppe, E., Cherkaoui, A., Lazarevic, V., Emonet, S., & Schrenzel, J. (2017). Establishing Genotype-to-Phenotype Relationships in Bacteria Causing Hospital-Acquired Pneumonia: A Prelude to

the Application of Clinical Metagenomics. *Antibiotics-Basel, 6*(4). doi:ARTN 30 10.3390/antibiotics6040030

Sánchez-de-la-Torre, M., Campos-Rodriguez, F., & Barbé, F. (2013). Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med, 1*(1), 61-72. doi:10.1016/s2213-2600(12)70051-6

Sanz, F., Morales-Suárez-Varela, M., Fernández, E., Force, L., Pérez-Lozano, M. J., Martín, V., Egurrola, M., Castilla, J., Astray, J., Toledo, D., Domínguez, Á., & Project, P. I. W. G. (2018). A Composite of Functional Status and Pneumonia Severity Index Improves the Prediction of Pneumonia Mortality in Older Patients. *Journal of General Internal Medicine, 33*(4), 437-444. doi:10.1007/s11606-017-4267-8

Sapey, E., Patel, J. M., Greenwood, H., Walton, G. M., Grudzinska, F., Parekh, D., Mahida, R. Y., Dancer, R. C. A., Lugg, S. T., Howells, P. A., Hazeldine, J., Newby, P., Scott, A., Nightingale, P., Hill, A. T., & Thickett, D. R. (2019). Simvastatin Improves Neutrophil Function and Clinical Outcomes in Pneumonia. A Pilot Randomized Controlled Clinical Trial. *American Journal of Respiratory and Critical Care Medicine, 200*(10), 1282-1293. doi:10.1164/rccm.201812-2328OC

Sapey, E., Patel, J. M., Greenwood, H. L., Walton, G. M., Hazeldine, J., Sadhra, C., Parekh, D., Dancer, R. C. A., Nightingale, P., Lord, J. M., & Thickett, D. R. (2017). Pulmonary Infections in the Elderly Lead to Impaired Neutrophil Targeting, Which Is Improved by Simvastatin. *Am J Respir Crit Care Med, 196*(10), 1325-1336. doi:10.1164/rccm.201704-0814OC

Sateia, M. J. (2014). International classification of sleep disorders-third edition: highlights and modifications. *Chest, 146*(5), 1387-1394. doi:10.1378/chest.14-0970

Sattar, S. B. A., & Sharma, S. (2021). *Bacterial Pneumonia*: StatPearls Publishing, Treasure Island (FL).

Satzke, C., Turner, P., Virolainen-Julkunen, A., Adrian, P. V., Antonio, M., Hare, K. M., Henao-Restrepo, A. M., Leach, A. J., Klugman, K. P., Porter, B. D., Sa-Leao, R., Scott, J. A., Nohynek, H., O'Brien, K. L., & Group, W. H. O. P. C. W. (2013). Standard method for detecting upper respiratory carriage of Streptococcus pneumoniae: updated recommendations from the World Health Organization Pneumococcal Carriage Working Group. *Vaccine, 32*(1), 165-179. doi:10.1016/j.vaccine.2013.08.062

Saukkoriipi, A., Palmu, A. A., Pascal, T., Verlant, V., Hausdorff, W. P., & Jokinen, J. (2017). LytA quantitative PCR on sputum and nasopharyngeal swab samples in the detection of pneumococcal

pneumonia among the elderly. *J Clin Microbiol*. doi:10.1128/jcm.01231-17

Sävje, F., Aronow, P., & Hudgens, M. (2021). AVERAGE TREATMENT EFFECTS IN THE PRESENCE OF UNKNOWN INTERFERENCE. *Ann Stat, 49*(2), 673-701. doi:10.1214/20-aos1973

Schlaberg, R., Queen, K., Simmon, K., Tardif, K., Stockmann, C., Flygare, S., Kennedy, B., Voelkerding, K., Bramley, A., Zhang, J., Eilbeck, K., Yandell, M., Jain, S., Pavia, A. T., Tong, S. X., & Ampofo, K. (2017). Viral Pathogen Detection by Metagenomics and Pan-Viral Group Polymerase Chain Reaction in Children With Pneumonia Lacking Identifiable Etiology. *Journal of Infectious Diseases, 215*(9), 1407-1415. doi:10.1093/infdis/jix148

Self, W. H., Courtney, D. M., McNaughton, C. D., Wunderink, R. G., & Kline, J. A. (2013). High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. *The American Journal of Emergency Medicine, 31*(2), 401-405. doi:10.1016/j.ajem.2012.08.041

Self, W. H., Williams, D. J., Zhu, Y., Ampofo, K., Pavia, A. T., Chappell, J. D., Hymas, W. C., Stockmann, C., Bramley, A. M., Schneider, E., Erdman, D., Finelli, L., Jain, S., Edwards, K. M., & Grijalva, C. G. (2015). Respiratory Viral Detection in Children and Adults: Comparing Asymptomatic Controls and Patients With Community-Acquired Pneumonia. *The Journal of Infectious Diseases, 213*(4), 584-591. doi:10.1093/infdis/jiv323

