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CLINICAL PRESENTATION AND OUTCOMES OF COVID-19 COMPARED WITH OTHER RESPIRATORY VIRUS INFECTIONS AND HOSPITAL POPULATIONS

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Clinical presentation and outcomes of COVID-19 compared with other respiratory virus infections and hospital populations
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By

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ABSTRACT

As of September 2022, more than 600 million cases of coronavirus disease 2019 (COVID-19) and 6.5 million deaths have been officially reported to the World Health Organization (WHO). The unfolding pandemic has exerted enormous strains on healthcare systems worldwide yet to be fully understood. The overarching aim of this thesis was to characterize clinical presentation and outcomes in adult patients hospitalized with COVID-19 and compare these with patients hospitalized with other respiratory virus infections as well as other hospital populations. Six retrospective cohort studies were conducted, all set in Stockholm Region in Sweden.

In study I, baseline characteristics, clinical presentation, and outcomes in patients hospitalized with COVID-19 were compared with patients hospitalized with influenza, respiratory syncytial virus (RSV) infection, and other respiratory virus infections. Despite being younger and having an overall better health status, adult patients hospitalized with COVID-19 had an increased risk of severe outcomes, in particular mortality, compared with the other infections. These risks were greater among the elderly and during the first months of the pandemic.

In study II, the prevalence of bacterial co-infections in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive community-acquired pneumonia (CAP) upon hospital admission was compared with patients hospitalized with influenza virus positive CAP and RSV positive CAP. The occurrence of detected bacterial co-infection upon hospital admission was substantially lower in the SARS-CoV-2 cohort compared with both the influenza and the RSV cohort.

In study III, we compared the occurrence of ventilator-associated lower respiratory tract infection (VA-LRTI) in patients mechanically ventilated with versus without COVID-19. The incidence rate was increased in the COVID-19 cohort when compared with influenza and other infectious diseases but decreased when compared with most of the non-infectious diseases. Further, the incidence rate was in the COVID-19 cohort increased during the second wave when compared with the first wave of the pandemic.

In study IV, the incidence rate and 30-day mortality rate of hospital-onset bacteraemia (HOB) were compared among patients hospitalized with COVID-19 and patients hospitalized without COVID-19 both before and during the pandemic. The incidence as well as mortality of HOB was increased for both COVID-19 and non-COVID-19 patients during the pandemic when compared with patients hospitalized before the pandemic.

In study V, we investigated one-year mortality among patients admitted to the intensive care unit (ICU) with versus without COVID-19. Furthermore, we compared the number of days alive and free from hospitalization during one year in those patients who were discharged alive from the ICU-associated hospitalization. An increased risk of acute mortality was observed in patients treated in the ICU with versus without COVID-19, primarily among the elderly. On the contrary, survivors of COVID-19 critical illness had compared with other critical illness survivors more days alive and free from further hospitalizations during the next year.

In study VI, we investigated the occurrence and characteristics of post COVID-19 condition (PCC) diagnosis across different severities of the acute COVID-19 episode. The occurrence of PCC diagnosis was substantially higher in individuals hospitalized versus not hospitalized during the acute COVID-19 episode. Associations between health status factors and PCC diagnosis differed by severity of the acute COVID-19 episode, with more and stronger associations among those not hospitalized during the acute infection. Increases in outpatient healthcare utilization up to one year after the acute infection indicated an incomplete recovery in individuals diagnosed with PCC.

Taken together, these studies contribute to our understanding of the clinical epidemiology of COVID-19, highlighting severe acute clinical outcomes in hospitalized patients as well as a different occurrence and trajectory of PCC across different severities of the acute infection. Given the life-saving rollout of COVID-19 vaccines and the evolving nature of the virus, the generalizability of these findings over time needs to be carefully considered. Further investigations of the acute and in particular long-term effects of COVID-19 are warranted. An improved understanding of how the pandemic has caused disruptions and backlogs in healthcare delivery is also necessary.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following six studies, referred to by their Roman numerals (I-VI):

I. **Clinical phenotypes and outcomes of SARS-CoV-2, influenza, RSV and seven other respiratory viruses: a retrospective study using complete hospital data**
Pontus Hedberg, John Karlsson Valik, Suzanne Desirée van der Werff, Hideyuki Tanushi, Ana Requena Mendez, Fredrik Granath, Max Bell, Johan Mårtensson, Robert Dyrdak, Olof Hertting, Anna Färnert, Anders Ternhag, Pontus Nauclér
Thorax. 2022 Feb;77(2):154-163
https://doi.org/10.1136/thoraxjnl-2021-216949

II. **Bacterial co-infections in community-acquired pneumonia caused by SARS-CoV-2, influenza virus and respiratory syncytial virus**
Pontus Hedberg, Niclas Johansson, Anders Ternhag, Lina Abdel-Halim, Jonas Hedlund, Pontus Nauclér
BMC Infect Dis. 2022 Jan 31;22(1):108
https://doi.org/10.1186/s12879-022-07089-9

III. **Ventilator-associated lower respiratory tract bacterial infections in COVID-19 compared with non-COVID-19 patients**
Pontus Hedberg, Anders Ternhag*, Christian Giske, Kristoffer Strålin, Volkan Özenci, Niclas Johansson, Carl Spindler, Jonas Hedlund, Johan Mårtensson, Pontus Nauclér*
Crit Care Med. 2022 May 1;50(5):825-836
https://doi.org/10.1097/CCM.0000000000005462
* Shared first authorship

IV. **Impact of the COVID-19 pandemic on the incidence and mortality of hospital-onset bloodstream infection: a cohort study**
John Karlsson Valik, Pontus Hedberg, Fredrik Holmberg, Suzanne Desirée van der Werff, Pontus Nauclér
BMJ Qual Saf. 2022 May;31(5):379-382
https://doi.org/10.1136/bmjqs-2021-014243

V. **One-year mortality and hospital-free days in COVID-19 versus non-COVID-19 critical illness**
Pontus Hedberg, Nicholas Baltzer, Fredrik Granath, Michael Fored, Johan Mårtensson, Pontus Nauclér
Manuscript in preparation

VI. **Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection**
Pontus Hedberg, Fredrik Granath, Judith Bruchfeld, Johan Askling, Daniel Sjöholm, Michael Fored, Anna Färnert, Pontus Nauclér
Submitted manuscript

SCIENTIFIC PAPERS NOT INCLUDED IN THIS THESIS

The following studies were published during the course of the doctoral studies but are outside the scope of this thesis:

Red blood cell blood group A antigen level affects the ability of heparin and PfEMP1 antibodies to disrupt *Plasmodium falciparum* rosettes
Pontus Hedberg, Madle Sirel, Kirsten Moll, Mpungu Steven Kiwuwa, Petter Höglund, Ulf Ribacke, Mats Wahlgren
Malar J 20, 441 (2021)
https://doi.org/10.1186/s12936-021-03975-w

SARS-CoV-2 testing in patients with low COVID-19 suspicion at admission to a tertiary care hospital, Stockholm, Sweden, March to September 2020
Ana Requena-Méndez, Aikaterini Mougkou, Pontus Hedberg, Suzanne Desirée van der Werff, Hideyuki Tanushi, Olof Hertting, Anna Färnert, Filippa Nyberg, Pontus Nauclér, COVID-19-data-review collaborators
Euro Surveill. 2022 Feb;27(7):2100079.
https://doi.org/10.2807/1560-7917.ES.2022.27.7.2100079

Incidence and severity of COVID-19 in adults with and without HIV diagnosis
Pontus Hedberg, Jan Vesterbacka, Ola Blennow, Catharina Missailidis, Piotr Nowak, Pontus Nauclér
J Intern Med. 2022 Jul;292(1):168-171
https://doi.org/10.1111/joim.13481

Prophylactic anticoagulation with low molecular weight heparin in COVID-19: cohort studies in Denmark and Sweden
Lars Christian Lund, Pontus Hedberg, Anne Helms Andreasen, Janne Petersen, Tonny Studsgaard Petersen, Anton Pottegård, Jacob Bodilsen, Pontus Nauclér, Jesper Hallas, Espen Jimenez-Solem
Clin Microbiol Infect. 2022 Mar 17;28(9):1291.e1–5
https://doi.org/10.1016/j.cmi.2022.03.006

Influenza of perioperative SARS-CoV-2 infection on mortality in orthopaedic inpatients with surgically treated traumatic fractures
Mathias Granqvist, Pontus Hedberg, Pontus Nauclér, Anders Enocson
Eur J Orthop Surg Traumatol. 2022 Mar 24:1–7
https://doi.org/10.1007/s00590-022-03226-x

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https://doi.org/10.1016/j.cmi.2022.05.014

Clinical prediction models for mortality in patients with covid-19: external validation and individual participant data meta-analysis
Valentijn M T de Jong, Rebecca Z Rousset, Neftali Eduardo Antonio-Villa, Arnoldus G Buenen, Ben Van Calster, Omar Yaxmehen Bello-Chavolla, Nigel J Brunskill, Vasa Curcin, Johanna A A Damen, Carlos A Fermin-Martinez, Luisa Fernandez-Chirino, Davide Ferrari, Robert C Free, Rishi K Gupta, Pranabashis Haldar, Pontus Hedberg, Steve Kwasi Korang, Steef Kurstjens, Ron Kusters, Rupert W Major, Lauren Maxwell, Rajeshwari Nair, Pontus Nauclér, Tri-Long Nguyen, Mahdad Noursadeghi, Rossana Rosa, Felipe Soares, Toshihiko Takada, Florien S van Royen, Maarten van Smeden, Laure Wynants, Martin Modrák, the CovidRetro collaboration, Folkert W Asselbergs, Marijke Linschoten, CAPACITY-COVID consortium, Karel G M Moons, Thomas P A Debray
BMJ. 2022 Jul 12;378:e069881
https://doi.org/10.1136/bmj-2021-069881

Association between time to appropriate antimicrobial treatment and 30-day mortality in patients with bloodstream infections: a retrospective cohort study.
Jasper Van Heuverswyn, John Karlsson Valik, Suzanne Desirée van der Werff, Pontus Hedberg, Christian Giske, Pontus Nauclér
Clin Infect Dis. 2022 Sep 6:ciac727
https://doi.org/10.1093/cid/ciac727

CONTENTS

LIST OF ABBREVIATIONS

ACE2	Angiotensin converting enzyme 2
AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
AUROC	Area under the receiver operating characteristic
BMI	Body mass index
BSI	Bloodstream infection
CAP	Community-acquired pneumonia
CCI	Charlson comorbidity index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRB-65	Confusion, Respiration, Blood pressure, >65 years
CRP	C-reactive protein
CSHR	Cause-specific hazard ratio
DVT	Deep vein thrombosis
EHR	Electronic health record
EMA	European Medicines Agency
HAI	Healthcare-associated infection
HOB	Hospital-onset bacteraemia
ICD-10	International Statistical Classification of Diseases and Related Health Problems – Tenth Revision
ICU	Intensive care unit
IFR	Infection fatality ratio
IL-1	Interleukin-1
IL-6	Interleukin-6
IRR	Incidence rate ratio
KDIGO	Kidney Disease: Improving Global Outcomes
KUH	Karolinska University Hospital
LLST	Limitation of life-sustaining treatment
LOS	Length of stay
mAb	Monoclonal antibody
ME/CFS	Myalgic encephalomyelitis/Chronic fatigue syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
Mpro	Main protease
mRNA	Messenger RNA

NAAT	Nucleic acid amplification test
NLR	Neutrophil-to-lymphocyte ratio
NPI	Non-pharmaceutical intervention
OR	Odds ratio
PACS	Post-acute COVID-19 syndrome
PANGO	Phylogenetic assignment of named global outbreak
PASC	Post-acute sequelae of COVID-19
PCC	Post COVID-19 condition
PE	Pulmonary embolism
PICS	Post-intensive care syndrome
PIN	Personal identity number
Q1-Q3	Quartile 1 to quartile 3
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized clinical trial
RDT	Rapid diagnostic test
RR	Risk ratio
RSV	Respiratory syncytial virus
SAPS 3	Simplified acute physiology score 3
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SHR	Subdistribution hazard ratio
SIR	Swedish intensive care registry
VA-LRTI	Ventilator-associated lower respiratory tract infection
VAP	Ventilator-associated pneumonia
VAT	Ventilator-associated tracheobronchitis
VOC	Variant of concern
VTE	Venous thromboembolism
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

The six studies presented in this thesis were conducted during the period June 2020 to August 2022 at the Department of Medicine, Solna at Karolinska Institutet in Stockholm, Sweden. The overarching aim was to characterize the clinical presentation and outcomes in adult patients hospitalized with coronavirus disease 2019 (COVID-19) and compare these with other respiratory virus infections and hospital populations.

Well before the emergence of the COVID-19 pandemic, my doctoral studies started with a completely different aim in mind: To elucidate the effect of the histo-blood group ABO system on the pathogenesis of *Plasmodium falciparum* malaria. To address this, experimental in vitro cultivation of *Plasmodium falciparum* laboratory strains and clinical isolates were used. The transition from such experimental research to register and electronic health record (EHR) based clinical epidemiology has been both challenging and rewarding and I am truly grateful to my principal supervisor, associate professor Pontus Nauclér, and my co-supervisor, professor Mats Wahlgren, for supporting me in this formative change.

Despite extensive differences in the aims and methodologies of these doctoral projects, important intersections and commonalities are worth a brief mention. COVID-19 and malaria are both infectious diseases, the former caused by the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the latter caused by five species of the parasite genus *Plasmodium*. The World Health Organization (WHO) estimated more than 600,000 malaria deaths during 2020, representing around 70,000 more deaths compared to the preceding year, of which two-thirds of these were linked to disruptions of malaria preventive, diagnostic, and therapeutic measures during the ongoing COVID-19 pandemic [1]. While extensive evidence for an association between the ABO blood group system and severe malaria exists [2], more recent evidence indicate that the ABO blood group system also might play a role in the pathogenesis of COVID-19 [3]. Furthermore, potential clinical interactions between malaria and COVID-19 in areas with overlapping epidemiology remain to be better understood [4].

Conducting research both during and about an unfolding pandemic has been a special experience. Remarkable clinical and scientific efforts have paved the way for our current understanding of SARS-CoV-2 and COVID-19. This includes, but is far from limited to, the tireless and lifesaving work of healthcare staff throughout the world, the development and roll-out of several safe and effective vaccines and treatments, the collaborative spirit among researchers, and the improvements of real-time tracking of pathogen evolution.

Collectively, my hope is for the studies of this thesis to contribute to an improved understanding of the clinical epidemiology of COVID-19 as well as to inspire to further research on such matters. More importantly, I hope this work can benefit patients by improving the clinical management and planning of healthcare during and beyond this pandemic.

2 BACKGROUND

2.1 INITIAL REMARKS

Research on COVID-19 is a quickly developing field, characterized by unprecedented data sharing and rapid dissemination of results [5,6]. This has partly been facilitated by uploading of non-peer-reviewed articles to preprint servers. While this has narrowed the gap between academic and general audiences, incorrect findings and conclusions have also become widely disseminated within media sources as reviewed by Brierley [7]. Over 125,000 COVID-19 related scientific articles were released within the first ten months of the pandemic, of which more than 30,000 were uploaded to preprint servers [8]. Currently, as of 27 September 2022, a search on COVID-19 returns more than 300,000 search results in the PubMed database. This can be compared with the number of search results related to other infectious diseases, as illustrated in figure 1.

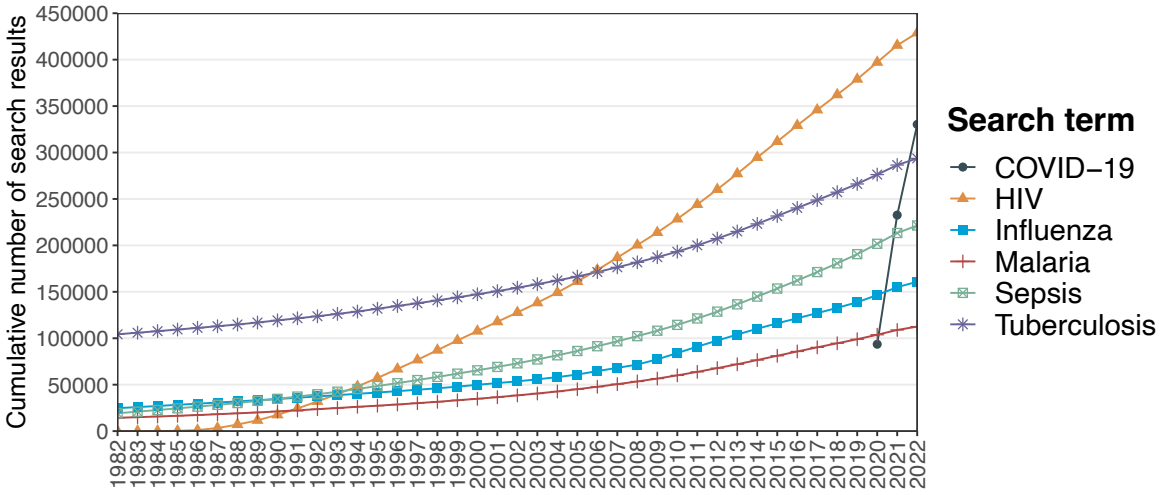

Figure 1. Cumulative number of search results for COVID-19 and other infectious diseases in the PubMed database as of 27 September 2022. The x-axis displays calendar year. The y-axis displays the cumulative number of search results by the end of each year.

The literature reviewed for this chapter comes almost exclusively from peer-reviewed articles and reports from national or international health agencies. Nonetheless, it is a remarkable challenge to provide an overview that is comprehensive and up to date with the latest literature. In line with the overarching aim of this thesis, this chapter is primarily focused on COVID-19 among adults.

2.2 A BRIEF OVERVIEW OF THE COVID-19 PANDEMIC

On 31 December 2019, the WHO was informed of cases of pneumonia of unknown cause in Wuhan in South Central China [9]. On 11 January 2020, the local health authorities reported the first death from the new disease, and a draft genome of the newly discovered virus was shared by a consortium of researchers [10]. Two days later, 13 January 2020, the first reported case outside of China came from Thailand [11]. On 11 February 2020, the International Committee on Taxonomy of Viruses announced SARS-CoV-2 as the name of the new emerging coronavirus,

and COVID-19 as the name of the disease caused by the virus [12,13]. On 11 March 2020, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, briefed the media on the decision to declare COVID-19 a pandemic, explaining "There are now more than 118,000 cases in 114 countries, and 4,291 people have lost their lives" [14].

Two and a half years later, as of 27 September 2022, around 600 million confirmed cases of COVID-19, and around 6.5 million deaths have been reported to the WHO [15]. However, due to the limited testing, the number of officially confirmed cases is much lower than the true number of infections [16]. Furthermore, both the testing intensity and attribution of cause of death has differed across different geographical settings throughout the pandemic. A systematic analysis of COVID-19 related mortality estimated 18.2 million (95% confidence interval (CI): 17.1-19.6 million) people to have died because of the COVID-19 pandemic in 2020 and 2021 [17]. The WHO estimates that around 12.5 billion COVID-19 vaccine doses have been administered [15]. According to a recent mathematical modelling study, COVID-19 vaccinations prevented 14.4 million (95% CI: 13.7-15.9 million) deaths due to COVID-19 during the first year of the vaccination programme (8 December 2020 to 8 December 2021) [18]. The vaccination coverage, however, is far from equally distributed across the globe, with around 75% of the population in high-income countries vaccinated compared with 19% in low-income countries [19].