Seo, H., Cha, S. I., Shin, K. M., Lim, J. K., Yoo, S. S., Lee, S. Y., Lee, J., Kim, C. H., & Park, J. Y. (2019). Community-Acquired Pneumonia with Negative Chest Radiography Findings: Clinical and Radiological Features. *Respiration, 97*(6), 508-517. doi:10.1159/000495068

Shahar, E., Whitney, C. W., Redline, S., Lee, E. T., Newman, A. B., Nieto, F. J., O'Connor, G. T., Boland, L. L., Schwartz, J. E., & Samet, J. M. (2001). Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med, 163*(1), 19-25. doi:10.1164/ajrccm.163.1.2001008

Shenoy, A. T., Beno, S. M., Brissac, T., Bell, J. W., Novak, L., & Orihuela, C. J. (2018). Severity and properties of cardiac damage caused by Streptococcus pneumoniae are strain dependent. *PLOS ONE, 13*(9), e0204032. doi:10.1371/journal.pone.0204032

Shi, T., Denouel, A., Tietjen, A. K., Lee, J. W., Falsey, A. R., Demont, C., Nyawanda, B. O., Cai, B., Fuentes, R., Stoszek, S. K., Openshaw, P., Campbell, H., Nair, H., & Investigators, R. (2019). Global and Regional Burden of Hospital Admissions for Pneumonia in Older Adults: A Systematic Review and Meta-Analysis. *The Journal of Infectious Diseases, 222*(Supplement_7), S570-S576. doi:10.1093/infdis/jiz053

Shoar, S., & Musher, D. M. (2020). Etiology of community-acquired pneumonia in adults: a systematic review. *Pneumonia, 12*(1), 11. doi:10.1186/s41479-020-00074-3

Shrank, W. H., Patrick, A. R., & Brookhart, M. A. (2011). Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med, 26*(5), 546-550. doi:10.1007/s11606-010-1609-1

Shur, N. F., Creedon, L., Skirrow, S., Atherton, P. J., MacDonald, I. A., Lund, J., & Greenhaff, P. L. (2021). Age-related changes in muscle architecture and metabolism in humans: The likely contribution of physical inactivity to age-related functional decline. *Ageing Research Reviews, 68*, 101344. doi:https://doi.org/10.1016/j.arr.2021.101344

Sigurdardóttir, B., Már Björnsson, Ó., Jónsdóttir, K. E., Erlendsdóttir, H., & Gudmundsson, S. (1997). Acute Bacterial Meningitis in Adults: A 20-Year Overview. *Archives of Internal Medicine, 157*(4), 425-430. doi:10.1001/archinte.1997.00440250077009

Silaba, M., Ooko, M., Bottomley, C., Sande, J., Benamore, R., Park, K., Ignas, J., Maitland, K., Mturi, N., Makumi, A., Otiende, M., Kagwanja, S., Safari, S., Ochola, V., Bwanaali, T., Bauni, E., Gleeson, F., Deloria Knoll, M., Adetifa, I., . . . Scott, J. A. G. (2019). Effect of 10-valent pneumococcal conjugate vaccine on the incidence of radiologically-confirmed pneumonia and clinically-defined pneumonia in Kenyan children: an interrupted time-series analysis. *The Lancet Global Health, 7*(3), e337-e346. doi:https://doi.org/10.1016/S2214-109X(18)30491-1

Simonetti, A. F., Garcia-Vidal, C., Viasus, D., García-Somoza, D., Dorca, J., Gudiol, F., & Carratalà, J. (2016). Declining mortality among hospitalized patients with community-acquired pneumonia. *Clinical Microbiology and Infection, 22*(6), 567.e561-567.e567. doi:https://doi.org/10.1016/j.cmi.2016.03.015

Skull, S. A., Andrews, R. M., Byrnes, G. B., Campbell, D. A., Nolan, T. M., Brown, G. V., & Kelly, H. A. (2008). ICD-10 codes are a valid tool for identification of pneumonia in hospitalized patients

aged ⩾65 years. *Epidemiology and Infection, 136*(2), 232-240. doi:10.1017/S0950268807008564

Smeeth, L., Thomas, S. L., Hall, A. J., Hubbard, R., Farrington, P., & Vallance, P. (2004). Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med, 351*(25), 2611-2618. doi:10.1056/NEJMoa041747

Snaebjarnardóttir, K., Erlendsdóttir, H., Reynisson, I. K., Kristinsson, K., Halldórsdóttir, S., Hardardóttir, H., Gudnason, T., Gottfredsson, M., & Haraldsson, Á. (2013). Bacterial meningitis in children in Iceland, 1975–2010: A nationwide epidemiological study. *Scandinavian Journal of Infectious Diseases, 45*(11), 819-824. doi:10.3109/00365548.2013.817680

Søgaard, M., Nielsen, R. B., Schønheyder, H. C., Nørgaard, M., & Thomsen, R. W. (2014). Nationwide trends in pneumonia hospitalization rates and mortality, Denmark 1997–2011. *Respiratory Medicine, 108*(8), 1214-1222. doi:https://doi.org/10.1016/j.rmed.2014.05.004

Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Iosifidis, C., & Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery, 76*, 71-76. doi:https://doi.org/10.1016/j.ijsu.2020.02.034

Song, J.-H., Huh, K., & Chung, D. R. (2016). Community-Acquired Pneumonia in the Asia-Pacific Region. *Semin Respir Crit Care Med, 37*(06), 839-854.