The first confirmed case of COVID-19 in Sweden was reported on 31 January 2020, when a woman who had visited Wuhan tested positive for SARS-CoV-2 [20]. As of 27 September 2022, around 2.6 million confirmed cases of COVID-19, and around 20,000 deaths related to COVID-19 have been reported to the Public Health Agency of Sweden [21]. In Stockholm Region, the geographical setting of this thesis, around 600,000 confirmed cases of COVID-19, and around 5,500 deaths have been reported. The first COVID-19 vaccination in Sweden took place on 27 December 2020 and currently, around 85% of the population aged 12 years or older has received two doses or more [22,23]. The Swedish response to the unfolding pandemic has been less invasive and more based on voluntary control measures when compared with neighbouring countries as well as many other countries [24–26]. In June 2020, the Swedish government appointed a Commission to evaluate the measures taken by the government and other agencies involved to limit the spread of SARS-COV-2 [27]. In their final report from February 2022, the Commission considered the focus on advice and recommendations rather than more intrusive measures to be correct, whereas the implementation of large scale testing and certain non-pharmaceutical interventions (NPI) such as limits on public gatherings and recommendation on face masks in indoor settings and on public transport were considered tardy [28].

An overview of reported cases and deaths over the course of the pandemic worldwide and in Sweden is presented in figure 2.

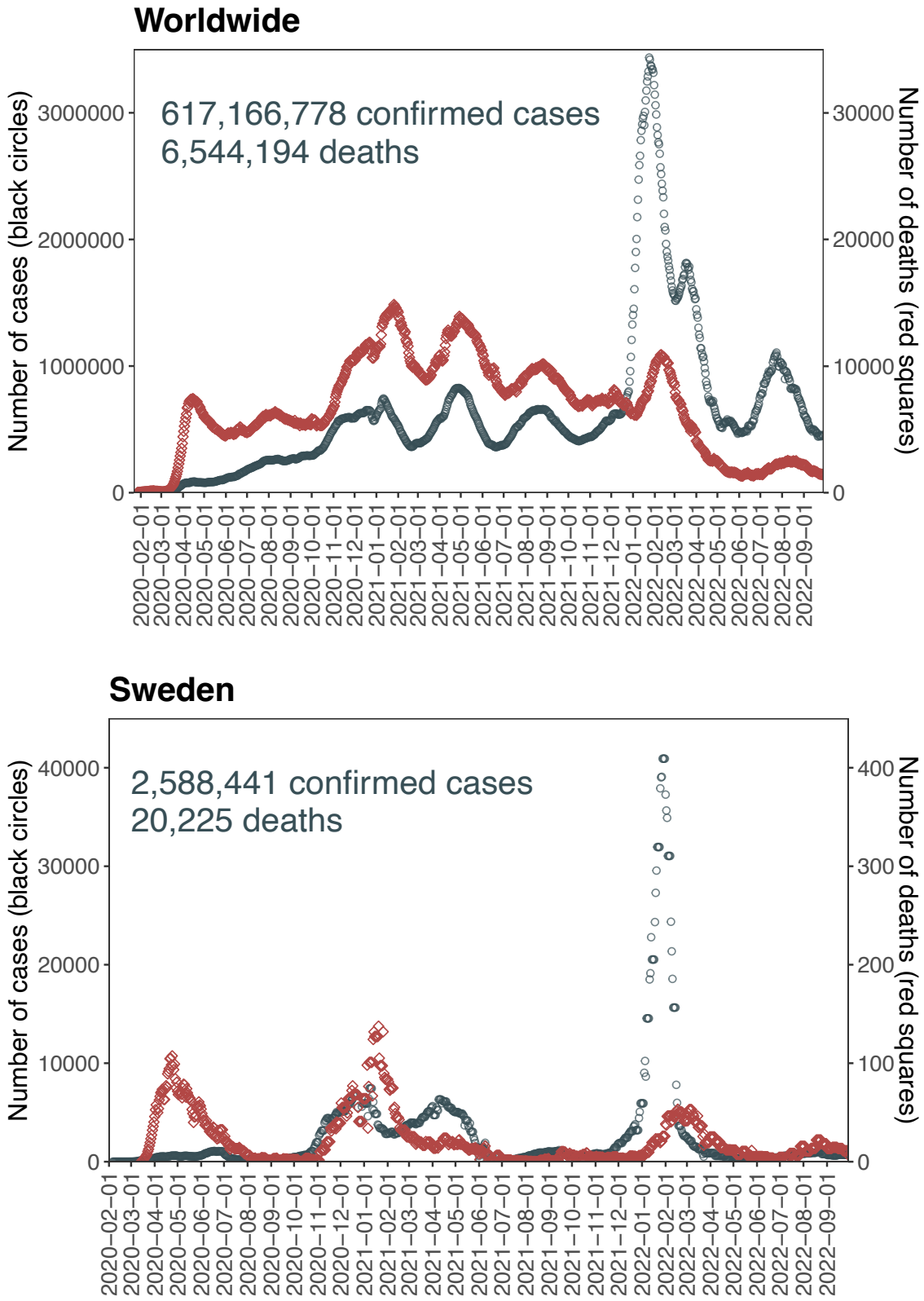

Figure 2. Number of global confirmed cases of COVID-19 and deaths attributed to COVID-19 (as of 29 September 2022). The x-axes display calendar time as year and month. The left y-axes display the 7-day rolling average of number of confirmed cases of COVID-19. The right y-axes display the 7-day rolling average of number of deaths attributed to COVID-19. The data were obtained from Our World in Data, published under a Creative Commons Attribution 4.0 International license (CC BY 4.0) [16].

2.3 SARS-COV-2

SARS-CoV-2 is a member of the family *Coronaviridae*, a diverse group of viruses which can infect humans and many other animals [29]. Human coronaviruses were discovered in the mid-1960s [30], and currently seven coronaviruses from two genera (Alphacoronavirus and Betacoronavirus) are known to infect humans [31]. Four of these coronaviruses, HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63, are seasonal coronaviruses most often causing mild-to-moderate disease. The remaining three coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, are all Betacoronaviruses causing more severe disease. SARS-CoV emerged in November 2002 in China and caused an epidemic in 2003 with more than 8,000 infections and nearly 800 deaths, primarily in the WHO Western Pacific Region [32]. MERS-CoV was first isolated in 2012 from a man with pneumonia in Saudia Arabia [33], and had by January 2020 caused more than 2,500 reported cases and around 900 deaths [34].

The SARS-CoV-2 virion (the complete infectious virus particle) is enveloped and has a spherical or ellipsoidal shape with an average diameter of 108 nm [35]. SARS-CoV-2 has a non-segmented, positive sense (5'-3'), single-stranded RNA genome of around 30,000 nucleotides [36,37]. This genome, similar in size to other coronaviruses, is among the largest known RNA genomes and encodes four structural proteins as well as non-structural and accessory proteins [38]. The structural characteristics of the SARS-CoV-2 virion are shown in figure 3.

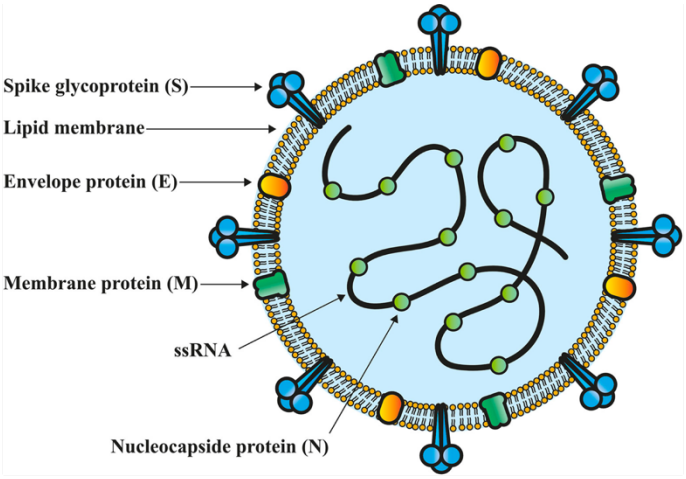

Figure 3. Structural characteristics of the SARS-CoV-2 virion. The figure was reprinted from Martinez-Florez et al, Frontiers in Immunology, 2022 under a Creative Commons Attribution 4.0 International license (CC BY 4.0).

The nucleocapside (N) protein is responsible for the genome packaging, whereas the envelope (E) and membrane (M) proteins are part of the viral outer membrane [35]. The virion is covered with spike (S) glycoproteins, giving it a crown-like appearance as implied from the name coronavirus (corona means crown in Latin). As viruses are dependent on the intracellular translation machinery for their propagation, SARS-CoV-2 as all other viruses needs to be able to enter the host cell, a process known as viral entry. This multistep process is mediated by the trimeric assemble of the S proteins and subsequent binding to the angiotensin-converting enzyme 2 (ACE2) [39]. ACE2 is a monocarboxypeptidase which acts by converting angiotensin-I and angiotensin-II into angiotensin-(1-9) and angiotensin-(1-7), respectively. ACE2 plays an integral role in the renin-angiotensin-aldosterone system (RAAS), a complex network involved in blood pressure control as well as electrolyte and fluid homeostasis [40]. The enzyme is widely expressed in many tissue types, including the respiratory epithelium. To what extent this potentially explains extrapulmonary effects from COVID-19 remains to be fully elucidated [41].

Although COVID-19 treatments will be described in section 2.4.3, it is here worth to make the connection between the viral characteristics of SARS-CoV-2 and the drugs used to treat COVID-19. Four out of the currently eight COVID-19 treatments authorized for use in the EU by the European Medicines Agency (EMA) work by attaching to the S protein [42]. Out of the remaining four treatments, one work by inhibiting the SARS-CoV-2 RNA-dependent RNA-polymerase and another by inhibiting the SARS-CoV-2 Main protease (Mpro). The remaining two work by blocking the human interleukin-1 (IL-1) and interleukin-6 (IL-6) receptor, respectively. As for COVID-19 vaccines, the S protein is the main target for all six vaccines currently authorized for use in the EU [43].

While modes of transmission such as vertical transmission and direct contact transmission have been described, respiratory transmission is the dominant mode of transmission of SARS-CoV-2 [44]. Proximity has been suggested as a key determinant of transmission risk, with the risk of transmission likely to be greatest when being less than two meters away from someone who is infected [44,45]. However, evidence from a systematic review suggests that also more long-distance airborne transmission might occur in indoor settings, possibly driven by insufficient air replacement, directional air flow, and activities with increased emissions of respiratory particles such as singing and shouting [45].

2.3.1 Variants of concern

As with all viruses, SARS-CoV-2 changes and mutates over time, with most mutations having a deleterious or neutral impact on the virus. However, some mutations affect the transmissibility or virulence of the virus, and potentially lead to increased disease severity or reduced effectiveness of therapies and vaccines. Such altered characteristics observed in different variants of SARS-CoV-2 are classified by the WHO as variants of concern (VOC) [46]. The strain of the virus that first emerged in Wuhan is often referred to as the primary strain, the Wuhan-Hu-1, B.1, or the wildtype strain [47]. Since then, five VOCs have been described and labelled with letters of the Greek alphabet: alpha, beta, gamma, delta, and omicron. These VOCs are also referred to by their Phylogenetic assignment of named global outbreak (PANGO) lineages: B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), B.1.617.2 (delta), B.1.1.529 (omicron). Figure 4 displays the distribution of the five VOCs in Sweden throughout the pandemic.

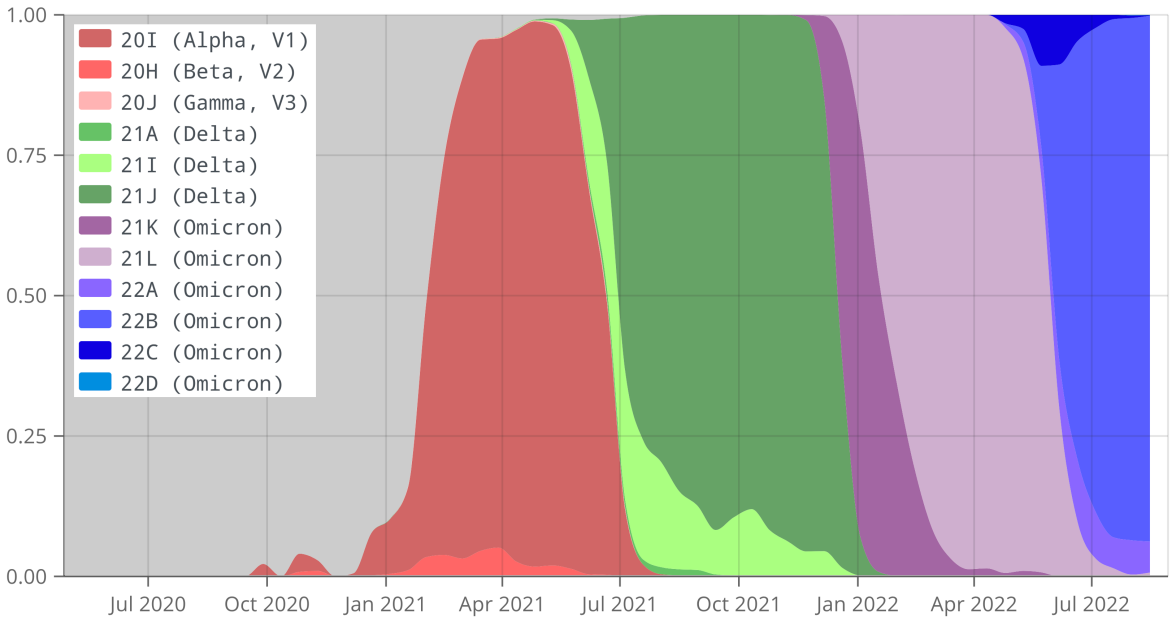

Figure 4. Distribution of VOCs among sequenced samples of SARS-CoV-2 in Sweden. The x-axis displays calendar month and year. The y-axis displays the proportion of sequenced samples. The grey colour represents samples not sequenced as any of the five VOCs. The figure was reprinted from CoVariants under a Creative Commons Attribution 4.0 International license (CC BY 4.0) [48].

The alpha variant was first classified as a VOC in the UK in December 2020 [49], and spread throughout Europe in January and February 2021. In Sweden, the alpha variant primarily circulated from January to July 2021 [48]. Several studies have demonstrated an increased transmissibility, risk of hospitalization, intensive care unit (ICU) admission, and death of the alpha variant compared with the primary strain [50–54].

The beta variant was first identified in South Africa and was just as the alpha variant classified as a VOC in December 2020 [46,55]. An increased risk of hospitalization with the beta variant compared with the primary strain was observed in a retrospective cohort study from Washington State in the US [56]. In Sweden, the beta variant was circulating at the same time as the alpha variant, with the highest proportion of sequenced samples being around 5% [48].

The gamma variant was first identified in Brazil and was classified as a VOC in January 2021 [46]. Just as with the alpha and beta variants, the gamma variant has been associated with increased transmissibility and severity compared with the primary strain [47,57]. The gamma variant was sequenced in rather few samples from January to July in Sweden [48].

The delta variant was first identified in India and was classified as a VOC in May 2021 [46]. An increased binding affinity to the ACE2 receptor most likely resulted in an enhanced transmissibility of the delta variant compared with other variants [58]. Several epidemiological studies have observed an increased disease severity for the delta variant compared with other variants. In a cohort study of 8,682 delta and 34,656 alpha positive patients in England, an increased risk of hospital admission or emergency care attendance was observed for the delta variant [59]. An increased risk of hospitalization was also observed in a Scottish cohort study comparing the delta variant with the alpha variant [60]. In a Canadian study of more than 200,000

individuals tested positive for SARS-CoV-2, of which around 6,000 individuals tested positive for the delta variant, the delta variant was associated with an increased risk of admission to the ICU and death compared with the other variants [61].

The earliest documented samples of omicron were from multiple countries in November 2021, the same month as the variant was designated a VOC [46]. Following its emergence, the omicron variant caused a major surge in infections throughout the world. Currently (as of 27 September 2022), the omicron variant is the only circulating VOC [46]. In Sweden, the first detected case of omicron was reported by the Public Health Agency of Sweden on 29 November [62]. Roughly one to one and a half month later, from 3-17 January 2022, 93% of sequenced samples were of the omicron variant [48]. Approximately 1.1 million confirmed cases (more than 10% of the Swedish population) were reported during January and February 2022 [21]. Several studies have since then reported a decreased severity of omicron compared with other SARS-CoV-2 variants. A South African study observed a substantially reduced odds of hospitalization for individuals infected with the omicron variant compared with non-omicron variants [63]. In an English cohort study of more than 1.5 million COVID-19 cases, omicron was associated with an approximately 44% lower risk of hospital attendance and 69% lower risk of death [64]. A reduced risk of hospitalization with omicron variant infection compared with delta variant infection was also observed in a Danish cohort study of around 190,000 SARS-CoV-2 positive individuals [65].

Collectively, virological features and clinical outcomes of different VOCs have differed extensively throughout the pandemic, making it difficult to extrapolate findings from one VOC on other phases of the pandemic. Furthermore, differences in demographic factors, underlying health status, vaccination status, and previous exposure among patients, as well as available treatment and non-pharmaceutical interventions, need to be considered for a meaningful comparison.

2.3.2 Preventive measures

COVID-19 vaccination is considered the most effective public health intervention against SARS-CoV-2 infections, followed by NPIs [66]. The first COVID-19 vaccine delivered outside of a clinical trial setting was on 8 December 2020, when a 90-year-old woman in England received the Pfizer/BioNTech messenger RNA (mRNA) vaccine [67]. Out of the currently six authorized vaccines in the EU, two are mRNA vaccines (Comirnaty by Pfizer/BioNTech and Spikevax by Moderna), two are adenovirus-based (Vaxzevria by AstraZeneca and Jcovden by Janssen Pharmaceutica NV), one is protein-based (Nuvaxovid by Novavax), and one is inactivated virus-based (COVID-19 vaccine Valneva by Valneva) [43]. Currently in Sweden, the mRNA vaccines from Pfizer/BioNTech and Moderna are used almost exclusively. Besides the inequitable vaccine distribution described in section 2.2, other challenges include vaccine hesitancy, waning immunity, and viral variants partially escaping antibodies [68]. Regarding the problem with viral variants, studies have shown that the currently available vaccines are less effective at blocking infection with the omicron variant when compared with previous variants [68]. Importantly, however, studies have repeatedly shown that these vaccines protect against

severe disease outcomes also from omicron infections [69–71]. Various NPIs have been implemented and recommended to prevent and control SARS-CoV-2 transmission throughout the pandemic, including but not limited to physical distancing, use of face masks, limitation of number of individuals at gatherings, working from home when possible, and closure of businesses, schools and educational settings [66]. The effectiveness of these NPIs seems to be dynamic in time and different countries have throughout the pandemic implemented different NPIs at different times and in different orders [72,73].

2.4 COVID-19

2.4.1 Clinical presentation

An infection caused by SARS-CoV-2 can range from being completely asymptomatic to fatal. As with most infections, several host factors, viral factors, and environmental factors seem to influence the severity of the SARS-CoV-2 infection. This includes for instance age, sex, several comorbidities, ethnicity, socioeconomic status, COVID-19 vaccination status and previous infection, SARS-CoV-2 variant, poverty and crowding, and air pollution [74–77,47,78,79].

The true proportion of individuals who experience a completely asymptomatic infection is difficult to estimate. Furthermore, the proportion who later develops a symptomatic infection among those testing positive for SARS-CoV-2 without symptoms is not fully understood. A meta-analysis including more than 350 studies estimated the percentage of completely asymptomatic infections to be 35.1% (95% CI: 30.7-39.9%) [80]. Another meta-analysis found a pooled percentage of asymptomatic infection among those testing positive for SARS-CoV-2 to be 40.50% (95% CI: 33.50-47.50%) [81]. Collectively, these two meta-analyses indicate that asymptomatic infections are rather prevalent.

Among those individuals who develop symptomatic COVID-19, common symptoms include fever, cough, sore throat, fatigue, dyspnoea, tachypnoea, malaise, headache, myalgia, ageusia, anosmia, nausea and vomiting, and diarrhoea [74]. Importantly, the symptoms can vary significantly with age and sex [82]. The mean incubation period of COVID-19 has been estimated to around 6 days [83], but this seems to have varied between different strains with shorter incubation period for the omicron variant [84]. The WHO classifies COVID-19 into mild, moderate, severe, and critical COVID-19. It is estimated that around 40% of symptomatic patients develop mild disease, 40% develop moderate disease, 15% develop severe disease, and 5% develop critical disease [74]. However, such proportions are subject to fluctuations depending on circulating SARS-CoV-2 variants, surveillance strategies, available therapies, COVID-19 vaccination status etc. The main features of the WHO COVID-19 severity classification are outlined in table 1.

Severity	Definition
Mild disease	- SARS-CoV-2 positive nucleic acid amplification test (NAAT) or rapid diagnostic test (RDT)

	-	Symptoms such as fever, cough, fatigue, anorexia, shortness of breath, myalgias, sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, anosmia, ageusia
	-	No evidence of viral pneumonia or hypoxia
Moderate disease	-	SARS-CoV-2 positive NAAT or RDT
	-	Clinical signs of pneumonia, including fever, cough, dyspnoea, and fast breathing.
	-	No signs of severe pneumonia and a peripheral arterial oxygen saturation ≥90% on room air.
Severe disease	-	SARS-CoV-2 positive NAAT or RDT
	-	Clinical signs of pneumonia, including fever, cough, and dyspnoea
	-	One of the following: Respiratory rate >30 breaths/min Severe respiratory distress Peripheral arterial oxygen <90% on room air
Critical disease	-	SARS-CoV-2 positive NAAT or RDT
	-	Acute respiratory distress syndrome (ARDS), sepsis, septic shock, or acute thrombosis

Table 1. Summary of the WHO COVID-19 disease severity classification. The table is based on table 6.3 from the living guidelines on clinical management of COVID-19 from the WHO [74]. For complete definitions, including severity classifications for children, please refer to the report.

As described in table 1, individuals with moderate or more severe forms of COVID-19 show evidence of lower respiratory disease, pneumonia, during the clinical assessment. Such distinguishing features includes dyspnoea, tachypnoea, hypoxia, and presence of pulmonary infiltrates upon medical imaging. Since moderate COVID-19 can progress rapidly to more severe forms, such patients should be closely monitored in an inpatient setting[85]. In contrast to patients admitted to hospital with other forms of viral pneumonia, caused by for instance influenza viruses and respiratory syncytial virus (RSV), patients with COVID-19 rarely seem to present with a bacterial co-infection upon hospital admission [86,87]. Reasons for such discrepancies remain to be understood.

Severe COVID-19 typically begins approximately one week after symptom onset, often with progressing hypoxaemia, dyspnoea, and respiratory failure [88]. Patients with more severe forms of COVID-19 usually show signs of hyperinflammation and immune dysregulation, with increased levels of pro-inflammatory cytokines and inflammatory markers [88–90]. In the most severe cases of COVID-19, the disease progresses to ARDS, a severe and life-threatening condition which before the emergence of COVID-19 has been associated with mortality rates exceeding 35% [91]. According to diagnostic criteria, the so called Berlin definition, ARDS is defined as an acute hypoxemic respiratory failure following an acute event that presents as bilateral pulmonary infiltrates in the absence of a purely cardiogenic or hydrostatic aetiology

[92]. Autopsies have found diffuse alveolar damage, which refers to injury to the alveolar capillary endothelium and cell lining with oedema, inflammation, and fibrosis, to be the predominant pattern of lung injury in deceased COVID-19 patients [93]. Whilst several studies have described the clinical pathology of COVID-19, our understanding of the mechanisms giving rise to such pathological processes are still poorly understood as reviewed by Lamers et Haagmans [88].

2.4.2 Acute outcomes

Several acute clinical outcomes of COVID-19 have been observed and reported throughout the pandemic. This section focuses on outcomes evaluated in the studies of this thesis.

2.4.2.1 Mortality

The reported infection-fatality ratios (IFR) for COVID-19 have varied substantially depending on population age structure, geography, and time periods of the pandemic. A comprehensive study estimating global patterns of COVID-19 IFRs from 15 April 2020 to 1 January 2021 reported an IFR of 0.06% for individuals aged 30 years, 0.18% for 40 years, 0.43% for 50 years, 1.00% for 60 years, 2.89% for 70 years, 8.01% for 80 years, and 20% for 90 years [94]. The study period covered a pre-vaccination period when the primary SARS-CoV-2 strain was the dominant strain, and as such it is difficult to extrapolate these numbers to the current pandemic situation with several effective vaccines and treatments available and a less severe SARS-CoV-2 variant. As for the omicron variant, Nyberg et al. observed a 28-day mortality rate of 0.83% among individuals aged 70-79 years, and 5.12% among individuals aged 80 years or older in England [64]. The corresponding proportions were for delta infected individuals 4.95% and 15.9%, respectively. Regarding hospitalized patients, a nationwide Swedish study observed a 17.2% 60-day mortality rate in patient hospitalized with COVID-19 between1 March and 30 September 2020 [95]. A study of more than 500,000 patients hospitalized with COVID-19 in Germany during a period from January 2020 to December 2021 observed an overall in-hospital mortality rate of around 17% [96]. Further, another study in the US observed a 15.1% in-hospital mortality rate for patients hospitalized primarily for COVID-19 during the delta period and 4.9% for the omicron period [97]. Collectively, COVID-19 mortality rates have differed extensively across different time periods and age groups.

2.4.2.2 Intensive care treatment

Just as with mortality, the proportion of COVID-19 patients undergoing intensive care treatment has varied between countries and different time periods of the pandemic. In Sweden, the weekly number of new COVID-19-associated ICU-admissions per 100,000 population has ranged from 0.00 to 2.78 throughout the pandemic, with the highest rates in April 2020 [98]. Among hospitalized COVID-19 patients, the proportion of patients admitted to the ICU has varied from below 10% to above 30% [99–102]. Several factors are likely to contribute to such varying proportions, including underlying health status of hospitalized patients, resource availability, number of beds and the occupancy in the ICU, and routines implemented for limitation of life-sustaining treatments (LLST) [103,104].

Regarding the use of mechanical ventilation, an integral part of intensive care treatment, highly varying proportions have been reported, ranging from around 30% to 90% of ICU-admitted patients [105]. It has become evident that both the length of the ICU-stay and the length of the mechanical ventilation are prolonged among patients with COVID-19 critical illness versus non-COVID-19 critical illness [106–108]. Reported durations of mechanical ventilation in COVID-19 patients have often approached or exceeded two weeks [109–111]. However, durations of mechanical ventilation throughout the pandemic might have varied depending on several factors such as provided treatments. In a randomized clinical trial (RCT) of 299 COVID-19 ARDS patients in 41 ICUs in Brazil, intravenous dexamethasone combined with standard care compared with standard care alone increased the number of ventilator-free days over an assessment period of 28 days (6.6 compared with 4.0 ventilator-free days) [112]. Mechanical ventilation has been described as a "necessary evil" due to its lifesaving potential but important potential complications [113]. Such complications include ventilator-induced lung injury and ventilator-associated lower respiratory tract infections (VA-LRTI). The term VA-LRTI includes both ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) [114]. The clinical and radiological distinction between VAT and VAP is often not straightforward, with VAT thought of as a distinct condition on a continuum between colonization of the lower respiratory tract and VAP [115]. Several studies have observed an increased risk of VAP or VA-LRTI in patients with COVID-19 [109,110,116–119]. However, there is a considerable overlap between the clinical and radiological manifestations of VAP and COVID-19 critical illness, including high fevers, leukocytosis, and extensive radiographic infiltrates, which makes the diagnosis of VAP more difficult in COVID-19 patients [120].

2.4.2.3 Venous thromboembolism

Several studies have demonstrated associations between COVID-19 and venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE) [121–125]. Reasons for such thrombotic disease seems to include excessive inflammation, platelet activation, and endothelial dysfunction implicated in COVID-19 [122]. In a self-controlled case series and matched cohort study including more than 1 million people testing positive for SARS-CoV-2 between February 2020 and May 2021 in Sweden, the overall absolute risk of a PE days 1 to 30 after COVID-19 was 0.17%, compared with 0.004% among matched controls [124]. The risks were increased among patients with comorbidities, patients with more severe COVID-19, and during the first wave of the pandemic when compared with the second and third waves.

2.4.2.4 Acute kidney injury

Studies have reported that up to 30-50% of patients hospitalized with COVID-19 develop some form of acute kidney injury (AKI) as reviewed by Legrand et al [126]. In a UK study of around 1,250 patients hospitalized with COVID-19, 39% experienced AKI, with AKI being a strong predictor of 30-day mortality [127]. This was also observed in a UK prospective multicentre cohort study of more than 80,000 patients hospitalized with COVID-19 between January and December 2020 [128]. Further, when compared with influenza, patients hospitalized with

COVID-19 have been observed to have an increased risk of AKI [129–132]. The underlying pathophysiological features of COVID-19 related AKI remain to be better understood, but seem to involve inflammatory, immunological, endothelial, and hormonal perturbations [126].

2.4.2.5 Acute myocardial injury

Cardiac manifestations and outcomes have been commonly reported in patients hospitalized with COVID-19 [133–135]. One such outcome includes acute myocardial injury, with definitions often including markers of myocardial necrosis and imaging methods [136–139]. The cardiac-specific troponin T and troponin I, are biomarkers mainly used for diagnosis of acute myocardial infarction, which are often elevated in patients hospitalized with COVID-19 [139–141]. Reasons for such elevations are not fully understood, but might include severe hypoxia, systemic inflammation, pulmonary embolism, cardiomyopathy, myocarditis, as well as concomitant myocardial infarction or renal failure [142].

2.4.2.6 Healthcare-associated infections

The delivery of both outpatient care and inpatient care has been significantly disrupted during the pandemic [143]. Several studies have reported an increased occurrence of healthcare-associated infections (HAIs) during the pandemic, including but not limited to bloodstream infections (BSIs), catheter-associated urinary tract infections, central-line associated BSIs, and hospital-onset bacteraemia (HOB) [144–148]. Reasons for this has seemed to be primarily driven by patients hospitalized with COVID-19, but underlying mechanisms are probably multifactorial.

2.4.3 Treatment

This section is not a comprehensive overview of all medications available for treatment of COVID-19, but rather a summary of some of the most commonly used treatments. For more comprehensive information, please refer to local or national guidelines as well as living guidelines from the WHO [149–151].

2.4.3.1 Respiratory support

Low arterial oxygenation is a fundamental feature of severe COVID-19 and as such, supplement oxygen therapy constitutes an indispensable part of the treatment of patients with severe COVID-19 [152]. Current guidelines from the WHO states that supplemental oxygen therapy should be used to target SpO2 $\geq$94% in patients with emergency signs and SpO2 >90% in patients without emergency signs and with stable hypoxemia [74]. The oxygen can be administered in several different ways, including nasal cannula, masks, high flow nasal oxygen, non-invasive ventilation, and invasive mechanical ventilation. There are different indications to the use of all these modes of oxygenation which are beyond the scope of this summary. Besides supplemental oxygen, respiratory support can be facilitated by physiotherapy, including for instance prone positioning, which has been investigated in clinical trials both before and during the pandemic [153].

2.4.3.2 Antiviral therapy

Antiviral therapy refers to therapeutic control of a viral infection and can involve virtually all aspects of the viral life cycle. As for SARS-CoV-2 antiviral therapy, this includes preventing viral cell entry, RNA replication, and cleavage of viral polyprotein [150]. Currently, four monoclonal antibody (mAb) drugs preventing viral cell entry are authorized for use in the EU by the EMA: tixagevimab/cilgavimab (Evusheld), regdanvimab (Regkirona), casirivimab/imdevimab (Ronapreve), and sotrovimab (Xevudy) [42]. The term monoclonal refers to that only one single epitope on an antigen is recognized by such antibodies. All four drugs have been designed to target epitopes on the S protein. Certain criteria are used to assess whether treatment with mAbs is indicated, including for example time since symptom-onset, vaccination status, presence of immunocompromising conditions, and risk of severe disease [149,154]. Another drug, remdesivir (Veklury), is a nucleoside analog that inhibits the SARS-CoV-2 RNA-dependent RNA polymerase. The molecule was however first developed during the search for a cure of hepatitis C virus, then being repurposed for COVID-19 treatment [155]. The WHO first suggested against the use of remdesivir in patients with COVID-19, but now recommends it in mild or moderate COVID-19 patients who are at high risk of hospitalization, and currently reviews its potential indications in severe or critical COVID-19 [149]. A systematic review and meta-analysis including eight randomized trials with around 11,000 patients found it likely that remdesivir reduces mortality for nonventilated patients with COVID-19 requiring supplemental oxygen therapy [156]. Nirmatrelvir/ritonavir (Paxlovid) is a combination of nirmatrelvir, first developed against SARS-CoV, and the HIV drug ritonavir that slows down the breakdown of nirmatrelvir [149]. It works by inhibiting the Mpro, an enzyme with a pivotal role in viral replication and transcription of SARS-CoV-2 [157]. Treatment of symptomatic COVID-19 with nirmatrelvir/ritonavir was shown to result in an 89% lower risk of progression to severe COVID-19 when compared with placebo [158]. This study was however conducted before the emergence of the omicron VOC, but a large retrospective cohort study from Israel has later shown that nirmatrelvir/ritonavir reduced the risk of severe COVID-19 in patients infected with the omicron variant as well [159].

2.4.3.3 Immunomodulating therapy

As mentioned previously, more severe forms of COVID-19 are typically marked by immune dysregulation and increased inflammatory processes and coagulation. Accordingly, various immunomodulatory substances are used in the treatment of severe COVID-19, including corticosteroids, interleukin inhibitors, and Janus kinase inhibitors. RCTs have demonstrated that systemic corticosteroids reduces mortality in patients hospitalized with more severe forms of COVID-19 requiring supplemental oxygen, particularly when given more than seven days after the onset of symptoms [160–162]. IL-6 is often elevated in patients with COVID-19 and have been found to be predictive of severe COVID-19 [88,163]. Tocilizumab (RoActemra) is an IL-6 inhibitor that is used for treatment of rheumatoid arthritis and other conditions. Tocilizumab was authorized for use in adult COVID-19 patients receiving systemic corticosteroids and supplemental oxygen therapy or mechanical ventilation by the EMA in December 2021 [164]. A meta-analysis including around 11,000 hospitalized patients from 27 trials found tocilizumab

to be associated with a lower 28-day all-cause mortality when compared with usual care or placebo [165].

2.4.3.4 Anticoagulation therapy

Early on during the pandemic, it became evident that thrombotic events occurred in patients hospitalized with COVID-19, despite the use of prophylactic low-molecular weight heparin [166]. As such, studies have been conducted to evaluate whether higher doses or longer treatment durations reduce the risk of thrombotic events. As commented by Bradbury et McQuilten, it has been demonstrated that the efficacy of antithrombotic treatment depends on both timing in relation to illness severity and dose [167]. Furthermore, it has been argued that more up-to-date studies with data on SARS-CoV-2 variants is needed to better understand which patient groups benefit from anticoagulation therapy during hospitalization with COVID-19 [168].

2.4.3.5 Antibiotic therapy

Evidence from a rapid living review and meta-analysis, currently encompassing 148 studies, indicates that bacterial co-infections is rare among patients admitted to the hospital with COVID-19, with a pooled prevalence of 5.3% (95% CI: 3.8-7.4%) [169]. In accordance with this, the treatment guidelines from the WHO recommends that antibiotics should not be given to COVID-19 patients as standard of care upon hospital admission, unless there is a strong clinical suspicion of a bacterial infection [74]. Similarly, Swedish COVID-19 treatment guidelines recommends that broad-spectrum antibiotics, primarily Cefotaxime, should only be considered for patients with severe COVID-19 where a bacterial co-infection is suspected [151]. Furthermore, these recommendations state that the antibiotic often can be withdrawn if cultures turn out negative, even if C-reactive protein (CRP) levels are high, often caused by the actual COVID-19 disease.

2.4.4 Post-acute and long-term outcomes

Whilst the majority of people who develop COVID-19 fully recover, it is estimated that approximately 10-20% continue to experience post-acute and long-term symptoms and effects according to the WHO [170]. The terminology to describe such effects has varied considerably, including long COVID, post-acute sequelae of COVID-19 (PASC), post-acute COVID-19 syndrome (PACS), and post COVID-19 condition (PCC) [171–173]. PASC most often refer to more organ-specific direct effects of the virus, whereas PCC refers to a much wider range of physical, psychological, and cognitive symptoms [174]. Estimates of the occurrence of PCC have ranged from well below 10% to above 50% in studies [175]. This could most probably, as summarized in figure 5, to a large extent be explained by substantial differences in study populations, assessment periods, and definitions used.

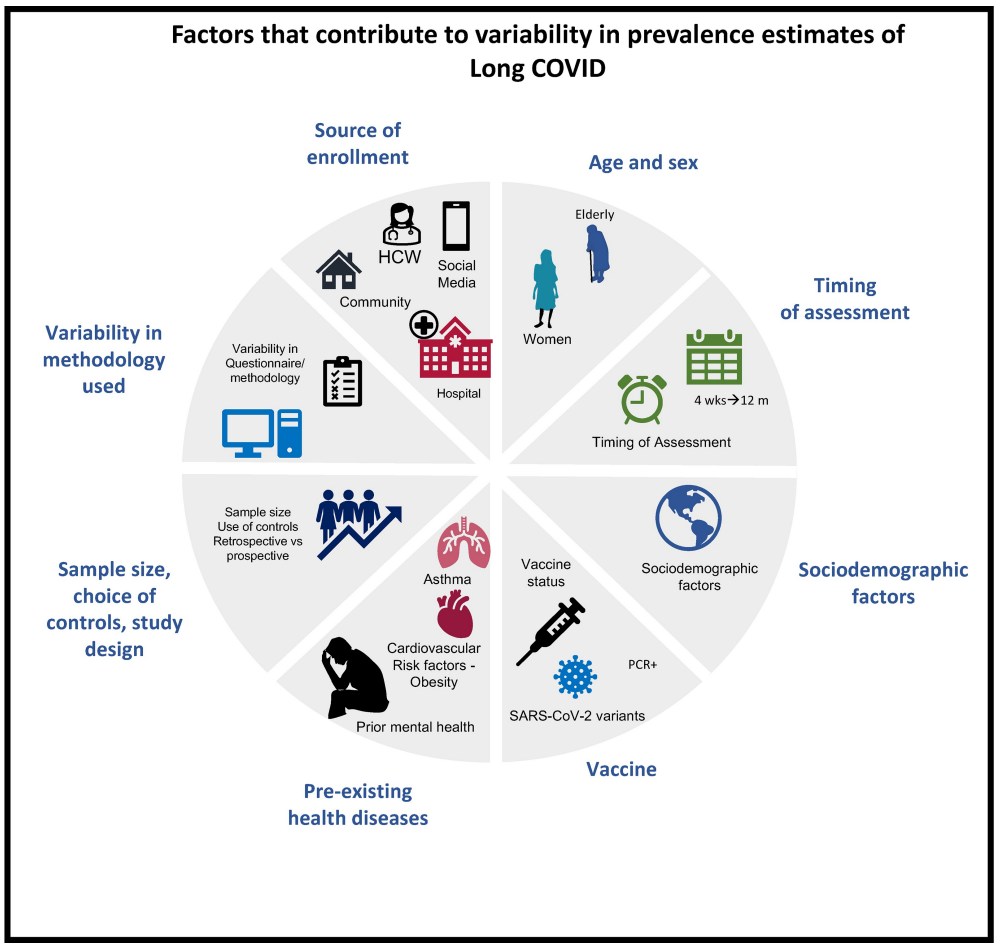

Figure 5. Factors that contribute to variability in prevalence estimates of PCC. The pie chart is divided into eight different groups of factors influencing prevalence estimates of PCC. The figure was reprinted from Raman et al. 2022 [175], distributed under a Creative Commons Attribution 4.0 International license (CC BY 4.0).