Song, J.-H., Thamlikitkul, V., & Hsueh, P.-R. (2011). Clinical and economic burden of community-acquired pneumonia amongst adults in the Asia-Pacific region. *International Journal of Antimicrobial Agents, 38*(2), 108-117. doi:https://doi.org/10.1016/j.ijantimicag.2011.02.017

Song, S., Moon, S. W., Kim, S. Y., Ko, M. S., & Kim, J. E. (2018). The prognostic value of the Charlson's comorbidity index in patients with bacteremic pneumonia. *European Respiratory Journal, 52*(suppl 62), PA2037. doi:10.1183/13993003.congress-2018.PA2037

Spaude, K. A., Abrutyn, E., Kirchner, C., Kim, A., Daley, J., & Fisman, D. N. (2007). Influenza Vaccination and Risk of Mortality Among Adults Hospitalized With Community-Acquired Pneumonia. *Archives of Internal Medicine, 167*(1), 53-59. doi:10.1001/archinte.167.1.53

Stelianides, S., Golmard, J. L., Carbon, C., & Fantin, B. (1999). Influence of Socioeconomic Status on Features and Outcome of

Community-Acquired Pneumonia. *European Journal of Clinical Microbiology and Infectious Diseases, 18*(10), 704-708. doi:10.1007/s100960050382

Strausz, S., Kiiskinen, T., Broberg, M., Ruotsalainen, S., Koskela, J., Bachour, A., Palotie, A., Palotie, T., Ripatti, S., & Ollila, H. M. (2021). Sleep apnoea is a risk factor for severe COVID-19. *BMJ Open Respir Res, 8*(1), e000845. doi:10.1136/bmjresp-2020-000845

Su, V. Y., Liu, C. J., Wang, H. K., Wu, L. A., Chang, S. C., Perng, D. W., Su, W. J., Chen, Y. M., Lin, E. Y., Chen, T. J., & Chou, K. T. (2014). Sleep apnea and risk of pneumonia: a nationwide population-based study. *Cmaj, 186*(6), 415-421. doi:10.1503/cmaj.131547

Sun, Y., Li, H., Pei, Z., Wang, S., Feng, J., Xu, L., Gao, P., Cao, B., & Zhan, S. (2020). Incidence of community-acquired pneumonia in urban China: A national population-based study. *Vaccine, 38*(52), 8362-8370. doi:https://doi.org/10.1016/j.vaccine.2020.11.004

Sundell, N., Andersson, L.-M., Brittain-Long, R., Sundvall, P.-D., Alsiö, Å., Lindh, M., Gustavsson, L., Westin, J., & Tang, Y.-W. (2019). PCR Detection of Respiratory Pathogens in Asymptomatic and Symptomatic Adults. *Journal of Clinical Microbiology, 57*(1), e00716-00718. doi:doi:10.1128/JCM.00716-18

Surme, S., Balkan, II, Bayramlar, O. F., Kara Ali, R., Mete, B., Tabak, F., & Saltoğlu, N. (2021). Predictors of Long-term Outcomes in the Older Adults with Community-Acquired Pneumonia. *J Infect Dev Ctries, 15*(12), 1910-1916. doi:10.3855/jidc.14881

Szakmany, T., Hollinghurst, J., Pugh, R., Akbari, A., Griffiths, R., Bailey, R., & Lyons, R. A. (2021). Frailty assessed by administrative tools and mortality in patients with pneumonia admitted to the hospital and ICU in Wales. *Scientific Reports, 11*(1), 13407. doi:10.1038/s41598-021-92874-w

Takada, T., Yamamoto, Y., Terada, K., Ohta, M., Mikami, W., Yokota, H., Hayashi, M., Miyashita, J., Azuma, T., Fukuma, S., & Fukuhara, S. (2017). Diagnostic utility of appetite loss in addition to existing prediction models for community-acquired pneumonia in the elderly: a prospective diagnostic study in acute care hospitals in Japan. *BMJ Open, 7*(11), e019155. doi:10.1136/bmjopen-2017-019155

Tatarelli, P., Magnasco, L., Borghesi, M. L., Russo, C., Marra, A., Mirabella, M., Sarteschi, G., Ungaro, R., Arcuri, C., Murialdo,