Post-acute and long-term effects from several different organ systems have been described, including but not limited to respiratory, cardiovascular, endocrine, neurological, renal, and mental health outcomes [176–188]. Many studies reporting an increased risk of such effects have been based on cohorts of White male veterans from the US, possibly limiting the generalizability of such findings to entire population settings[182–188]. The risk of developing various organ-specific sequelae seems to differ depending on the severity of the acute infection. In a study of 181,384 US veterans with COVID-19, the burden of PASC was estimated to around 4.5% in non-hospitalized individuals, 22% in hospitalized individuals and 36% in ICU-treated individuals [182]. Furthermore, in a cohort study including around 250,000 individuals, the COVID-19 illness severity was observed to be associated with mental morbidities up to 16 month after COVID-19 diagnosis [181]. In a Danish population-based cohort study of around 9,000 SARS-CoV-2 positive individuals not requiring hospital admission compared with SARS-CoV-2 negative controls, no difference was observed in the risk of initiating 12 out of 15 assessed medications, and receiving 25 out of 27 assessed hospital diagnoses two weeks to six months after the SARS-CoV-2 PCR test [189]. Further, in a Dutch study of more than 200 patients discharged alive from a COVID-19 critical illness episode, 74% reported physical

symptoms, 26% mental symptoms, and 16% cognitive symptoms one year later [190]. However, the occurrence of long-term physical, cognitive or mental health impairments persisting beyond intensive care treatment, known as post-intensive care syndrome (PICS), has been reported to exceed 50% well before the emergence of COVID-19 [191]. What possibly distinguishes PCC from PICS is to date not fully understood [192].

An international classification of disease 10th revision (ICD-10) code for PCC was issued by the WHO in September 2020 [193]. Around one year later, in October 2021, a clinical case definition of PCC was released by the WHO, stating "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time." [194]. Besides fatigue, shortness of breath, and cognitive dysfunction mentioned in the definition, 22 other groups of symptoms are also mentioned in the clinical case definition, as summarized in figure 6 below.

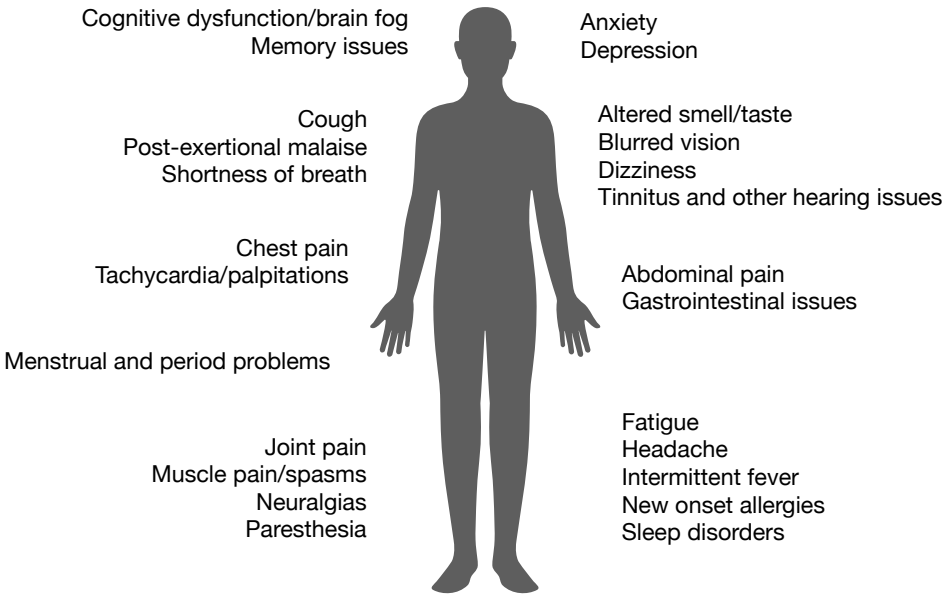

Figure 6. Symptoms included in the WHO clinical case definition of PCC.

A large body of literature has been published on long-term effects of COVID-19 well before both an ICD-10 diagnosis code and a clinical case definition was available. As such, comparison of different estimates before and after the introduction of the diagnosis code and clinical case definition might be difficult. A recent international consensus study defined a core outcome set of twelve outcomes to be measured in adults living with PCC in clinical research and practice settings [195]. This includes cardiovascular effects, fatigue or exhaustion, pain,

cognitive effects, mental effects, physical functioning, occupational changes, survival, and recovery.

Importantly, the risk of long-term effects and PCC might differ between different SARS-CoV-2 variants. In a UK study making use of self-reported data from the COVID Symptom Study app, the proportion of study participants experiencing PCC was 4.5% among omicron cases and 10.8% among delta cases [196]. The observed odds ratios (ORs) of PCC with the omicron versus delta variant ranged from 0.25 to 0.50 depending on age and time since vaccination. Furthermore, COVID-19 vaccination might reduce the risk of PCC following an infection. In an observational cohort study of around 28,000 participants aged 18 to 69 years in the UK, COVID-19 vaccination reduced the odds of PCC symptoms [197]. A decreased prevalence of PCC was also observed among health care workers with COVID-19 not requiring hospitalization who were vaccinated with two or three doses of vaccine compared with no vaccination [198]. However, more studies with longer follow-up times are needed to better understand the potential reduction in the population health burden of PCC attributed to COVID-19 vaccines.

Regarding treatment of PCC, the Swedish Agency for Health Technology Assessment and Assessment of Social Services was commissioned by the Swedish Government to evaluate which treatments are effective for PCC [199]. Out of 24,729 screened abstracts, 536 articles were screened in full, and 19 articles were found to include treatment and rehabilitation of PCC, of which eight articles had a high risk of bias. Of the remaining eleven articles, zero were found to have low risk of bias, and it was concluded that by 1 June 2022, the scientific basis for treatments of PCC had very low reliability.

2.5 OTHER RESPIRATORY VIRUS INFECTIONS

Since a particular emphasis is placed on comparisons of COVID-19 with other respiratory virus infections in this thesis, characteristics of such infections, in particular influenza and RSV infection, are described below.

2.5.1 Influenza

Influenza viruses belong to the family *Orthomyxoviridae* and are divided into four types (A-D) depending on antigenic differences in core proteins [200]. Influenza viruses infect humans and animals such as horses, cats, birds, and pigs. Influenza in humans is caused by influenza A and influenza B viruses, whereas influenza C and influenza D viruses do not seem to cause substantial disease [201]. Influenza viruses are enveloped viruses with a negative-sense (3'-5'), single-stranded segmented RNA genome of around half the size (~14 kB) of SARS-CoV-2 [202].

Influenza viruses circulate in all parts of the world and primarily cause annual seasonal epidemics usually occurring from November to April in the Northern hemisphere and from June to October in the Southern hemisphere [203]. Four pandemics of human influenza have occurred in the past 100 years: the 1918 (H1N1), 1957-1958 (H2N2), 1968 (H3N2), and 2009

(H1N1) pandemics. The 1918 (H1N1) pandemic, often referred to as the 'Spanish flu', infected an estimated 500 million people worldwide and caused approximately 50 million deaths [204].

Regarding the annual burden of seasonal epidemics of influenza, estimates are dependent on factors such as characteristics of the circulating virus strains and immunity in the population. A previous modelling-based study estimated the global seasonal influenza epidemics to result in approximately 290,000 to 650,000 respiratory deaths each year between 1999 and 2015 [205]. The Global Burden of Disease Study estimated around 55 million lower respiratory tract infections attributable to influenza in 2017 with around 100,000-200,000 deaths .

Estimates of the fraction of asymptomatic influenza have varied considerably, partly due to differences in study design, and definition of infection and symptomatic illness [207]. A cohort study of seasonal and pandemic influenza in England from 2006 to 2011 found up to 75% of infections to be asymptomatic [208]. Uncomplicated seasonal influenza normally presents with a rapid onset of symptoms such as fever, headache, cough, sore throat, myalgia, fatigue, and malaise. As with COVID-19, a combination of factors influences the severity of influenza. This includes age, underlying health status, pathogenicity of the influenza strain, and influenza vaccination status [209]. Furthermore, bacterial co-infections are rather prevalent in patients with influenza, associated with increases in hospital admissions, more severe symptoms, and increases in mortality [210].

According to data on around 10% of the US population, 40-50% of all influenza-associated hospitalizations from the influenza season 2017-2018 and onwards were from individuals aged 65 years or older [211]. A study of the 2017-2018 influenza season found approximately 10% of all hospitalized cases of influenza to result in ICU-admission, need for mechanical ventilation, or death [212]. A study including around 1,300 patients hospitalized with influenza in 2018 or 2019 observed a 3% in-hospital mortality [213]. The same crude in-hospital mortality rate was also observed in a study including 27,870 patients hospitalized with influenza in 2017-2020 [214]. In a French nationwide cohort study including 45,819 patients hospitalized with influenza observed, 5% had acute kidney failure, 1% had myocardial infarction, and 1% had pulmonary embolism [100]. Furthermore, a self-controlled case-series study of 364 hospitalizations for acute myocardial infarction in Canada, found a significant association between respiratory infections, in particular influenza, and acute myocardial infarction [215].

The literature on long-term outcomes following influenza is not as extensive as for COVID-19. Long-term pulmonary dysfunction, lung abnormalities, and psychological impairment have been observed in survivors of A(H7N9) infection [216,217]. Furthermore, a study of one-year outcomes in survivors of A(H1N1)-associated ARDS observed lung disabilities, psychologic impairment, and poorer health-related quality of life compared with an age- and sex-matched general population group [218]. In a Norwegian study investigating the effect of pandemic influenza and pandemic influenza vaccine on myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) found A(H1N1) infection to be associated with a more than two-fold increased risk of ME/CFS [219].

2.5.2 RSV infection

RSV belongs to the *Pneumoviridae* family, with two major subtypes of human RSV (A and B). RSV have a negative-sense, single-stranded non-segmented RNA genome, encoding for eleven proteins [220]. The virus can cause more substantial infections of the lungs and respiratory tract in infants, immunocompromised, and the elderly. RSV infection is so common that most children have been infected by the age of two years [221]. However, immunity from RSV infection is incomplete, and RSV reinfections are relatively common in both children and adults [220]. The infection is estimated to cause between 55,000 and 200,000 deaths in children under the age of five years and the most serious infections are typically seen in infants less than one year of age in low-income countries [222]. Both the seasonality and the clinical presentation of RSV infection overlaps with those of other respiratory virus infections [109]. Despite being more common in children, RSV infection can be dangerous for adults as well, in particular those aged 65 years or older and those with immunosuppression or chronic heart or lung disease. In the United States, it is estimated that more than 175,000 older adults are hospitalized with RSV infection, of which around 8% die [223]. Previous studies have shown that hospitalizations due to RSV infection often is complicated by cardiovascular events such as worsening heart failure, acute coronary syndrome, and arrythmias [224].

2.5.3 Other infections

Besides SARS-CoV-2, influenza viruses, and RSV, several other viruses can cause respiratory infections, including but not limited to adenovirus, bocavirus, enterovirus, metapneumovirus, parainfluenza viruses, rhinovirus, and seasonal coronaviruses [225]. Adenovirus and bocavirus are DNA viruses, whereas the others are RNA viruses. Whilst most of these viruses typically cause mild and self-limiting infections, children, elderly, people with underlying comorbidities, and individuals with immunocompromising conditions can be more severely affected [226]. Just as with influenza viruses and RSV, many of these other exhibit seasonality on the Northern Hemisphere.

2.6 NON-COVID CARE DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has also exerted a great impact on several aspects of non-COVID care. A Danish population based cohort study found hospital admissions for all major non-COVID-19 disease groups to decrease during periods of national lockdowns when compared with a prepandemic baseline period [227]. Similarly, a study set in north west London observed a 35% decrease in emergency department attendances during the first months of the pandemic [228]. Interestingly, this decrease was primarily amongst individuals aged less than 65 years and individuals arriving by their own means, possibly related to emergency department avoidance behaviors. Furthermore in England, at the end of November 2020 around 190,000 patients had been waiting more than one year for planned surgery, compared with around 1,400 patients the same month in 2019 [229]. Another study of around 8.5 million admissions to more than 4,500 hospitals in the US during and before the pandemic, observed an elevation in 30-day mortality rates for non-COVID-19 diagnoses throughout 2020 and 2021 [230]. On a similar note, a Brazilian cohort study found the outcomes of non-COVID-19 critically ill patients to worsen during the

pandemic in 2020 when compared with a prepandemic baseline period [231]. Furthermore, a recent report demonstrated that an increased non-COVID-19-related mortality in people with diabetes in England was associated with a reduction in diabetes care following the pandemic onset in 2020 [232]. Such excess mortality is most probably not only observed for diabetes patients and more research is needed to understand what groups have been particularly affected by the disruptions of non-COVID services.

2.7 LACK OF KNOWLEDGE AND RATIONALE FOR THE STUDIES

At the time of conception and planning of the studies included in this thesis, several important clinical and scientific questions regarding COVID-19 remained partly or fully unanswered. Due to the fast-evolving evidence on different aspects of COVID-19 epidemiology, the studies were adapted accordingly.

Study I was planned in early July 2020, roughly three to four months into the pandemic. By then, around 20,000 cases and 2,300 deaths had been reported to the Public Health Agency of Sweden [21]. We considered it likely for a second wave of the pandemic to emerge during the fall and winter months, possibly coinciding with an epidemic of influenza or other respiratory virus infections. As such, it was considered important to understand similarities and differences in clinical presentation and outcomes of COVID-19 compared with such other respiratory virus infections.

Study II was planned in February 2021, after the second wave in Stockholm and Sweden. It was not understood to what extent SARS-CoV-2 caused pneumonia by itself or by acting in conjunction with other bacterial pathogens as is commonly seen in other respiratory virus infections [86]. This was considered important to guide microbiological testing strategies, and more importantly, facilitate antibiotic stewardship among patients hospitalized with COVID-19. This was further motivated by an by then observed mismatch between an extensive use of broad-spectrum antibiotic agents and a rather low prevalence of reported bacterial co-infections in previous reports [87,233].

Study III was planned in January 2021. Early on during the pandemic, it was evident that COVID-19 caused a surge in number of patients in need of both intensive care treatment and mechanical ventilation. As mentioned previously, mechanical ventilation is a life-saving procedure associated with complications such as infections and injuries. As described in section 2.4.2.2, several studies conducted during the first months of the pandemic had shown an increased risk of VAP in COVID-19. Given the major changes in clinical management of COVID-19 throughout the pandemic, including increased use of steroids, anticoagulants, and prone positioning, we considered it important to investigate the occurrence of VA-LRTI during a longer time period of the pandemic and to take duration of mechanical ventilation into account.

Study IV was planned in May 2021. After more than one year since the emergence of the COVID-19 pandemic, it was evident that an unprecedented strain had been put on healthcare systems and healthcare workers throughout the world. However, the consequences this had had

on the quality of the provided care in entire hospital settings were not well understood, including its effect on HAIs. As such, we considered it important to investigate the effect the pandemic had exerted on the incidence and mortality of HOB. This HAI was chosen since it had been suggested to function as an important quality measure for provided care and covered both CLABSI and bacteraemia secondary to other HAIs [234].

Both studies V and VI were planned during the summer months in 2021. After more than one year of the COVID-19 pandemic, it was clear that the effects of COVID-19 were not confined to the acute infection, with several post-acute and long-term sequelae being reported. This included a wide range of symptoms and effects from multiple organ systems, referred to as PCC, with the PCC diagnosis code issued in September 2020. We considered it important to understand the population-based occurrence of the PCC diagnosis and its associated factors and healthcare utilization. Survivors of intensive care treatment were already known to frequently suffer from long-term physical, psychological, and cognitive impairments [191]. With improved clinical management of COVID-19 and a substantial proportion of patients surviving COVID-19 critical illness, we considered it important to understand the long-term health trajectories in survivors of COVID-19 versus non-COVID-19 critical illness, potentially facilitating planning of follow-up strategies in the healthcare system.

3 AIMS

The overarching aim was to characterize the clinical presentation and outcomes in adult patients hospitalized with COVID-19 and compare these with other respiratory virus infections and hospital populations. Specific aims of each constituent study are listed below.

Study I

- Investigate differences in baseline characteristics, clinical presentation, and outcomes for adult and paediatric patients hospitalized with COVID-19 compared with other respiratory virus infections.

Study II

- Investigate the prevalence of bacterial co-infections in patients with SARS-CoV-2 compared with influenza or RSV positive community-acquired pneumonia (CAP) upon hospital admission.
- Compare co-infection testing rates, positivity rates, and the use of antibiotics at admission in the three virus cohorts.
- Compare clinical outcomes in patients with and without a detected bacterial co-infection.
- Assess the capacity of models with and without inflammatory markers to discriminate bacterial co-infections in the SARS-CoV-2 cohort.

Study III

- Investigate the occurrence of microbiologically defined bacterial VA-LRTI among mechanically ventilated COVID-19 versus non-COVID-19 patients.

Study IV

- Compare the incidence of HOB as well as the 30-day mortality of HOB in patients hospitalized with COVID-19 and patients hospitalized without COVID-19 both before and during the pandemic.

Study V

- Investigate one-year mortality in patients admitted to the ICU with versus without COVID-19.
- Compare the number of days alive and free from hospitalization during one year in patients discharged alive from the ICU-associated hospitalization.
- Assess reasons for hospitalizations during one year in patients discharged alive from the ICU-associated hospitalization.

Study VI

- Investigate the occurrence of PCC diagnosis among patients with a verified SARS-CoV-2 infection, stratified by severity of acute infection.
- Investigate health status factors associated with getting a PCC diagnosis.
- Investigate the healthcare utilization in individuals with and without a PCC diagnosis.

4 MATERIALS AND METHODS

This chapter describes methodological considerations for the six studies included in this thesis. Table 2 provides a methodological overview of the studies. For more detailed information, please refer to the methods sections of the studies attached at the end of this thesis.

4.1 ETHICAL APPROVALS AND CONSIDERATIONS

All studies in this thesis were approved by the Regional Ethical Review Board in Stockholm (registration number 2018/1030-31), with two COVID-19-related research amendments approved by the Swedish Ethical Review Board (registration numbers 2020-01385 and 2020-02145).

All studies were performed in accordance with the ethical principles laid down in the Declaration of Helsinki [235]. The need for informed consent from study subjects was waived since analyses were based on retrospectively collected data from EHR systems and administrative health registries. Requirements to request informed consent in registry-based research has been suggested to lead to selection bias in large-scale observational research [236]. However, careful consideration of whether potential benefits exceed the breach of integrity is warranted. The investigators followed the rules for handling of personal information as mandated by Karolinska Institutet. All data used in this thesis were pseudonymized, and none of the researchers had access to the code keys, which were stored at the IT department at Karolinska University Hospital (KUH) in Stockholm, Sweden. All researchers signed confidentiality agreements prior to conducting any research and all study analyses were performed in a database environment stored on a server at KUH, accessed through a virtual private network. Only variables relevant for each constituent study were collected and the results were only presented at a group level. The studies had no impact on the care that individual participants were receiving, and all studies were considered to provide important knowledge on the clinical epidemiology of COVID-19. Collectively, we considered the benefits of all studies to exceed any potential harm.

4.2 STUDY SETTINGS

All studies were set in Stockholm Region, Sweden. The main emphasis was put on an inpatient setting, with five out of six studies restricted to hospitalized COVID-19 and non-COVID-19 patients. Only study VI included SARS-CoV-2 infections not leading to hospital admission as well. Stockholm Region has a population of 2.4 million inhabitants (more than 20% of Sweden's total population), served by six acute care hospitals. The largest of these six hospitals, KUH, is one of the largest university hospitals in Europe with more than 85,000 yearly admissions divided between two sites: Solna and Huddinge [237]. Studies I to IV were all based on patients admitted to KUH, whereas studies V and VI included individuals from the whole of Stockholm Region.

	Study I	Study II	Study III	Study IV	Study V	Study VI
Study setting	KUH	KUH	KUH	KUH	Stockholm Region	Stockholm Region
Data sources	KarDa	KarDa	KarDa, SIR	KarDa	SIR, SmiNet, Statistics Sweden, VAL	SIR, SmiNet, Statistics Sweden, VAL
Study period	Oct 2011-Sep 2020	Jan 2011-Dec 2020	Jan 2011-Dec 2020	Jan 2018-Jan 2021	Jan 2017-Feb 2021	Mar 2020-Jul 2021
Study population	Hospitalized patients with a respiratory virus infection at admission	Hospitalized patients with a SARS-CoV-2-, influenza-, or RSV-positive community-acquired pneumonia at admission	Mechanically ventilated patients	Hospitalized patients	ICU-admitted patients	SARS-CoV-2-positive individuals
Main comparisons	COVID-19 versus influenza, RSV infection, and other virus infections	COVID-19 versus influenza and RSV infection	COVID-19 versus non-COVID-19	COVID-19 versus non-COVID-19 hospitalizations before and during the pandemic	COVID-19 versus non-COVID-19 ICU admissions before and during the pandemic, including an LRTI subgroup	Several comparisons of different exposures across different severities of SARS-CoV-2 infection
Main outcomes	30-day all-cause mortality	Bacterial co-infection at admission	VA-LRTI	HOB	One-year mortality and days alive and free from hospitalization	PCC diagnosis

Table 2. Methodological overview of the studies included in this thesis.

Figure 7 presents the study inclusion periods for the COVID-19 cohorts in relation to the timeline of the COVID-19 pandemic in Sweden. Study I-III only covered the period when the primary strain was the dominating variant. Study IV and V covered the very initial period when alpha was the dominating variant, whereas study VI covered this entire period as well as the very initial period when delta became the dominating variant.

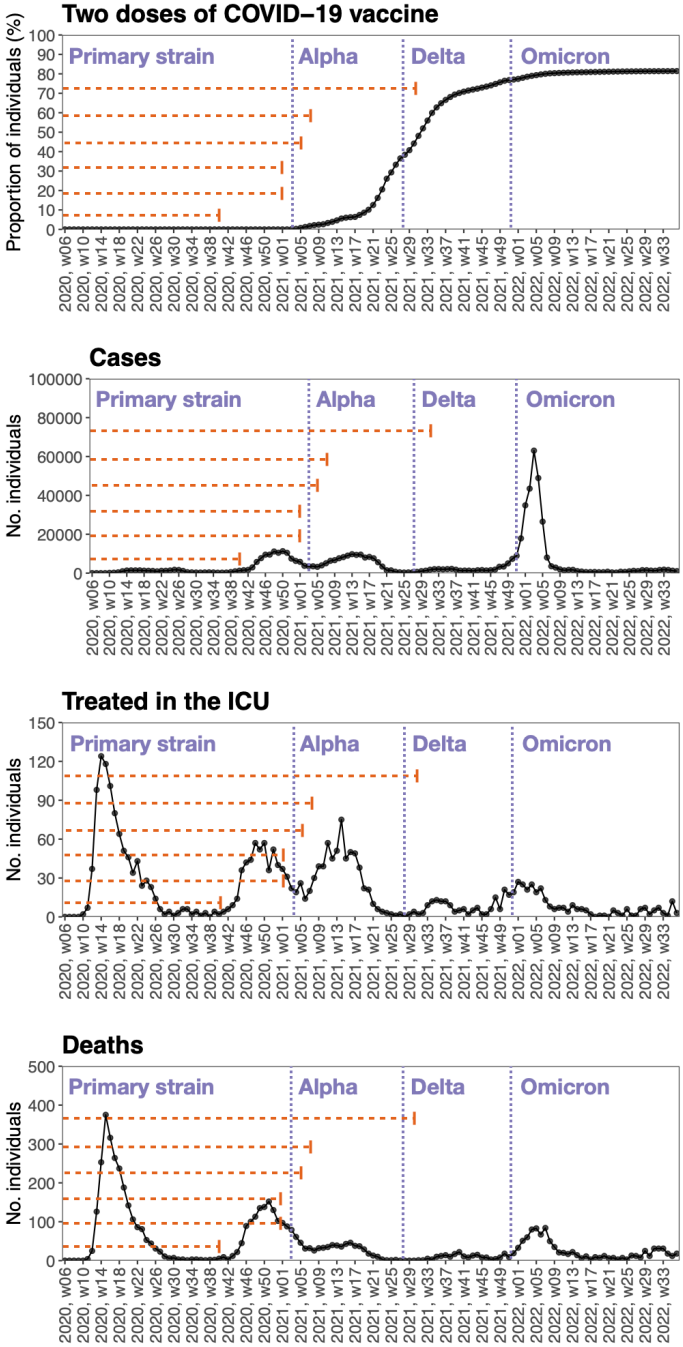

Figure 7. Study inclusion period for COVID-19 patients in relation to the timeline of the COVID-19 pandemic in Stockholm Region. The x-axes display calendar time and the y-axes show the number or the proportion of individuals. The dashed horizontal lines represent the periods when subjects with COVID-19 were included in the studies (lowest line for study I and highest line for study VI). The dashed vertical lines mark approximately when each variant of concern (alpha, delta, omicron) became the dominant variant. The data were obtained from the Public Health Agency of Sweden [21,23], distributed under a Creative Commons Attribution 4.0 International license (CC BY 4.0).

4.3 DATA SOURCES

All individuals registered in the Swedish Population Register receives a unique personal identity number (PIN) from the Swedish Tax Agency. The PIN serves as an unambiguous identifier across several societal functions, including but not limited to education, healthcare, migration, social security, and taxation. Consequently, the PIN enables linkage of data from different sources, to generate statistics and facilitate research within different domains. In medical research, the PIN serves as a linkage tool between different registries, biobanks, EHR databases, and other data sources [238]. The results presented in this thesis, were together based on data from five different sources, described in more detail below.

KarDa

KarDa is the internal data warehouse of KUH, consisting of information from different data sources, including the EHR system TakeCare® [239]. Data from KarDa were used in studies I-IV, including patient characteristics (age, sex, body mass index (BMI), comorbidities), hospitalization characteristics (vital signs, laboratory parameters, microbiological testing, radiology, drug administrations), and clinical outcomes (mortality, ICU-admission, length of stay (LOS), AKI, acute myocardial injury, HOB, PE, VA-LRTI). Importantly, data on mortality in KarDa is continuously updated from the Swedish population register.

The Swedish Intensive Care Registry

The Swedish Intensive Care Registry (SIR) is a national quality register for intensive care, established in August 2001 [240]. Individual patient data is collected within the legal framework of the Swedish National Quality Registries, comprising a system of around 100 national quality registries [241]. SIR prospectively collects data from ICU-admissions in Sweden, currently including data from all 83 ICUs in Sweden [111]. Data from SIR were used in study III, V, and VI, including data on start, stop, and length of intensive care treatment, simplified acute physiology score (SAPS) 3 scores and other variables measured upon admission, and diagnoses and procedures throughout the entire stay in the ICU.

VAL

Region Stockholm operates a central healthcare data warehouse, called VAL, which contains data from multiple administrative healthcare databases within the Stockholm Region [242,243]. This includes data on inpatient stays (coverage over 99%), outpatient specialist visits, and primary care visits (coverage of around 94%, personal communication Göran Lord, Region Stockholm) reimbursed by Region Stockholm [244]. Furthermore, VAL also contains data on demographics, migration status, and collected drug prescriptions. Data from VAL were used in Paper V, and VI, including data on age, sex, migration status, medical diagnoses, drug prescriptions and healthcare utilization.

SmiNet

SmiNet is an electronic system used for communicable disease surveillance in Sweden, owned and operated by The Public Health Agency of Sweden and the communicable disease control units in Sweden [245]. It was first introduced in 1997 and is used for surveillance of more than 60 notifiable diseases, including COVID-19, according to the Communicable Diseases Act and the Communicable Diseases Ordinance [246]. Data on SARS-CoV-2 positive PCR testing in the Stockholm Region reported to SmiNet were used in Paper V and VI.

Statistics Sweden

Statistics Sweden is a governmental agency supplying statistics for decision making, debate, and research [247]. Statistics Sweden is responsible for the coordination of national statistics from 29 government agencies, including data on population statistics and demographic analyses. Data from Statistics Sweden were used in Paper V, and VI, including data on region of birth, disposable income, education level, days with sickness benefit, and residential area type.

4.4 THE RETROSPECTIVE COHORT STUDY DESIGN

All studies included in this thesis were retrospective cohort studies. This is an observational study design, in contrast to an experimental study design. The term cohort, from the Latin cohors, referred to a military unit of a Roman legion, typically consisting of 300-600 men [248]. In an epidemiological context, a cohort refers to a group of subjects sharing a defining characteristic [249]. Subjects are followed from a certain point in time for one or more events of interest, such as onset of a particular disease or death. The subjects are followed until the event of interest or until censoring. In most situations, all subjects will not experience the event of interest during follow-up, and as such, censoring constitutes an almost ever-present feature of these kinds of time-to-event analyses [250,251]. Left-censoring refers to situations when the event of interest occurred before a certain point in time, but it is unknown exactly when the event occurred. Right-censoring is when the event of interest has not occurred at a point in time when a subject will no longer be followed for the event. Common reasons for right-censoring includes administrative censoring, i.e. the study observation period ends, emigration, and death. Cohort studies often involve multiple cohorts which differ in certain defining characteristics, e.g. individuals with COVID-19, individuals with influenza, and individuals without both COVID-19 and influenza. These differences in defining characteristics are most often referred to as exposures in epidemiology.

Typically, cohort studies are classified as prospective or retrospective cohort studies, but the classification is not always straightforward and just as exposures and outcomes can be misclassified in epidemiological studies, so can the design of the study [249,252]. Typically, a prospective cohort study is defined as a cohort study where none of the study subjects have developed the outcome of interest before the investigators conceive the study and starts enrolling subjects and collecting data. Conversely, in a retrospective cohort study one or more of the study subjects have developed the outcome of interest before the investigators conceive the study and starts enrolling subjects and collecting data.

Several studies and books have provided a comprehensive evaluation of advantages and disadvantages of the cohort study design [248,249,253,254]. Some aspects are worth a brief mention in this context. One major advantage of the cohort study design is the ability to study multiple outcomes of interest, potentially associated with one or more of the studied exposures. Furthermore, in a cohort study, subjects can often be seen to be free of the outcome at time zero. This is in contrast to case-control studies, which often are more subject to such potential of reverse causation. Given the longitudinal nature of cohort studies, it is often possible to take dynamics in exposure intensity into account. Furthermore, the cohort study enables estimation of quantities such as exposure-specific absolute and relative risk ratios and differences. Despite such advantages, several limitations need to be considered. This includes exposure and outcome adjudication based on data collected in the past, often collected with a different purpose in mind. This often results in varying degrees of incomplete records, with the possibility of inaccurate or inconsistent data collection and subsequent information bias. Furthermore, cohorts are seldomly similar in all important respects except for the exposure of interest. Several of these potential advantages and disadvantages will be discusses in relation to the findings presented in this thesis.

4.5 STUDY POPULATIONS

The term study population refers to all subjects in a research study, regardless of exposure and outcome status. The general outline of the study populations is described below.

Study I

The study population consisted of patients admitted to KUH any time from 1 October 2011 to 30 September 2020, with a PCR-confirmed respiratory virus infection detected any time from 24 hours before to 48 hours after hospital admission. The included respiratory viruses were SARS-CoV-2, influenza A and B, RSV, seasonal coronaviruses (229E, NL63, OC43, HKU1), adenovirus, enterovirus, human bocavirus, human metapneumovirus, parainfluenza virus 1-4, and rhinovirus.

Study II

In study II, adult patients (≥18 years) admitted to KUH through the emergency department any time from 1 January 2011 to 31 December 2020, were identified. Among these, hospitalizations testing positive for SARS-CoV-2, influenza A or B, or RSV any time from 24 hours before to 48 hours after hospital admission were further reviewed for presence of CAP upon admission. CAP was defined as a body temperature >38°C, peripheral oxygen saturation <95% or respiratory rate >20 breaths per minute as well as presence of new pulmonary infiltrates on a chest radiograph or computed tomography within the first two days of hospital admission.

Study III

In study III, adult patients (≥18 years) admitted to any of the four ICUs at KUH any time from 1 January 2011 to 31 December 2020 and treated with mechanical ventilation were included in the study cohort.

Study IV

The study population consisted of all adult patients (≥18 years) admitted to KUH any time from 1 January 2018 to 31 January 2021.

Study V

In study V, adult residents (≥18 years) in the Stockholm Region with an ICU admission any time from 1 January 2017 to 31 December 2018 or 1 March 2020 to 15 February 2021, were identified. The study population was restricted to individuals residing in the Stockholm Region from three years before admission to the hospital. Individuals were followed from their first identified ICU admission during the study period.

Study VI

In study VI, adult residents (≥18 years) in the Stockholm Region with a first SARS-CoV-2-positive PCR test any time from 1 March 2020 to 31 July 2020 were identified. The study population was restricted to individuals residing in the Stockholm Region from three years before to 90 days after the positive PCR test. Furthermore, individuals should be alive 90 days after the PCR test and if hospitalized with COVID-19 have at least 90 days of follow-up after hospital discharge.

4.6 COHORTS

As mentioned in section 4.4, cohort studies most often involve more than one cohort, with differences in the cohort defining characteristics hypothesized to be associated with the outcome of interest. In all studies except study VI, the main emphasis was on comparing a COVID-19 cohort to cohorts of other respiratory viruses or hospital populations. In study VI, however, only individuals with a PCR-verified SARS-CoV-2 infection were included, and multiple exposures were analysed, such as age, sex, comorbidities, and sociodemographic factors. The main definitions used for cohort classification is presented in table 3.

Study	COVID-19 cohort	Non-COVID-19 cohorts
I	A SARS-CoV-2 positive PCR-test any time from 24 hours before to 48 hours after admission to the hospital.	A PCR-test positive for any of the below listed respiratory viruses any time from 24 hours before to 48 hours after admission to the hospital: Influenza virus (A or B), RSV, seasonal coronaviruses (229E, NL63, OC43, HKU1), adenovirus, enterovirus, human bocavirus, human metapneumovirus, parainfluenza virus (1-4), and rhinovirus.

		The respiratory viruses were analysed separately as well as categorized into influenza, RSV, and other viruses.
II	A SARS-CoV-2 positive PCR-test any time from 24 hours before to 48 hours after admission to the hospital.	An influenza (A or B) or RSV positive PCR-test any time from 24 hours before to 48 hours after admission to the hospital. Influenza and RSV were analysed separately.
III	An ICD-10 diagnosis for COVID-19 (U07.1 or U07.2) and/or a SARS-CoV-2 positive test registered during the ICU stay.	All other individuals in the study population. Subjects were analysed as a pooled cohort as well as classified into specific diagnoses.
IV	A SARS-CoV-2 positive PCR test any time from 14 days before admission to the hospital to the day of hospital discharge or an ICD-10 diagnosis for COVID-19 (U07.1 or U07.2) registered during the hospitalization.	All other individuals in the study population. Hospitalizations before the pandemic (controls) and hospitalizations during the pandemic (non-COVID-19) were analysed separately.
V	An ICD-10 diagnosis for COVID-19 (U07.1 or U07.2) and/or a SARS-CoV-2 positive test registered during the ICU stay.	All other individuals in the study population. ICU-admissions before the pandemic (historic) and ICU-admissions during the pandemic (non-COVID-19) were analysed separately. Further, a subgroup of LRTIs were identified.
V	A SARS-CoV-2 positive PCR test any time from 1 March 2020 to 31 July 2021	None, since only individuals with SARS-CoV-2 infection were included in the study.

Table 3. Definitions of COVID-19 and non-COVID-19 cohorts used in the studies.

4.7 OUTCOMES AND FOLLOW-UP

The studies in this thesis investigated both acute and more long-term outcomes. Studies I-IV evaluated a range of acute clinical outcomes, study V investigated acute as well as long-term outcomes, and study VI investigated the occurrence of PCC diagnosis. The main outcomes are presented in more detail below.

Study I

The primary outcome was 30-day all-cause mortality from the day of hospital admission. Secondary outcomes were hospital LOS, 90-day all-cause mortality, 31-90-day all-cause mortality, admission to the ICU, ICU LOS, 30-day all-cause mortality from the day of ICU admission, AKI, acute myocardial injury, HOB, and PE. The definition of AKI was based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria but did not include urine volume measurements due to expected inadequate recording in the EHRs [255]. Acute myocardial injury was herein defined as having a cardiac troponin T of more than 50 ng/mL. HOB was defined as having a blood culture positive for a significant pathogen taken >48 hours after

hospital admission [256]. PE was classified as having an ICD-10 codes for PE (I26.0 or I26.9) registered at hospital discharge. Study subjects were followed for admission to the ICU, AKI, and acute myocardial injury from 24 hours before hospital admission for 30 days or until death or hospital discharge, whichever occurred first. Study subjects were followed for HOB from 48 hours after hospital admission for 30 days or until death or hospital discharge, whichever occurred first.

Study II

The primary outcome of study II was bacterial co-infection upon hospital admission (any time from one day before to two days after hospital admission). The microbiological testing used for classification of bacterial co-infection included nasopharyngeal cultures, lower respiratory tract cultures, blood cultures, urinary bacterial antigen tests, and bacterial DNA tests. Further, 30-day all-cause mortality from the day of hospital admission, hospital LOS, and admission to the ICU (followed during the entire hospitalization) was for each virus cohort analysed among individuals with and without a bacterial co-infection.

Study III

The outcome measure of study III was VA-LRTI, encompassing VAT and VAP as described in section 2.4.2.2. This outcome was used due to the considerable overlap between the clinical and radiological manifestations of VAP and COVID-19 critical illness, including high fevers, leucocytosis, and extensive radiographic infiltrates [120]. In the main analysis, we used a VA-LRTI definition strictly based on microbiological findings of significant bacterial pathogens from the lower respiratory tract. All intubations with a preceding extubation within the last 48 hours were grouped as one ventilator episode. Patients were followed for VA-LRTI from 48 hours of mechanical ventilation until the end of the first ventilator episode (extubation dead or alive).