G., Viscoli, C., Del Bono, V., & Nicolini, L. A. (2020). Prevalence and clinical impact of VIral Respiratory tract infections in patients hospitalized for Community-Acquired Pneumonia: the VIRCAP study. *Internal and Emergency Medicine, 15*(4), 645-654. doi:10.1007/s11739-019-02243-9

Tavares, D. A., Handem, S., Carvalho, R. J., Paulo, A. C., de Lencastre, H., Hinds, J., & Sa-Leao, R. (2019). Identification of Streptococcus pneumoniae by a real-time PCR assay targeting SP2020. *Sci Rep, 9*(1), 3285. doi:10.1038/s41598-019-39791-1

Tavares, L. P., Galvão, I., & Ferrero, M. R. (2021). Novel Immunomodulatory Therapies for Respiratory Pathologies. *Reference Module in Biomedical Sciences*, B978-970-912-820472-820476.800073-820476. doi:10.1016/b978-0-12-820472-6.00073-6

Team, R. (2021a). RStudio: Integrated Development for R.: RStudio, PBC, Boston, MA, URL: http://www.rstudio.com/. Retrieved from http://www.rstudio.com/.

Team, R. C. (2021b). R: A language and environment for statistical computing.: R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/. Retrieved from https://www.R-project.org/.

Theilacker, C., Fletcher, M. A., Jodar, L., & Gessner, B. D. (2022). PCV13 Vaccination of Adults against Pneumococcal Disease: What We Have Learned from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA). *Microorganisms, 10*(1), 127. Retrieved from https://www.mdpi.com/2076-2607/10/1/127

Therneau, T. M., & Lumley, T. (2015). Package 'survival'. *R Top Doc*, *128*(10), 28-33.

Thor Aspelund (2021). [Discussion on ATE and ATT].

Þórðardóttir, Á., Erlendsdóttir, H., Sigurðardóttir, B., Harðardóttir, H., Reynisson, I. K., Gottfreðsson, M., & Guðmundsson, S. (2014). Bacterial meningitis in adults in Iceland, 1995–2010. *Scandinavian Journal of Infectious Diseases, 46*(5), 354-360. doi:10.3109/00365548.2014.880184

Tian, F., Yang, R., & Chen, Z. (2022). Safety and efficacy of COVID-19 vaccines in children and adolescents: A systematic review of randomized controlled trials. *Journal of Medical Virology*, *94*(10), 4644-4653. doi:https://doi.org/10.1002/jmv.27940

Ticinesi, A., Lauretani, F., Nouvenne, A., Mori, G., Chiussi, G., Maggio, M., & Meschi, T. (2016). Lung ultrasound and chest x-

ray for detecting pneumonia in an acute geriatric ward. *Medicine, 95*(27), e4153-e4153. doi:10.1097/md.0000000000004153

Tin Tin Htar, M., Stuurman, A. L., Ferreira, G., Alicino, C., Bollaerts, K., Paganino, C., Reinert, R. R., Schmitt, H.-J., Trucchi, C., Vestraeten, T., & Ansaldi, F. (2017). Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. *PLOS ONE, 12*(5), e0177985. doi:10.1371/journal.pone.0177985

Tokgoz Akyil, F., Yalcinsoy, M., Hazar, A., Cilli, A., Celenk, B., Kilic, O., Sayiner, A., Kokturk, N., Sakar Coskun, A., Filiz, A., & Cakir Edis, E. (2018). Prognosis of hospitalized patients with community-acquired pneumonia. *Pulmonology, 24*(3), 164-169. doi:https://doi.org/10.1016/j.rppnen.2017.07.010

Torres, A., Blasi, F., Dartois, N., & Akova, M. (2015). Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax, 70*(10), 984. doi:10.1136/thoraxjnl-2015-206780

Torres, A., Peetermans, W. E., Viegi, G., & Blasi, F. (2013a). Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax, 68*(11), 1057-1065. doi:10.1136/thoraxjnl-2013-204282

Torres, A., Peetermans, W. E., Viegi, G., & Blasi, F. (2013b). Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax, 68*(11), 1057. doi:10.1136/thoraxjnl-2013-204282

Torres, A., & Rello, J. (2010). Update in Community-acquired and Nosocomial Pneumonia 2009. *American Journal of Respiratory and Critical Care Medicine, 181*(8), 782-787. doi:10.1164/rccm.201001-0030UP

Townsend, L., Dowds, J., O'Brien, K., Sheill, G., Dyer, A. H., O'Kelly, B., Hynes, J. P., Mooney, A., Dunne, J., Cheallaigh, C. N., O'Farrelly, C., Bourke, N. M., Conlon, N., Martin-Loeches, I., Bergin, C., Nadarajan, P., & Bannan, C. (2021). Persistent Poor Health after COVID-19 Is Not Associated with Respiratory Complications or Initial Disease Severity. *Annals of the American Thoracic Society, 18*(6), 997-1003. doi:10.1513/AnnalsATS.202009-1175OC