Study IV

The primary outcome of study IV was HOB, defined as a positive blood culture obtained any time from 48 hours after admission to 24 hours after discharge, with a pathogen not cultured any time from 24 hours before to less than 48 hours after hospital admission. Only the first HOB per hospitalization was included in the study. A subgroup analysis was performed with exclusion of potential contaminant bacteria in accordance with the list of common commensals from the National Healthcare Safety Network within the Centers for Disease Control and Prevention (CDC) [257]. The 30-day all-cause mortality from the day of admission was also analysed among individuals with HOB.

Study V

In study V, we assessed the one-year mortality among individuals admitted to the ICU with or without COVID-19 critical illness. Study subjects were followed for the outcome from the day of admission to the ICU and censored at 360 days or date of moving out of the Stockholm

Region, whichever occurred first. In order to better understand how the trajectory of mortality potentially differed between the different study groups, separate analyses were also performed for day 1-60 and day 61-360 mortality. These assessment windows were based on previous reports on mortality following admission to the ICU for COVID-19 patients, where most mortality occurred within the first 60 days [111,258]. Further, among individuals who were discharged alive from the critical illness hospitalization, we assessed days alive and free from hospitalization from 1 to 360 days after the hospital discharge. Study subjects were censored at 360 days after hospital discharge or date of moving out of the Stockholm Region, whichever occurred first.

Study VI

The primary outcome of study VI was a PCC diagnosis. In line with the WHO clinical case definition of PCC, we started following subjects for the outcome from 90 days after first SARS-CoV-2 positive PCR test [194]. Subjects were followed to 360 days after first SARS-CoV-2 positive PCR test, 15 February 2022, date of death, or date of moving out of the region, whichever occurred first.

4.8 STATISTICAL CONSIDERATIONS

In all studies, quantitative data were presented as mean and standard deviation or median and first to third quartile as deemed appropriate. Qualitative data were presented as frequencies and percentages. An alpha level of 0.05 was used for all inferential statistical analyses. All statistical analyses were conducted in R (version 4.0.3 for study I-III and version 4.1.0 for study IV-VI) [259].

Study I

Paediatric (<16 years) and adult (≥16 years) patients were analysed separately. For paediatric patients, all analyses were performed using the ten virus categories, and baseline characteristics and outcomes in all groups were compared using Chi-square tests and Kruskal-Wallis tests. These analyses were also performed for baseline characteristics among adult patients. Further, unadjusted as well as age- and sex-adjusted logistic regression models were used to compare the baseline characteristics and laboratory parameters and vital signs at admission in the adult SARS-CoV-2-positive group with the influenza group, RSV-group, and other viruses group. Three logistic regression models were also defined to investigate the potential overall differences in baseline characteristics and clinical presentation between the four virus groups. The first model included age, sex, and BMI-category, whereas the second model also included specific comorbidities, and the third model also included laboratory parameters and vital signs. The performance of these three models were evaluated using Area Under the Receiver Operating Characteristics (AUROC). Five to thirteen percent of data were missing for BMI, vital signs, and laboratory parameters. To address this, we performed complete case analyses as well as using multiple imputation by predictive mean matching. All other baseline variables and outcomes were used as predictor variables for the multiple imputation.

The 30-day and 90-day all-cause mortality among the virus groups of adult patients were estimated using the Kaplan Meier estimator and standardized survival functions [260]. Further, all clinical outcomes were compared using unadjusted and adjusted regression models. The adjusted regression models were adjusted for age, sex, BMI, and each of the investigated comorbidities. Cox proportional hazards regression models were used for mortality, ICU-admission, acute myocardial injury, AKI, and HOB, whereas logistic regression models were used for PE, and negative binomial regression models were used for hospital and ICU LOS.

Study II

The proportions with a bacterial co-infection in the SARS-CoV-2, influenza, and RSV cohorts were compared using confidence intervals calculated with the Wilson score interval without Yate's continuity correction. The outcomes among patients with and without a bacterial co-infection within each virus cohort were compared using age-, sex-, and Charlson comorbidity index- (CCI) adjusted regression models. Hospital LOS was analysed with subdistribution hazards models, with in-hospital mortality being a competing event to hospital discharge alive. Cox proportional hazards regression models were used for both ICU-admission and 30-day all-cause mortality.

Logistic regression models were used in the SARS-CoV-2 group to analyse potential associations between baseline characteristics as well as four inflammatory markers (CRP, white blood cell (WBC) count, procalcitonin, and neutrophil-to-lymphocyte ratio (NLR)) at admission and bacterial co-infection. Unadjusted models as well as age-, sex, and Confusion-Respiration-Blood pressure >65 years- (CRB-65) adjusted models were used. Finally, two scoring systems were defined in order to assess the potential added capacity to discriminate bacterial co-infection from the four inflammatory markers. The first scoring system included CRB-65 and presence of any comorbidity, whereas the second scoring system also included the inflammatory markers. The scoring systems were analysed using logistic regression models and the AUROC were compared with confidence intervals based on 2,000 stratified bootstrap replicates. Only complete case analyses were performed for all above-described analyses.

Study III

Competing-risks analyses were used to analyse the incidence and risk of VA-LRTI in the COVID-19 cohort compared to the non-COVID-19 cohorts. The term 'competing risks' refers to situations where observation of the event of interest is preceded by other events, thus preventing observation of the event of interest. In this context, extubation (dead or alive) is a competing event to VA-LRTI [261]. The VA-LRTI cumulative incidence was estimated using the Aalen and Johansen estimator [262]. We then estimated crude and adjusted cause-specific hazard ratios (CSHRs) and subdistribution hazard ratios (SHRs) for VA-LRTI and extubation, respectively. CSHRs and SHRs were estimated with Cox proportional hazard regression models and Fine and Gray models, respectively. We adjusted for age, sex, and CCI in the comparisons of the COVID-19 cohort with the non-COVID-19 cohorts. When comparing the

first and second wave in the COVID-19 cohort, we also adjusted for obesity, prone positioning, and steroid use before ICU admission.

Study IV

Crude incidence rates and incidence rate ratios (IRR) for HOB across the three different cohorts (COVID-19, non-COVID-19, and controls) were estimated using Poisson regression models. Further, IRRs adjusted for age, sex, CCI, and urgent versus planned admissions were estimated. Person-time was defined as the LOS in days from 48 hours after hospital admission until either hospital discharge, death or HOB, whichever occurred first. As such, a hospitalization with a total LOS of 36 hours contributed with 0 days of person-time, whereas a hospitalization with a total LOS of 8 days contributed with 8 days of person-time. The odds of 30-day mortality among individuals with a HOB was compared using crude and adjusted logistic regression models. The adjusted logistic regression models were also adjusted for age, sex, CCI, and urgent versus planned admissions.

Study V

The day 1-360, day 1-60, and day 61-360 cumulative incidence of all-cause mortality was estimated with the Aalen and Johansen estimator [262], with moving out of the region as a competing event. Three separate Cox proportional hazards regression models were used to estimate the all-cause mortality hazard ratio. The first model was unadjusted, whereas the second adjusted for age and sex, and the third also adjusted for number of comorbidities, region of birth, yearly disposable income, and residential area. Age and disposable income were included as continuous variables, using restricted cubic splines with four knots [263]. Days alive and free from hospitalization was analysed with Poisson regression with a robust variance estimate.

Study VI

All analyses were stratified by severity of the SARS-CoV-2 infection (non-hospitalized, hospitalized, ICU-treated) to account for potential differences in follow-up strategies within the healthcare system. Several Cox proportional hazards regression models were used to explore factors associated with getting a PCC diagnosis. Such factors included age, sex, comorbidities, previous healthcare use, days with sickness benefit, region of birth and residential area type. The first model included age, sex, and the interaction between age and sex. The other models included age, sex, the interaction between age and sex, and each specific factor, respectively. All models were stratified on the calendar month of the first SARS-CoV-2-positive PCR test. This was done to account for similar follow-up time and probability of receiving a PCC diagnosis. Age was modelled as a continuous variable using restricted cubic splines with four knots.

Individuals diagnosed with PCC was matched with up to three individuals without such a diagnosis. Exact matching was used for calendar month of SARS-CoV-2 positive PCR test, age group, and sex, whereas propensity score matching was used for comorbidities, region of

birth, residential area type, previous days with sickness benefit, and previous healthcare use. Healthcare use trajectories before and after the acute infection were then analysed descriptively as well as with difference-in-differences analyses [264].

5 RESULTS & DISCUSSION

This chapter summarizes main results from the studies included in this thesis, compares them with relevant peer-reviewed literature, and highlights important strengths and limitations. For complete results, including study tables and figures, please refer to the studies attached at the end of this thesis.

5.1 STUDY I

Study I aimed to investigate differences in baseline characteristics, clinical presentation, and outcomes for adult and paediatric patients hospitalized with COVID-19 compared with other respiratory virus infections.

Summary of main results

The study included 12,700 hospitalizations: 6,321 adult hospitalizations (1,721 COVID-19 hospitalizations) and 6,379 paediatric hospitalizations (101 COVID-19 hospitalizations).

Compared with the other virus infections, adult patients with COVID-19 were in general more likely to be male, be overweight or obese, have diabetes, or have hypertension. On the contrary, COVID-19 patients were less likely to be aged 70 years or more, have chronic pulmonary disease, have malignancy, or have immunosuppression. Regarding vital signs and laboratory parameters at admission, COVID-19 patients were in age- and sex-adjusted analyses more likely to have tachypnoea, but less likely to have tachycardia, abnormal WBC counts, abnormal platelet counts, or abnormal creatinine levels. Models including age, sex, BMI, comorbidities, laboratory parameters, and vital signs upon admission had an AUROC of 0.75 for discriminating patients with COVID-19 from patients with influenza, 0.84 for discriminating patients with COVID-19 from patients with RSV-infection, and 0.83 for discriminating patients with COVID-19 from patients with other respiratory virus infections.

Overall, the COVID-19 cohort had more unfavourable outcomes compared with the other cohorts, including increased hospital LOS and increased risk of ICU-admission, pulmonary embolism, and mortality. The 30-day all-cause mortality was 13% in the COVID-19 cohort, 5% in the influenza cohort, 7% in the RSV-infection cohort, and 5% in the other virus infections cohort. The COVID-19 cohort had in adjusted models an approximate three-fold increased risk of 30-day all-cause mortality compared to the three other cohorts. The risk was greater among individuals aged 60 years or older and was more pronounced during the first months of the pandemic.

The median (quartile one to quartile three (Q1-Q3)) age was 7 years (1-12 years) in the paediatric COVID-19 cohort, which was much older when compared with all other virus infections (median ages ranging from 0-2 years). The median (Q1-Q3) hospital LOS was 3 days (1-8 days) in the COVID-19 cohort, 4% were treated in the ICU, and 1% died within 30 days from hospital admission. These findings were rather similar when compared with the other virus infections.

Comparison with other studies

Several other studies have compared characteristics and outcomes of patients hospitalized with COVID-19 and patients hospitalized with influenza, whereas to the best of my knowledge, few such comparisons have been made with other respiratory virus infections. As such, this section focuses on comparisons between COVID-19 and influenza, first discussing the results observed in the adult cohort, followed by the paediatric cohort. A total of twelve relevant studies comparing patients hospitalized with COVID-19 and patients hospitalized with influenza were identified. These are summarized in table 4 below.

Study	COVID-19 inclusion period	Number of COVID-19 patients	Number of influenza patients	Remarks
Cates et al [265]	1 March-31 May 2020	3,948	5,453	US veterans
Delahoy et al [266]	1 October 2020-30 September 2021	3,461	6,774	Only paediatric patients in the US
Fröhlich et al [267]	19 February-22 July 2020	2,843	1,381	14 hospitals in Switzerland
Ludwig et al [132]	17 February-21 July 2020	2,343	6,762	Based on German healthcare claims data
Monteinos et al [268]	1 March-1 May 2020	187	187	Single centre in Barcelona
Nersesjan et al [269]	1 March-1 June 2020	1,657	31,483	Population-based in Denmark
Pawelka et al [270]	1 March-25 April 2020	142	566	Single centre in Vienna
Piroth et al [100]	1 March-30 April 2020	89,530	45,819	French nationwide study
Seligman et al [271]	1 March-31 December 2020	15,474	7,867	US veterans ≥65 years
Taniguchi et al [214]	2020	16,790	27,870	Based on Japanese healthcare claims data
Woodcock et al [213]	1 February-2 November 2020	3,799	1,333	Hospitals in North West London

Xie et al [272]	1 February-17 June 2020	3,641	12,676	US veterans

Table 4. Summary of the identified studies comparing hospitalized COVID-19 and influenza patients.

All but one of the identified studies included patients hospitalized with COVID-19 only during 2020, thus primarily covering a pre-vaccination time period with the primary strain as the main circulating variant. Seven studies were based on data from Europe, one study was based on data from Japan, one study was based on data from only children in the US, and three studies were based on data from US veterans. The largest COVID-19 cohort was in the study by Piroth et al, with 89,530 patients of which 1,227 were aged less than 18 years [100].

The median (Q1-Q3) age of the adult patients hospitalized with COVID-19 in our study was 58 years (42-71 years), with 14% being aged 80 years or older. The age distribution varied in the other studies. Piroth et al observed a median (Q1-Q3) age of 68 years (52-82 years), with 27% aged 80 years or older [100]. Similarly, in the study by Woodcock et al, 27% were aged 80 years or older [213]. Reasons for such differing age distributions could potentially include differential SARS-CoV-2 testing strategies and different strains on healthcare systems. We observed COVID-19 patients to be more likely to be male, which was also observed in most [100,213,214,267,269,270], but not all studies [132,268] (the three studies of US veterans were not considered). Neither of the studies performed age- and sex-adjusted comparisons of baseline characteristics and clinical presentation in the COVID-19 and influenza cohorts. As such, I do not present any comparisons for these results.

Our finding of a substantially increased risk of acute mortality among adult patients hospitalized with COVID-19 compared with influenza is in line with all included studies. We found the 30-day mortality hazard ratio to be more increased for the COVID-19 cohort when restricting the study population to patients ≥70 years. This is in line with findings from Piroth et al., where the COVID-19 and influenza mortality rates diverged substantially among the elderly patients [100]. In our study, 5% of COVID-19 patients had a pulmonary embolism ICD-10 code registered at discharge, compared with 1% of influenza patients. The corresponding proportions in the study by Piroth et al were 3.4% and 0.9% [100]. In a study of around 3,500 US veterans hospitalized with COVID-19 and 5,500 US veterans hospitalized with influenza, 2.8% of COVID-19 patients and 1.3% of influenza patients had a diagnosis of pulmonary embolism [265].

Regarding the paediatric cohort, we found children hospitalized with COVID-19 to be older compared with all other infections. Such different age distributions were also observed in a recent large study from the US, including 3,461 children with COVID-19 and 6,774 children hospitalized with influenza, with a median (Q1-Q3) age of 9 years (1-15 years) in the COVID-19 cohort and 3 years (1-7 years) in the influenza cohort [266]. Similar findings were also observed by Piroth et al, with 50% of the COVID-19 cohort and 78% of the influenza cohort aged 5 years or less [100]. We observed a median (Q1-Q3) hospital LOS of 3 days (1-8 days) in the COVID-19 cohort, compared with 3 days (2-4 days) in the influenza cohort. In the study by

Delahoy et al, the median (Q1-Q3) LOS was 3 days (2-5 days) in the COVID-19 cohort and 2 days (1-4 days) in the influenza cohort [266]. The corresponding numbers were not presented in the study by Piroth et al [100]. In our study, 4% of children with COVID-19 as well as children with influenza were treated in the ICU. Corresponding proportions in the study by Piroth et al were 3% in the COVID-19 cohort and 1% in the influenza cohort [100]. These results differ from those observed by Delahoy et al, with more than 20% of both children hospitalized with COVID-19 and influenza treated in the ICU [266]. We observed a 30-day mortality rate of 1.0% in the COVID-19 cohort and 0.7% in the influenza cohort. Whilst Delahoy et al did not assess the 30-day mortality, they observed an in-hospital mortality rate of 0.7% in the COVID-19 cohort and 0.5% in the influenza cohort [266]. An in-hospital mortality rate of 0.7% for the COVID-19 cohort was also observed by Piroth et al, whereas the in-hospital mortality rate was 0.2% for the influenza cohort [100].

Strengths & limitations

In our study, ample access to clinical data for patients hospitalized with COVID-19 as well as patients hospitalized with nine other respiratory virus infections, enabled extensive comparisons between COVID-19 and these infections. The same criterion of a positive PCR-test from a respiratory sample any time from 24 hours before to 48 hours after admission was used for all ten infections. Making use of the PCR-testing rather than ICD-10 codes for the different respiratory virus infections ought to have reduced the risk of misclassification and increased the internal validity of the study. Furthermore, ICD-10 codes are registered at hospital discharge within Swedish inpatient settings, and as such it is not possible with certainty to know whether the patient was admitted with COVID-19 or contracted COVID-19 later during the hospitalization. Furthermore, by using the microbiological testing at admission, we reduced the risk of including patients transferred from other hospitals to KUH. Transfers of COVID-19 patients between hospitals in Stockholm have been more common when compared with the other respiratory virus infections.

Several limitations are important to acknowledge. Our study was based completely on the secondary use of already collected EHR data. Importantly, the main purposes of EHR data include supporting clinical care and financial billing processes [273]. There are several cav eats to the secondary use of EHR data, including potentially inaccurate, inconsistent, and incomplete registration of data [274]. Importantly, the measurement frequency of for instance vital signs, clinical chemistry tests, microbiological tests, and medical imaging reflects actual healthcare processes rather than optimal data collection procedures for the specific research questions to be addressed. However, many of the variables included in the study analyses were based on routinely collected data, thus potentially reducing the risk of differential misclassification and missingness between the different virus cohorts. Furthermore, we performed analyses using both complete cases as well as data imputed by multiple imputation by chained equation.

This was a single-centre retrospective cohort study at KUH in Stockholm, Sweden. The generalizability increases when studies include many hospitals, cities, countries, and/or even

continents. KUH is a large university hospital, providing highly specialized care within several medical fields, and as such, the results might be more generalizable to similar hospital settings with regards to admission patterns, healthcare capacity, resource availability, and microbiological testing intensities. Importantly, several clinics at KUH implemented routine SARS-CoV-2 testing of patients upon admission from 25 March 2020 and onwards [275]. Given our inclusion of all patients testing positive upon hospital admission, a significantly larger proportion of asymptomatic COVID-19 patients might have been included in our study, compared with using the same inclusion criteria in a hospital-setting without SARS-CoV-2 screening implemented. Furthermore, the SARS-CoV-2 testing indications most probably differed compared with the testing indications for the other respiratory viruses. This is particularly true for the other respiratory viruses, where testing primarily is performed in immunocompromised and frail patient populations testing negative for influenza viruses and RSV. Yet, the results for ICU admission and mortality were robust when restricting the study population to patients with fever, reduced oxygen saturation or tachypnoea at admission. However, similar comparisons were not performed for the comparisons of baseline characteristics and clinical presentation, and as such the observed differences might partly be driven by the differential testing indications. Furthermore, the COVID-19 cohort was almost exclusively compared with other respiratory virus infections occurring before the pandemic. This might have had an impact on hospitalization patterns across different age groups, as well as LOS, admission to the ICU, and other quality of care-related aspects.

5.2 STUDY II

The main aim of study II was to investigate the prevalence of bacterial co-infections in hospitalized patients with SARS-CoV-2 compared to influenza or RSV-positive community-acquired pneumonia upon admission. Further, we aimed to compare co-infection testing rates and the use of antibiotics at admission in the three virus groups, as well as clinical outcomes in patients with and without a detected bacterial co-infection. Finally, the bacterial co-infection diagnostic accuracy of CRP, WBC, NLR and procalcitonin was assessed in the SARS-CoV-2 group.