Troeger, C., Blacker, B. F., Khalil, I. A., Rao, P. C., Cao, S. J., Zimsen, S. R. M., Albertson, S., Stanaway, J. D., Deshpande, A., Farag, T., Forouzanfar, M. H., Abebe, Z., Adetifa, I. M. O., Adhikari, T. B., Akibu, M., Al Lami, F. H., Al-Eyadhy, A., Alvis-Guzman, N., Amare, A. T., . . . Infecti, G. L. R. (2018). Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infectious Diseases, 18*(11), 1191-1210. doi:10.1016/s1473-3099(18)30310-4

Trotter, C. L., Stuart, J. M., George, R., & Miller, E. (2008). Increasing hospital admissions for pneumonia, England. *Emerging Infectious Diseases, 14*(5), 727.

Trzcinski, K., Bogaert, D., Wyllie, A., Chu, M. L., van der Ende, A., Bruin, J. P., van den Dobbelsteen, G., Veenhoven, R. H., & Sanders, E. A. (2013). Superiority of trans-oral over trans-nasal sampling in detecting Streptococcus pneumoniae colonization in adults. *PLOS ONE, 8*(3), e60520. doi:10.1371/journal.pone.0060520

Tsaban, G., & Ben-Shimol, S. (2017). Indirect (herd) protection, following pneumococcal conjugated vaccines introduction: A systematic review of the literature. *Vaccine, 35*(22), 2882-2891. doi:https://doi.org/10.1016/j.vaccine.2017.04.032

Tschernig, T. (2016). Hospital-acquired pneumonia and community-acquired pneumonia: two guys? *Annals of translational medicine*, 22. Retrieved from https://atm.amegroups.com/article/view/12214

Upchurch, C. P., Grijalva, C. G., Wunderink, R. G., Williams, D. J., Waterer, G. W., Anderson, E. J., Zhu, Y., Hart, E. M., Carroll, F., Bramley, A. M., Jain, S., Edwards, K. M., & Self, W. H. (2017). Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs: Pathogens, Severity, and Clinical Outcomes. *Chest*(1931-3543 (Electronic)), 601-610.

van Buuren, S., Groothuis-Oudshoorn, K., Robitzsch, A., Vink, G., Doove, L., & Jolani, S. (2015). Package 'mice'. *Computer software*.

van de Garde, E. M. W., Oosterheert, J. J., Bonten, M., Kaplan, R. C., & Leufkens, H. G. M. (2007). International classification of diseases codes showed modest sensitivity for detecting community-acquired pneumonia. *Journal of Clinical Epidemiology, 60*(8), 834-838. doi:https://doi.org/10.1016/j.jclinepi.2006.10.018

Van Eeden, S., Leipsic, J., Paul Man, S. F., & Sin, D. D. (2012). The Relationship between Lung Inflammation and Cardiovascular Disease. *American Journal of Respiratory and Critical Care Medicine, 186*(1), 11-16. doi:10.1164/rccm.201203-0455PP

van Smeden, M., Moons, K. G. M., de Groot, J. A. H., Collins, G. S., Altman, D. G., Eijkemans, M. J. C., & Reitsma, J. B. (2018). Sample size for binary logistic prediction models: Beyond events per variable criteria. *Statistical Methods in Medical Research, 28*(8), 2455-2474. doi:10.1177/0962280218784726

van Vught, L. A., Scicluna, B. P., Wiewel, M. A., Hoogendijk, A. J., Klein Klouwenberg, P. M. C., Franitza, M., Toliat, M. R., Nürnberg, P., Cremer, O. L., Horn, J., Schultz, M. J., Bonten, M. M. J., & van der Poll, T. (2016). Comparative Analysis of the Host Response to Community-acquired and Hospital-acquired Pneumonia in Critically Ill Patients. *American Journal of Respiratory and Critical Care Medicine, 194*(11), 1366-1374. doi:10.1164/rccm.201602-0368OC

van Vugt, S. F., Broekhuizen, B. D. L., Lammens, C., Zuithoff, N. P. A., de Jong, P. A., Coenen, S., Ieven, M., Butler, C. C., Goossens, H., Little, P., Verheij, T. J. M., & Consortium, G. (2013). Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study. *Bmj-British Medical Journal, 346*. doi:Artn F2450 10.1136/Bmj.F2450

Vardakas, K. Z., Trigkidis, K. K., Apiranthiti, K. N., & Falagas, M. E. (2017). The dilemma of monotherapy or combination therapy in community-acquired pneumonia. *Eur J Clin Invest, 47*(12). doi:10.1111/eci.12845

Velavan, T. P., & Meyer, C. G. (2020). The COVID-19 epidemic. *Tropical medicine & international health : TM & IH, 25*(3), 278-280. doi:10.1111/tmi.13383

Veronese, N., Petrovic, M., Benetos, A., Denkinger, M., Gudmundsson, A., Knol, W., Marking, C., Soulis, G., Maggi, S., & Cherubini, A. (2021). Underrepresentation of older adults in clinical trials on COVID-19 vaccines: A systematic review. *Ageing Research Reviews, 71*, 101455. doi:https://doi.org/10.1016/j.arr.2021.101455

Viasus, D., Garcia-Vidal, C., Simonetti, A. F., Dorca, J., Llopis, F., Mestre, M., Morandeira-Rego, F., & Carratalà, J. (2015). The effect of simvastatin on inflammatory cytokines in community-acquired pneumonia: a randomised, double-blind, placebo-

controlled trial. *BMJ Open, 5*(1), e006251. doi:10.1136/bmjopen-2014-006251

Violi, F., Cangemi, R., Falcone, M., Taliani, G., Pieralli, F., Vannucchi, V., Nozzoli, C., Venditti, M., Chirinos, J. A., Corrales-Medina, V. F., & Thrombosis-Rel, S. (2017). Cardiovascular Complications and Short-term Mortality Risk in Community-Acquired Pneumonia. *Clinical Infectious Diseases, 64*(11), 1486-1493. doi:10.1093/cid/cix164

Vittinghoff, E., & McCulloch, C. E. (2007). Relaxing the Rule of Ten Events per Variable in Logistic and Cox Regression. *American Journal of Epidemiology, 165*(6), 710-718. doi:10.1093/aje/kwk052

Voncken, S., Feron, T., Karaca, U., Beerhorst, K., Klarenbeek, P., Straetmans, J., de Vries, G., Kolfoort-Otte, A., & de Kruif, M. (2022). Impact of obstructive sleep apnea on clinical outcomes in patients hospitalized with COVID-19. *Sleep and Breathing, 26*(3), 1399-1407.

Wallace, B. I., Kenney, B., Malani, P. N., Clauw, D. J., Nallamothu, B. K., & Waljee, A. K. (2021). Prevalence of Immunosuppressive Drug Use Among Commercially Insured US Adults, 2018-2019. *JAMA Network Open, 4*(5), e214920-e214920. doi:10.1001/jamanetworkopen.2021.4920

Walters, K.-A., D'Agnillo, F., Sheng, Z.-M., Kindrachuk, J., Schwartzman, L. M., Kuestner, R. E., Chertow, D. S., Golding, B. T., Taubenberger, J. K., & Kash, J. C. (2016). 1918 pandemic influenza virus and Streptococcus pneumoniae co-infection results in activation of coagulation and widespread pulmonary thrombosis in mice and humans. *The Journal of Pathology, 238*(1), 85-97. doi:https://doi.org/10.1002/path.4638

Wang, H., Naghavi, M., Allen, C., Barber, R. M., Bhutta, Z. A., Carter, A., Casey, D. C., Charlson, F. J., Chen, A. Z., Coates, M. M., Coggeshall, M., Dandona, L., Dicker, D. J., Erskine, H. E., Ferrari, A. J., Fitzmaurice, C., Foreman, K., Forouzanfar, M. H., Fraser, M. S., . . . Murray, C. J. L. (2016). Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet, 388*(10053), 1459-1544. doi:https://doi.org/10.1016/S0140-6736(16)31012-1

Wang, M. T. M., Bolland, M. J., & Grey, A. (2015). Reporting of Limitations of Observational Research. *JAMA Internal Medicine, 175*(9), 1571-1572. doi:10.1001/jamainternmed.2015.2147

Wang, W., Tian, J.-H., Chen, X., Hu, R.-X., Lin, X.-D., Pei, Y.-Y., Lv, J.-X., Zheng, J.-J., Dai, F.-H., Song, Z.-G., Chen, Y.-M., & Zhang, Y.-Z. (2022). Coronaviruses in wild animals sampled in and around Wuhan at the beginning of COVID-19 emergence. *Virus Evolution, 8*(1). doi:10.1093/ve/veac046

Waterer, G. (2021). What is pneumonia? *Breathe (Sheffield, England), 17*(3), 210087. doi:10.1183/20734735.0087-2021

Whitney, C. G., Farley, M. M., Hadler, J., Harrison, L. H., Bennett, N. M., Lynfield, R., Reingold, A., Cieslak, P. R., Pilishvili, T., Jackson, D., Facklam, R. R., Jorgensen, J. H., & Schuchat, A. (2003). Decline in Invasive Pneumococcal Disease after the Introduction of Protein–Polysaccharide Conjugate Vaccine. *New England Journal of Medicine, 348*(18), 1737-1746. doi:10.1056/NEJMoa022823

Wiemken, T. L., Carrico, R. M., Furmanek, S. P., Guinn, B. E., Mattingly, W. A., Peyrani, P., & Ramirez, J. A. (2020). Socioeconomic Position and the Incidence, Severity, and Clinical Outcomes of Hospitalized Patients With Community-Acquired Pneumonia. *Public Health Reports, 135*(3), 364-371. doi:10.1177/0033354920912717