Summary of main results

The study included 2,260 hospitalizations: 1,243 SARS-CoV-2 positive, 775 influenza-positive, and 242-RSV positive. The SARS-CoV-2 group had the lowest testing frequency for all included test modalities, including blood cultures, respiratory cultures, urinary antigen testing, and bacterial DNA testing. The occurrence of detected bacterial co-infection at admission was 4% (95% CI: 3-5%) in the SARS-CoV-2 group, 27% (95% CI: 24-30%) in the influenza group, and 29% (95% CI: 23-35%) in the RSV group. Streptococcus pneumoniae was the most common detected bacterial agent in all three virus groups: 28% of all bacterial co-infections in the SARS-CoV-2 group, compared to 56% in the influenza group, and 61% in the RSV group. When restricting the analysis to individuals where extensive bacterial co-infection testing were performed, the positivity rate was 5% (95% CI: 1-17%) in the SARS-CoV-2 group, 53% (95% CI: 43-62%) in the influenza group, and 47% (95% CI: 32-63%) in

the RSV group. Thirty-three percent of the SARS-CoV-2 group had antibiotics administered at admission, compared to 84% in the influenza group and 88% in the RSV group. Third-generation cephalosporins were the most commonly administered type of antibiotics for all three groups. The 30-day all-cause mortality was 22% in SARS-CoV-2 patients with a bacterial co-infection and 11% in those without a detected bacterial co-infection. For all three virus groups, no significant difference in the 30-day all-cause mortality hazard ratio were observed for patients with compared to without bacterial co-infection. In the SARS-CoV-2 group, two scoring systems were developed with the aim to determine the likelihood of bacterial co-infection. The AUROC for a scoring system based on CRB-65 and presence of any comorbidity was 0.63 (95% CI: 0.56-0.70). When including one point each for CRP >50 mg/L, WBC>12x109 cells/L, and procalcitonin >2.00 □g/L, the AUROC was 0.66 (95% CI: 0.59-0.74).

Comparison with other studies

Our finding of a low occurrence of bacterial co-infection in patients with SARS-CoV- positive CAP is in line with a rapid living review and meta-analysis of 148 studies, reporting a pooled prevalence of 5.3% (95% CI: 3.8-7.4%) [169]. Similar results were observed in studies from both Spain and the UK not included in the meta-analysis [276,277]. Another systematic review and meta-analysis, including 3,834 patients hospitalized with COVID-19, observed a 7% (95% CI: 3-12%) occurrence of bacterial co-infection [278]. Finally, a review article including ten studies that evaluated a minimum of 100 COVID-19 patients, found all studies except one study to report a less than 4% occurrence of bacterial co-infection [279]. This study also assessed the positivity rate for different test modalities. Blood cultures had a positive rate ranging from around 1% to 4%, similar to the 2% observed in our study. Respiratory cultures had a positivity rate ranging from 0% to 21%, whereas we observed a 10% positivity rate. Finally, the positivity rate for pneumococcal or *Legionella* antigen ranged from 0% to 10%, whereas we observed a 2% positivity rate.

Our finding of a 27% occurrence in patients with influenza virus-positive CAP is similar to a pooled occurrence of 23% (95% CI: 18-28%) observed in a systematic review and meta-analysis [210]. Another study of around 16,000 adult patients hospitalized with respiratory viral infection in Hong Kong from 2013 to 2017 found 53% to be clinically suspected viral-bacterial co-infections and 7% to be laboratory-confirmed viral-bacterial co-infections [280]. Besides influenza viruses, this study also included RSV and parainfluenza viruses 1-4.

We observed 33% of patients hospitalized with SARS-CoV-2 positive CAP to have antibiotics administered upon hospital admission. Another retrospective cohort study, including 1,705 patients hospitalized with COVID-19 in 38 hospitals in Michigan, found around 57% of patients to be prescribed early empiric antibacterial therapy, whereas 3.5% had a confirmed bacterial co-infection [281]. A meta-analysis of 154 studies observed a 75% prevalence of antibiotic prescription in COVID-19 patients any time during the course of the COVID-19 episode [282]. However, this meta-analysis included infections across all health care settings (both outpatient and inpatient settings), with most studies not reporting the timing of the antibiotic

prescription, making comparisons with our findings difficult. Another study of 554 patients hospitalized with COVID-19, of which 114 patients had a bacterial co-infection, did not observe a higher adjusted odds of mortality among patients with bacterial co-infection [283].

We could neither demonstrate nor exclude an association between bacterial co-infection and 30-day mortality in the COVID-19 cohort. In the cohort study in Michigan by Vaughn et al, the in-hospital mortality was 48% in those with a bacterial co-infection compared with 18% in those without a bacterial co-infection (P<0.001) [281]. However, patients with bacterial co-infection were older, had higher CCI score, and more often had moderate or severe chronic kidney disease, possibly leading to important confounding bias.

We did not find the investigated inflammatory markers to accurately discriminate bacterial co-infection in patients with COVID-19. A UK study including around 1,000 patients hospitalized with COVID-19, did not find procalcitonin to be diagnostically useful to discriminate bacterial co-infection (AUROC 0.56, 95% CI: 0.51-0.60) [284]. Similarly, a retrospective cohort study of individuals admitted with severe COVID-19 to 84 ICUs in ten countries found the bacterial co-infection discriminative capacity of procalcitonin as well as CRP to be poor [285]. However, the authors found a baseline value of procalcitonin <0.3 ng/mL to have the potential to rule out bacterial co-infection, with a negative predictive value of 91%. Similarly, a UK study proposed an absence of both elevated WBC count and antibiotic-related decrease in CRP to accurately exclude bacterial co-infections in patients with COVID-19 [286].

Strengths & limitations

Similar to study I, strengths of study II were the ample access to clinical data and the similar inclusion criteria for all three virus cohorts.

Many of the limitations discussed for study I also applied to study II, including the single-centre retrospective cohort design and secondary use of EHR data. Around one third of SARS-CoV-2 positive patients did not have a thoracic radiograph or computed tomography scan performed, compared with 16% of influenza positive patients and 8% of RSV positive patients. As such, a much larger proportion of the SARS-CoV-2 positive patients were excluded from the study compared with the other respiratory virus infections. This might for instance be due to differences in medical imaging routines among COVID-19 patients compared with other respiratory virus infections, possibly due to insufficient capacity or attempts to minimize unnecessary patient flows in hospitals during an ongoing pandemic. If different indications for radiology were used between the different respiratory virus infections, differential exclusion of for example patients with milder course of disease might have been introduced, possibly affecting the external validity of the observed occurrence of bacterial co-infection at admission among the included patients. Furthermore, the testing frequency was lower for all microbiological testing modalities in the COVID-19 group when compared with the influenza cohort as well as the RSV cohort. Such lower testing frequency might lead to a more underestimated prevalence of bacterial co-infection in the COVID-19 cohort compared with the other respiratory virus infections. However, a lower observed positivity rate for all testing

modalities in the COVID-19 cohort, as well as among those patients with extensive testing performed, indicates no severe differential underestimation of the occurrence of bacterial co-infection upon hospital admission. Importantly, the magnitude of the difference in testing frequency also varied between the test modalities, with a much lower use of LRT cultures in the COVID-19 cohort compared with the other cohorts. This might have affected the etiological distribution in the COVID-19 cohort compared with the other cohorts, possibly not reflecting biological processes but rather different healthcare processes with fear of aerosol-generating procedures [287]. Finally, whilst restricting the study cohort to patients admitted through the ED, preceding hospitalizations or pre-hospital antibiotic usage could not be ruled out, possibly influencing the observed occurrences of bacterial co-infections as well as the etiological distributions.

5.3 STUDY III

Study III aimed to investigate the occurrence of microbiologically defined bacterial VA-LRTI among mechanically ventilated COVID-19 versus non-COVID-19 patients. Furthermore, the study aimed to compare the occurrence during the first and second wave of the pandemic for both COVID-19 and non-COVID-19 patients.

Summary of main results

The study included 20,223 ICU episodes where the first (if more than one) episode of mechanical ventilation was included for analysis: 479 COVID-19 episodes and 19,744 non-COVID-19 episodes. The median (Q1-Q3) duration of mechanical ventilation was 10 days (5-18 days) in the COVID-19 cohort and 1 day (0-3 days) in the pooled non-COVID-19 cohort. Eighty-nine percent (n=426) of the COVID-19 episodes were ventilated for 48 hours or longer, thus being at risk for VA-LRTI. The corresponding proportion was 30% (n=5,907) in the non-COVID-19 group. Only these patients were included in the analysis of VA-LRTI incidence proportions and rates.

The VA-LRTI incidence proportion was 30% in the COVID-19 cohort and 18% in the pooled non-COVID-19 cohort, with a VA-LRTI incidence rate per 1,000 days at risk of 31 (95% CI: 26-37) in the COVID-19 cohort and 34 (95% CI: 32-36) in the non-COVID-19 cohort. COVID-19 patients had a VA-LRTI higher incidence rate compared with patients with ARDS as well as patients with other infectious diseases (bacterial pneumonia, influenza, sepsis). However, the VA-LRTI incidence was lower compared with many non-infectious diseases. The age-, sex-, and comorbidity-adjusted VA-LRTI SHR for the pooled non-COVID-19 cohort was 0.98 (95% CI: 0.82-1.17) compared with the COVID-19 cohort. All infectious diseases as well as the ARDS group had significantly decreased SHRs compared to the COVID-19 group, whereas non-infectious had overall increased SHRs. The SHR for influenza compared to the COVID-19 group was 0.32 (95% CI: 0.16-0.66).

In the COVID-19 cohort, 381 were during the first wave (9 March 2020 to 31 July 2020) and 93 episodes were during the second wave (1 October 2020 to 31 December 2020). The corresponding number of episodes for the non-COVID-19 group were 567 and 324

respectively. The VA-LRTI incidence rate per 1,000 days at risk in the COVID-19 group was 28 (95% CI: 22-34) during the first wave and 52 (95% CI: 35-75) during the second wave. These rates were in the non-COVID-19 group 37 (95% CI: 26-50) and 52 (95% CI: 34-75), respectively. The adjusted VA-LRTI SHR during the second wave compared to the first wave was 1.85 (95% CI: 1.14-2.99) in the COVID-19 group and 1.37 (95% CI: 0.84-2.24) in the non-COVID-19 group.

Comparison with other studies

Previous reports on VAP incidence proportions in mechanically ventilated patients with COVID-19 have ranged from around 30% to 85% [109,110,116–119,288]. A systematic literature review of sixteen studies including around 6,500 ICU-admitted COVID-19 patients found a weighted average VAP incidence proportion of 50% (range 21% to 64%) [289]. Among the five out of sixteen studies reporting incidence rates, the pooled mean incidence rate was 27 VAP per 1,000 ventilatory days. We observed a VA-LRTI incidence proportion of 30% and an incidence rate of 31 per 1,000 ventilator days at risk. These incidence rates are substantially higher than those observed in a pre-pandemic prospective cohort study from 114 ICUs, with a VAP incidence rate per 1,000 mechanically ventilated days of 8.8 and a VAT rate of 10.2 [290].

We only identified one study which specifically investigated the occurrence of VA-LRTI (i.e. both VAP and VAT) in patients mechanically ventilated with versus without COVID-19 [109]. This was a European cohort study including mechanically ventilated patients from March 2016 through May 2020 from 36 ICUs, primarily in France, but also in Spain, Greece, Portugal and Ireland. Three cohorts were defined, a COVID-19 cohort (568 patients), an influenza-cohort (482 patients) and a cohort free from viral infection (526 patients). The VA-LRTI incidence proportion was 51% in the COVID-19 cohort, 30% in the influenza cohort, and 25% in the cohort free from viral infection. The VA-LRTI incidence rate was not reported. Reasons for the overall lower VA-LRTI incidence proportions in our study compared with the study by Rouzé et al are unknown, but both studies observed the highest incidence proportions in the COVID-19 group compared with the other groups. Interestingly, Rouzé et al had a stricter outcome classification compared with our main analysis, also considering altered body temperature and WBC count, as well as the presence of purulent tracheal secretions. When we applied similar criteria in a predefined sensitivity analysis, we observed a VA-LRTI incidence proportion of 25% in the COVID-19 cohort and 15% in the pooled non-COVID-19 cohort.

Our finding of different VA-LRTI incidence rates across the different waves of the pandemic warrants further investigation. To the best of my knowledge, no other study has compared the VA-LRTI or VAP incidence rates during different phases of the pandemic and as such these results cannot be directly compared with other studies. We observed a big difference in the proportion with steroid treatment administered before the ICU admission during the second wave (87%) when compared with the first wave (24%). In a study of 670 mechanically ventilated COVID-19-ARDS patients, the VAP cumulative incidence was higher in the patients who had been treated with corticosteroids when compared to the patients not treated with corticosteroids [291]. Furthermore, a slightly higher proportion were prone positioned during the

second wave (66%) compared with the first wave (53%). Prone positioning has previously been associated with a higher incidence rate of VAP when compared with supine positioning [292]. Collectively, the reasons for the observed differences in VA-LRTI incidence during the first and second wave are not well understood, but could include differences in patient case mixes, COVID-19 interventions, demands of the healthcare systems, as well as healthcare worker shortages and fatigue [293].

Strengths & limitations

The main strength of study III was the possibility to link high-resolution clinical data from EHRs with data on all KUH ICU admissions from SIR, a national quality register for intensive care, enabling comparisons of the COVID-19 cohort with several other infectious as well as non-infectious disease cohorts. Furthermore, by including patients from both the first and the second wave of the pandemic, comparisons could be made between different time periods of the pandemic, with different COVID-19 interventions rolled out.

Given the challenges to diagnose VAP, in particular in patients with COVID-19, in combination with the retrospective study design, we decide upon a more conservative outcome measure, VA-LRTI (i.e. both VAP and VAT). This could be considered both a strength and a limitation. The advantage of this would be to reduce the risk of wrongly adjudicating radiographic and clinical findings as VAP rather than being part of the clinical course of COVID-19. This could lead to an overestimation of the difference in the COVID-19 cohort compared with the other non-COVID-19 cohorts, since the probability of the underlying disease mimicking the outcome of interest would be higher in the COVID-19 cohort. However on the other hand, the clinical implications and outcomes might be greater for a VAP compared with a VAT, and as such, this could be more relevant to measure.

Some other limitations should also be acknowledged. First, as for study I and study II, this was a retrospective cohort study confined to one hospital, thus limiting the generalizability to other settings. Second, the LRTI sampling indications might have differed between different time periods. However, the results from the main analysis were robust when restricting the study population to patients mechanically ventilated during the pandemic period as well as when restricting the study population to patients with a LRTI culture performed. Further, we did not have access to data on vital signs and drugs administered throughout the entire course of the ICU stay, as well as preventive measures, and the use of sedative or neuromuscular blocking agents.

5.4 STUDY IV

Summary of main results

The study included 186,945 hospitalizations: 133,193 hospitalizations before the pandemic (controls), 48,791 non-COVID-19 hospitalizations during the pandemic (non-COVID-19), and 4,961 COVID-19 hospitalizations (COVID-19). The incidence rate of HOB per 1,000 days at risk was 10.92 (95% CI: 9.83-12.09) in the COVID-19 cohort, 4.23 (95% CI: 3.88-4.60) in the

non-COVID-19 cohort, and 3.48 (95% CI: 3.30-3.67) in the control cohort. When excluding possible contaminants, this was 4.64 (95% CI: 3.99-5.37) in the COVID-19 cohort, 2.17 (95% CI: 1.93-2.43) in the non-COVID-19 cohort, and 1.87 (95% CI: 1.74-2.01) in the control cohort. The 30-day mortality rate among patients with HOB was 20% in the COVID-19 cohort, 17% in the non-COVID-19 cohort, and 12% in the historic cohort. The HOB incidence rate was significantly increased in adjusted regression models in the COVID-19 cohort compared with both the non-COVID-19 cohort (adjusted IRR 2.69, 95% CI: 2.34-3.08) and the control cohort (adjusted IRR 3.34, 95% CI: 2.97-3.75). This was also true when comparing the 30-day mortality rates (COVID-19 versus non-COVID-19: adjusted OR 1.53, 95% CI: 1.05-2.22, COVID-19 versus control: adjusted OR 2.44, 95% CI: 1.75-3.38). The HOB incidence rate and the 30-day mortality among patients with HOB was also increased in the pandemic non-COVID-19 cohort compared with the pre-pandemic control cohort (incidence: adjusted IRR 1.20, 95% CI: 1.08-1.32, mortality: adjusted OR 1.63, 95% CI: 1.22-2.16).

Comparison with other studies

Our finding of the COVID-19 pandemic period to be associated with increased incidence rates of HOB is partly in line with a study evaluating the occurrence of BSIs before and during the pandemic in 69 US hospitals [147]. Sturm et al found a pre-pandemic HOB rate of 2.78 per 10,000 patient days and a pandemic HOB rate of 3.56 per 10,000 patient days. The HOB rate among those with COVID-19 was 9.64 per 10,000 patient days, compared with a HOB rate of 2.74 per 10,000 patient days among those without COVID-19. These findings corroborate our findings of increased rates of HOB in COVID-19 patients compared with non-COVID-19 patients, but no difference in rates between non-COVID-19 patients before and after the pandemic was observed. The HOB rates observed by Sturm et al are substantially lower compared with our observed rates. Two important differences could explain these differences. While we included all positive blood cultures, Sturm et al only evaluated HOBs from five organisms: *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Candida* spp. Further, we calculated the HOB rates based on days at risk, whereas Sturm et al included the entire hospital LOS in the denominator. Further in line with our findings, a previous French multicentre case-cohort study observed an increased risk of BSI in 235 ICU-admitted patients with COVID-19 (14.9% developed BSI) when compared with 235 ICU-admitted patients without COVID-19 (3.4% developed BSI) [294]. Moreover, a prospective cohort study in 148 hospitals in the US evaluated the potential association between COVID-19 surges and HAIs, including (amongst others) central-line associated BSIs, catheter-associated urinary tract infections, *Clostridioides difficile* infection, and BSIs [146]. This study differed from our study, since it included only a pandemic time period (March to December 2020), evaluating potential association between the number of COVID-19 discharges and the relative rates of HAIs. Positive associations were found between the number of COVID-19 discharges and the relative rates of several of the HAIs. In 81 hospitals with available microbiology data, there was a greater absolute number of hospital-onset BSIs associated with an increase in the number of COVID-19 hospitalizations. In line with the findings of this study, a study of around 7,800 ICU-admitted patients in seven low- and middle-income countries

(LMIC), observed an increased rate of HAIs during the COVID-19 pandemic, including central-line associated BSIs and ventilator-associated events [295]. Furthermore, a recent study from the UK showed increased rates of hospital-onset *Klebsiella* spp. and *Pseudomonas aeruginosa* bacteraemia, coinciding with a sharp increase in cases that were co-infections or secondary infections to COVID-19 cases [296]. Our finding of an increased mortality rate in COVID-19 patients with HOB compared with without HOB is in line with a US multicentre case-control study [297]. The study included 128 patients hospitalized with COVID-19 with a secondary BSI and 247 patients hospitalized with COVID-19 without a secondary BSI. The in-hospital mortality was 53% in those with a secondary BSI and 33% in those without a secondary BSI.

Strengths & limitations

The main strength of this study was the assessment of HOB incidence and mortality in COVID-19 patients as well as entire non-COVID-19 hospital populations both before and during the pandemic. This enabled us to evaluate whether the incidence of HOB and its associated outcomes also were affected in non-COVID-19 populations during the pandemic.