Williams, G. R., Dai, C., Giri, S., Al-Obaidi, M., Harmon, C., Kenzik, K. M., McDonald, A., Gbolahan, O., Outlaw, D., Khushman, M. d., Richman, J., & Bhatia, S. (2022). Geriatric Assessment Predictors of 1-Year Mortality in Older Adults With GI Malignancies: A Survival Tree Analysis. *JCO Clinical Cancer Informatics*(6), e2200065. doi:10.1200/cci.22.00065

Williamson, E. J., Walker, A. J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C. E., Curtis, H. J., Mehrkar, A., Evans, D., Inglesby, P., Cockburn, J., McDonald, H. I., MacKenna, B., Tomlinson, L., Douglas, I. J., Rentsch, C. T., Mathur, R., Wong, A. Y. S., Grieve, R., . . . Goldacre, B. (2020). Factors associated with COVID-19-related death using OpenSAFELY. *Nature, 584*(7821), 430-436. doi:10.1038/s41586-020-2521-4

Wilson, D., Drew, W., Jasper, A., Crisford, H., Nightingale, P., Newby, P., Jackson, T., Lord, J. M., & Sapey, E. (2020). Frailty Is Associated With Neutrophil Dysfunction Which Is Correctable With Phosphoinositol-3-Kinase Inhibitors. *The Journals of Gerontology: Series A, 75*(12), 2320-2325. doi:10.1093/gerona/glaa216

Wolff, B. J., Bramley, A. M., Thurman, K. A., Whitney, C. G., Whitaker, B., Self, W. H., Arnold, S. R., Trabue, C., Wunderink, R. G., McCullers, J., Edwards, K. M., Jain, S., & Winchell, J. M. (2017). Improved Detection of Respiratory Pathogens by Use of

High-Quality Sputum with TaqMan Array Card Technology. *J Clin Microbiol, 55*(1), 110-121. doi:10.1128/jcm.01805-16

Wong, J. L., & Evans, S. E. (2017). Bacterial Pneumonia in Patients with Cancer: Novel Risk Factors and Management. *Clin Chest Med, 38*(2), 263-277. doi:10.1016/j.ccm.2016.12.005

Woodhead, M., Blasi, F., Ewig, S., Garau, J., Huchon, G., Ieven, M., Ortqvist, A., Schaberg, T., Torres, A., van der Heijden, G., Read, R., & Verheij, T. J. M. (2011). Guidelines for the management of adult lower respiratory tract infections - Summary. *Clinical Microbiology and Infection, 17*, 1-24. doi:10.1111/j.1469-0691.2011.03602.x

Woodhead, M. A., & Macfarlane, J. T. (1987). Comparative clinical and laboratory features of legionella with pneumococcal and mycoplasma pneumonias. *Br J Dis Chest, 81*(2), 133-139. doi:10.1016/0007-0971(87)90130-6

World Health Organization. (2015). *World report on ageing and health*: World Health Organization.

World Health Organization. (2021). Pneumonia. Retrieved from https://www.who.int/news-room/fact-sheets/detail/pneumonia#:~:text=In%20children%20under%205%20years,the%20chest%20expands%20during%20inhalation).

World Health Organization. (2022). COVID-19 weekly epidemiological update, edition 119, 23 November 2022.

Worobey, M., Levy, J. I., Serrano, L. M., Crits-Christoph, A., Pekar, J. E., Goldstein, S. A., Rasmussen, A. L., Kraemer, M. U. G., Newman, C., Koopmans, M. P. G., Suchard, M. A., Wertheim, J. O., Lemey, P., Robertson, D. L., Garry, R. F., Holmes, E. C., Rambaut, A., & Andersen, K. G. The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. *Science*, *0*(0), abp8715. doi:doi:10.1126/science.abp8715

Wu, C., Chen, X., Cai, Y., Xia, J. a., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., . . . Song, Y. (2020a). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Internal Medicine*, *180*(7), 934-943. doi:10.1001/jamainternmed.2020.0994

Wu, X., Li, Y., Zhang, M., Li, M., Zhang, R., Lu, X., Gao, W., Li, Q., Xia, Y., Pan, P., & Li, Q. (2020b). Etiology of Severe

Community-Acquired Pneumonia in Adults Based on Metagenomic Next-Generation Sequencing: A Prospective Multicenter Study. *Infectious Diseases and Therapy, 9*(4), 1003-1015. doi:10.1007/s40121-020-00353-y

Wu, Z., & McGoogan, J. M. (2020). Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA, 323*(13), 1239-1242. doi:10.1001/jama.2020.2648

Wuerth, B. A., Bonnewell, J. P., Wiemken, T. L., & Arnold, F. W. (2016). Trends in pneumonia mortality rates and hospitalizations by organism, United States, 2002–2011. *Emerging Infectious Diseases, 22*(9), 1624.

Wyllie, A. L., Pannekoek, Y., Bovenkerk, S., Gastelaars, J. V., Ferwerda, B., van de Beek, D., Sanders, E. A. M., Trzcinski, K., & van der Ende, A. (2017). Sequencing of the variable region of rpsB to discriminate between Streptococcus pneumoniae and other streptococcal species. *Open Biology, 7*(9). doi:ARTN 170074 10.1098/rsob.170074

Xie, Y., Xu, E., Bowe, B., & Al-Aly, Z. (2022). Long-term cardiovascular outcomes of COVID-19. *Nature Medicine, 28*(3), 583-590. doi:10.1038/s41591-022-01689-3

Ye, X., Xiao, H., Chen, B., & Zhang, S. Y. (2015). Accuracy of Lung Ultrasonography versus Chest Radiography for the Diagnosis of Adult Community-Acquired Pneumonia: Review of the Literature and Meta-Analysis. *PLOS ONE, 10*(6). doi:ARTN e0130066 10.1371/journal.pone.0130066

Yende, S., Angus, D. C., Ali, I. S., Somes, G., Newman, A. B., Bauer, D., Garcia, M., Harris, T. B., Kritchevsky, S. B., & Study, f. t. H. A. (2007). Influence of Comorbid Conditions on Long-Term Mortality After Pneumonia in Older People. *Journal of the American Geriatrics Society, 55*(4), 518-525. doi:https://doi.org/10.1111/j.1532-5415.2007.01100.x

Yende, S., D'Angelo, G., Kellum, J. A., Weissfeld, L., Fine, J., Welch, R. D., Kong, L., Carter, M., & Angus, D. C. (2008). Inflammatory Markers at Hospital Discharge Predict Subsequent Mortality after Pneumonia and Sepsis. *American Journal of Respiratory and Critical Care Medicine, 177*(11), 1242-1247. doi:10.1164/rccm.200712-1777OC

Yende, S., D'Angelo, G., Mayr, F., Kellum, J. A., Weissfeld, L., Kaynar, A. M., Young, T., Irani, K., Angus, D. C., & for the Gen, I. M. S. I. (2011). Elevated Hemostasis Markers after Pneumonia

Increases One-Year Risk of All-Cause and Cardiovascular Deaths. *PLOS ONE, 6*(8), e22847. doi:10.1371/journal.pone.0022847

Yoshikawa, T. T., & Marrie, T. J. (2000). Community-Acquired Pneumonia in the Elderly. *Clinical Infectious Diseases, 31*(4), 1066-1078. doi:10.1086/318124

Yousufuddin, M., Shultz, J., Doyle, T., Rehman, H., & Murad, M. H. (2018). Incremental risk of long-term mortality with increased burden of comorbidity in hospitalized patients with pneumonia. *European Journal of Internal Medicine, 55*, 23-27. doi:https://doi.org/10.1016/j.ejim.2018.05.003

Zhai, P., Ding, Y., Wu, X., Long, J., Zhong, Y., & Li, Y. (2020). The epidemiology, diagnosis and treatment of COVID-19. *International Journal of Antimicrobial Agents, 55*(5), 105955. doi:https://doi.org/10.1016/j.ijantimicag.2020.105955

Zhang, Z. (2016). Multiple imputation with multivariate imputation by chained equation (MICE) package. *Annals of translational medicine, 4*(2).

Zhang, Z., Hong, Y., & Liu, N. (2017). Association of ambient Particulate matter 2.5 with intensive care unit admission due to pneumonia: a distributed lag non-linear model. *Sci Rep, 7*(1), 8679. doi:10.1038/s41598-017-08984-x

Zhang, Z., Reinikainen, J., Adeleke, K. A., Pieterse, M. E., & Groothuis-Oudshoorn, C. G. M. (2018). Time-varying covariates and coefficients in Cox regression models. *Ann. Transl. Med., 6*(7), 11. Retrieved from https://atm.amegroups.com/article/view/18820

Zhou, H., Larkin, P. M. K., Zhao, D., Ma, Q., Yao, Y., Wu, X., Wang, J., Zhou, X., Li, Y., Wang, G., Feng, M., Wu, L., Chen, J., Zhou, C., Hua, X., Zhou, J., Yang, S., & Yu, Y. (2021). Clinical Impact of Metagenomic Next-Generation Sequencing of Bronchoalveolar Lavage in the Diagnosis and Management of Pneumonia: A Multicenter Prospective Observational Study. *The Journal of Molecular Diagnostics, 23*(10), 1259-1268. doi:https://doi.org/10.1016/j.jmoldx.2021.06.007

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., Chen, H.-D., Chen, J., Luo, Y., Guo, H., Jiang, R.-D., Liu, M.-Q., Chen, Y., Shen, X.-R., Wang, X., . . . Shi, Z.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature, 579*(7798), 270-273. doi:10.1038/s41586-020-2012-7

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., & Tan, W. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine, 382*(8), 727-733. doi:10.1056/NEJMoa2001017