Important limitations include the single-centre retrospective cohort study design, limiting generalizability. Furthermore, we did not have information on potential transfers from other hospitals. This could mean that patients who were transferred to KUH already had experienced a HOB or already had been hospitalized for enough time to make the patient at risk for HOB upon hospital admission. This could have a differential effect on the COVID-19 cohort, since COVID-19 patients more often were transferred between different hospitalizations. Furthermore, we cannot rule out residual confounding due to insufficient adjustment for comorbidities or unmeasured confounding from socioeconomic factors.

5.5 STUDY V

Study V aimed to investigate one-year mortality in patients admitted to the ICU with versus without COVID-19. The study also aimed to compare the number of days alive and free from hospitalization during one year in patients discharged alive from the ICU-associated hospitalization. Furthermore, the main discharge diagnoses registered during subsequent hospitalizations were analysed.

Summary of main results

The study included 13,793 patients admitted to the ICU: 1,427 in the COVID-19 group, 3,253 in the non-COVID-19 group, and 9,113 in the historic group. Furthermore, a subgroup of 860 patients with LRTI were identified from the non-COVID-19 and historic groups. The crude one-year all-cause mortality rate was 32% in the COVID-19 group, 30% in the non-COVID-19 group, 29% in the historic group, and 35% in the LRTI group. The mortality trajectories differed between the groups, with 94% of deaths in the COVID-19 group occurring during the first 60 days from admission to the ICU, compared with 78% in the non-COVID-19 group, 76% in the historic group, and 83% in the LRTI group. The COVID-19 group had in

comorbidity- and sociodemographic-adjusted models a significantly increased risk of one-year mortality compared to the non-COVID-19 and historic group, but not compared to the LRTI group. However, the instantaneous risk differed extensively between day 1-60 and day 61-360, with increased risks during day 1-60 and decreased risks during day 61-360 compared to the three other groups. Furthermore, the increased one-year mortality risk observed in the COVID-19 group was primarily driven by individuals aged 70 years or more.

Seventy percent of the COVID-19 patients were discharged alive from the ICU-associated hospitalization, compared to 78% in the non-COVID-19 group, 80% in the historic group, and 72% in the LRTI group. A total of 73% in the COVID-19 group were alive and free from hospitalization during the entire follow-up (360 days), compared to 45% in the non-COVID-19 group, 42% in the historic group, and 44% in the LRTI group. Among the remaining individuals, the median (Q1-Q3) number of days alive and free from hospitalization were 353 (342-357) in the COVID-19 group, 343 (284-354) in the non-COVID-19 group, 341 (287-354) in the historic group, and 341 (300-354) in the LRTI group. The COVID-19 patients had in comorbidity- and sociodemographic-adjusted models more days alive and free from hospitalization compared to the non-COVID-19 group (adjusted rate ratio (RR) 1.05, 95% CI: 1.04-1.07), the historic group (adjusted RR 1.06, 95% CI: 1.04-1.07), and the LRTI group (adjusted RR 1.05, 95% CI: 1.02-1.07).

The three most common main diagnoses given within inpatient care the year following the ICU-associated hospitalization in the COVID-19 cohort were COVID-19 (2%, n=14), chest pain (1%, n=11), and dyspnoea (1%, n=1) (Figure E4). The most common hospitalization diagnosis was mental and behavioural disorders due to psychoactive substance use in both the non-COVID-19 (7%, n=169) and the historic group (7%, n=497), whereas this was bacterial pneumonia in the LRTI group (5%, n=29). Two percent (n=59) of individuals in the non-COVID-19 group were hospitalized with COVID-19 during follow-up, of which 17% (n=10) died within 60 days.

Comparison with other studies

Our finding of a 32% one-year mortality rate overall among individuals admitted to the ICU with COVID-19 is similar to a 35% one-year mortality rate reported from a Spanish retrospective cohort study of 3,210 patients treated in the ICU with COVID-19 [258]. Furthermore, the 30% in-hospital mortality is also rather similar to the 34% in-hospital mortality rate observed by Ceccato et al [258]. Although not measuring the in-hospital mortality rate, similar findings were also observed in a multinational prospective cohort study including around 20,000 patients admitted to the ICU with COVID-19, with a 28-day mortality ratio of 31% [298]. Interestingly, this study compared the 28-day mortality rate in patients hospitalized with an ICU-admission and patients hospitalized without an ICU-admission. After adjusting for age, sex, comorbidities, and other factors, the authors found patients admitted to the ICU to be less likely to die within 28 days (OR 0.70, 95% CI: 0.65-0.75). Whether the observed difference is due to a protective effect of the ICU-treatment, residual confounding, careful

prognostic selection of patients admitted to the ICU, or other factors remain to be better understood.

We observed a low one-year mortality rate among those individuals surviving the COVID-19 critical illness episode. This also corroborates the findings from the Spanish study by Ceccato et al, where 1% died after hospital discharge [258]. Furthermore, a previous nationwide Swedish study of 2,354 patients admitted to the ICU with COVID-19 during the first three months of the pandemic, observed only 11 deaths after 90 days from the date of ICU-admission [111]. Reasons for this relatively low mortality among survivors of COVID-19 critical illness remain largely unknown but could be due to differential long-term follow-up programs or better underlying health status [258]. Furthermore, another potential reason could be the high acute mortality rates among vulnerable and frail individuals.

We observed 73% of survivors of COVID-19 critical illness to be alive and free from hospitalization during the one-year follow-up period. As such, 27% of COVID-19 patients were readmitted, died, or moved out (<0.5%) of the region during follow-up. Interestingly, in the study by Ceccato et al, only 67 out of 2,108 individuals surviving the COVID-19 critical illness hospitalization were readmitted [258]. Reasons for this big difference is unknown. A study of 106,543 patients hospitalized (with or without treatment in the ICU) with COVID-19 in the US found 9% to be readmitted within two months of discharge [299]. However, different to our study, this study only assessed readmissions to the same hospital as the COVID-19 index hospitalization. A study of 1,775 US veterans surviving an index hospitalization for COVID-19, of which 22% had been treated in the ICU, observed 27% to have been readmitted or died within 60 days [300]. However, making comparisons between a study population enrolled from a general population and a study population drawn from US veterans is difficult, given US veterans are older and almost exclusively men.

Given the difficulties in retrospective analysis of outpatient care services, with potential of differential detection bias in the different groups, we herein focused solely on inpatient care, deemed less prone to such bias. However, as such, we might not have covered extensive parts of health problems following treatment in the ICU. A Dutch study of one-year survivors of COVID-19 related critical illness that observed post-ICU sequelae to be common, with 74% of patients reporting physical symptoms, 26% reporting mental symptoms, and 16% reporting cognitive symptoms [190]. Furthermore, a recent prospective longitudinal study of 114 survivors of COVID-19-ARDS in Italy, found patients to be affected by impaired handgrip strength, worse six-minute walk distance, and severe fatigue, whereas cognitive and mental health status, return to work, and health-related quality of life were less frequently impaired. Whether this indicates that individuals suffering from such symptoms do not require inpatient care, are managed within outpatient healthcare services, or refrain from seeking medical care, is not clear. Primary care physicians play an integral role in the management of sequelae following critical illness, be it after COVID-19 or not, in particular due to their expertise in comprehensive medicine and coordination of care [301,302].

Strengths & limitations

The main strength of this study is the access to four population-based health registries with complete data on SARS-CoV-2 positive testing, inpatient and ICU care, and mortality for the population in the Stockholm Region. Using these data sources, we could identify the three study cohorts as well as the LRTI subgroup and follow these during and beyond the ICU-associated hospitalization for mortality and subsequent inpatient care. Importantly, we had access to data on ICU-admissions both before and during the pandemic, which enabled us to compare the COVID-19 cohort with both pandemic and historic non-COVID-19 cohorts. As such, we included a cohort free from COVID-19 exposure as well as a cohort affected by potentially different strains on ICUs or other structural differences in ICU care during compared with before the pandemic. Furthermore, the near complete data on primary care, outpatient specialist care, drug prescriptions, and socioeconomic information enabled us to adjust for potential confounding health and socioeconomic factors in regression models.

One important limitation of this study is it sole focus on mortality and inpatient care, thus not considering important functional and quality of life-related health outcomes not warranting inpatient care. This includes many physical, psychological, and cognitive impairments of both PICS and PCC. Our findings of more days alive and free from hospitalization in the COVID-19 cohort compared with the other cohorts doesn't necessarily translate into better quality of life or better health status concordant with patient-identified goals. Furthermore, the inclusion period for COVID-19 patients, March 2020 to February 2021, mainly covered a pre-vaccination period of the pandemic with the primary strain as the predominantly circulating strain. As such, the findings might not be generalizable to patients admitted to the ICU with COVID-19 later during the pandemic. Finally, we cannot rule out residual or unmeasured confounding, in particular since the COVID-19 cohort differed extensively from the other cohorts regarding age distribution, sex, region of birth, and comorbidities. Whilst appropriately adjusting for age, sex, and region of birth, we only adjusted for the number of comorbidities without more granular adjustment of specific comorbidities with potentially different confounding characteristics.

5.6 STUDY VI

Study VI aimed to investigate the occurrence of PCC diagnosis, sociodemographic and health status factors associated with the diagnosis, and its effect on healthcare utilization.

Summary of main results

The study included 204,805 SARS-CoV-2 positive individuals: 191,459 not hospitalized during the acute infection, 12,070 hospitalized, and 1,276 treated in the ICU. The overall proportion receiving a PCC diagnosis during follow-up was 1.5%, being 1% among non-hospitalized, 6% among hospitalized, and 32% among ICU-treated individuals. Longer hospitalizations and treatments in the ICU were associated with increased risks of PCC diagnosis. Middle-aged women had compared with men an increased risk of PCC diagnosis among non-hospitalized and hospitalized individuals, with interactions observed between age and sex. A similar, but weaker, trend was observed for ICU-treated individuals. Regarding

health and sociodemographic factors, the strongest associations with PCC diagnosis were observed among non-hospitalized individuals, in particular for more previous primary health care visits, outpatient specialist care visits, and days with sickness benefit, as well as a diagnosis of mental health disorders, and asthma. Among individuals with PCC diagnosis, the proportions with a monthly outpatient care visit after the infection was substantially elevated up to one year after the acute infection compared with matched controls without PCC diagnosis. A large proportion of the outpatient care in individuals with PCC diagnosis was related to PCC, particularly in the primary care setting.

Comparison with other studies

Our finding of an overall 1.5% occurrence of PCC diagnosis is difficult to directly compare with findings from other studies. Previously reports on the occurrence of PCC have varied substantially, ranging from below 10% to well above 50% [175]. According to the WHO, approximately 10 to 20% of people who have had COVID-19 continue to suffer from different mid- and long-term effects [170]. Such estimates differ from a recent meta-analysis of 41 studies, estimating the pooled prevalence of PCC to be 43% (95% CI: 39-46%) [303]. In a recent study from the UK, investigating the occurrence of PCC in around 7,000 individuals with self-reported COVID-19, the proportion reporting PCC-related symptoms for twelve weeks or more ranged from around 8 to 17%, whereas around 1 to 5% reported debilitating symptoms [304]. Interestingly, this study also analysed the occurrence of PCC diagnosis codes in primary care among around 1.1 million individuals with an acute COVID-19 diagnostic code. In this analysis, 0.4% (4,189 individuals) had a recorded PCC code. As discussed by Thompson et al, the discrepancies in proportions with self-reported symptoms and PCC diagnosis codes in primary care indicate that only a minority of people with PCC-related symptoms actively seek care, or the awareness of the diagnosis code is still limited amongst primary care practitioners. Contrasting these lower proportions, a recent prospective cohort study from South Africa reported around two thirds of study participants to report new or persistent COVID-19-related symptoms three months after discharge from a COVID-19 hospitalization [305]. However, this study only included patients who had been hospitalized with COVID-19, in contrast to our study and the study by Thompson et al also including non-hospitalized individuals [304]. Furthermore, among around 8,300 study participants randomly selected for enrolment, Dryden et al were able to contact around 37%, of whom 61% consented to participate at three months after hospital discharge [305]. However, the observed 67% are still much higher compared with a pooled proportion of 20% with a PCC diagnosis among hospitalized and ICU-treated individuals in our study. A study of around 1,000 patients discharged from a COVID-19 hospitalization in the UK observed only 29% to feel fully recovered at follow-up visits around 6 months later [306]. This proportion was 19% among individuals with the most severe disease during hospitalization compared with 31% among individuals with the least severe disease during hospitalization. Our finding of a major difference in occurrence of PCC diagnosis by different severities of the acute COVID-19 episode is also in line with a study of 181,385 US veterans with COVID-19, where the burden of PASC was 4.5% in non-hospitalized individuals, 22% in hospitalized individuals, and 36% in ICU-treated individuals [182]. Similarly,

a Danish registry-based study of around 7,500 patients with varying severity of COVID-19 observed hospital admission, and in particular ICU-admission, to be associated with a lower chance of returning to work among individuals 18-64 years old who were available to the workforce and who survived the first 30 days [307].

On a general note, our understanding of factors associated with developing PCC are much less understood compared with our understanding of factors associated with severe COVID-19 [308]. This discrepancy could possibly be due to our still limited understanding of how to best define PCC, and if it should be regarded as several distinct phenotypes with differences in underlying risk factors, pathogenesis, and pathophysiology [309]. We observed female sex to be associated with PCC, in particular among non-hospitalized and hospitalized individuals. This finding is in line with several previous reports [303–306,310–312]. Reasons for this still remain largely unknown but could potentially be due to differences in sex hormones and innate and acquired immunological profiles [313,314]. Importantly, the associations between female sex and PCC diagnosis not only differed across the different severities of the acute infection, but also across the ages, with most pronounced differences observed among middle aged individuals. These findings are in line with estimates of the prevalence of self-reported PCC data from the Office for National Statistics in the UK, where the prevalence was higher in people aged 35 to 69 years and females [315]. As mentioned by Ortona et Malorni, no significant difference in PCC occurrence has been observed between male and female children, which could indicate sex hormones and their immunomodulating activity to play a potential role in the pathophysiological processes of PCC [314]. The non-linear relationship we observed between age and PCC diagnosis is also consistent with findings from some previous reports. Evans et al found ages 40-59 years to be associated with worse recovery and Thompson et al found the proportion of COVID-19 cases with a subsequent PCC diagnosis to be lower among the younger as well as older age groups [304,306]. Whether such associations are due to biological processes or differences in healthcare seeking behaviour, attitudes towards normal recovery, or access to healthcare remains to be better understood.

Regarding comorbidities associated with PCC, we observed both asthma and mental health disorders to be associated with PCC in non-hospitalized and hospitalized individuals. Dryden et al and Thompson et al also found asthma to be associated with PCC [304,305]. Asthma was also found to be the only pre-existing condition significantly associated with symptoms persisting over 28 days by Sudre et al [310]. However, a Spanish case-control study found the presence of PCC-related symptoms to be similar between patients with and without pre-existing asthma [316]. Thompson et al found an increased odds of a PCC code in individuals with a previous psychiatric condition and in individuals who had experienced greater pre-pandemic psychological distress [304]. Furthermore, a recent cohort study including primarily females, found pre-infection depression, anxiety, worry about COVID-19, perceived stress, and loneliness to be associated with PCC [317]. A US multistate telephone survey of individuals with an outpatient SARS-CoV-2 positive test also found reporting a psychiatric condition to be associated with an increased odds of not returning to the usual health status two to three weeks after the positive test [318].

Regarding healthcare utilization after and before the acute infection in individuals with and without a PCC diagnosis, our observation of increased outpatient healthcare use up to one year after the infection in individuals with PCC indicates incomplete recovery. To the best of my knowledge, no previous study has compared healthcare utilization in individuals with and without a PCC diagnosis before and after the infection. As such, these specific findings cannot be compared with other studies. However, large studies have been conducted on the healthcare utilization among individuals following COVID-19 in general. In a UK study including around 1,400 general practices and 450,000 patients with a diagnosis of COVID-19, found the consultations rates and contact reasons to differ between those patients who had been admitted to hospital with COVID-19 and those who had been managed in the community [319]. Furthermore, Whittaker et al observed that for those individuals who had been managed in the community, some sequelae decreased over time, whereas others such as anxiety and depression, persisted throughout the follow-up period [319]. A Norwegian population-wide study of around 1.4 million adults testing for SARS-CoV-2 between 1 March 2020 and 1 February 2021 found COVID-19 not requiring hospitalization to result in a transient increased utilization of primary care, vanishing around 2-3 months after the positive test [320]. A retrospective cohort study based on data from the US and seven other countries observed different risk trajectories for different neurological and psychiatric outcomes following COVID-19 when compared with other respiratory infections [176]. Such differences included more transient increases in risk of mood and anxiety disorders, whereas for instance psychotic disorders, cognitive deficits, and dementia persisted throughout the entire study period. Importantly, our analysis of healthcare utilization in individuals with PCC and matched controls indicated that the non-hospitalized controls did not consume more healthcare after compared with before the acute infection. This could indicate that the diagnosis code accurately captured those with symptoms and sequelae after the acute infection.

Strengths & limitations

The main strength of this study was the access to population-based data from multiple health registries, which enables us to identify all individuals with a verified SARS-CoV-2 infection in the region who met the study inclusion criteria. This leads to an increased external validity and reduced selection bias when compared with studies enrolling the study population from patients seen in outpatient clinics specialized in PCC, users of symptom tracking applications, or specific population groups such as veterans or healthcare workers. These data sources further enabled us to stratify the study population by severity of the SARS-CoV-2 infection, including both non-hospitalized, hospitalized, and ICU-treated individuals. In a living systematic review of PCC, only one-third of the included studies (13 out of 39 studies) included non-hospitalized study subjects [173]. Finally, we had access to near complete data on medical diagnoses, drug prescriptions, socioeconomic information, and outpatient and inpatient healthcare utilization before and after the infection, enabling assessment of several factors potentially associated with getting a PCC diagnosis and the healthcare utilization trajectory in individuals with and without such a diagnosis. Having access to primary care data is particularly important since primary care plays an integral role in the management and diagnosis of PCC [301].

Despite the above-mentioned strengths, several important limitations should be acknowledged. First and foremost, despite being population-based, this was a retrospective cohort study set in the Stockholm Region in Sweden, a high-income country which has gained much attention for its distinctive strategy and response throughout the COVID-19 pandemic. Consequently, our results might not be generalizable to other geographical settings, including low- and middle-income countries as well as other high-income countries. Furthermore, the PCC outcome classification was based on getting a PCC diagnosis within the healthcare system. A large proportion of those experiencing symptoms after COVID-19 might not have had easy access to outpatient healthcare services during parts of the pandemic and differences in healthcare seeking behaviour, rather than differences in experienced symptoms, might have influenced our findings on the occurrence of PCC as well as associated factors and healthcare utilization. However, Thompson et al analysed both data based on reporting of PCC-related symptoms and diagnostic codes for PCC in EHRs and found several risk factor associations to be consistent across these two different data sources [304]. Maybe more importantly, since the PCC diagnosis code was first introduced in Sweden in October 2020, individuals infected during the first months of the pandemic might not have had the same possibility to get the diagnosis compared with later parts of the study inclusion period. This is further complicated by the fact that a clinical case definition from the WHO was not available until one year later, in October 2021. As such, the interpretation of PCC and the subsequent use of the PCC diagnosis might have varied substantially between different healthcare facilities and practitioners, possibly resulting in diagnostic misclassification and underreporting. Finally, we did not have access to COVID-19 vaccination status for the study population. As such, we could not address this in our analyses of individuals with a first positive SARS-CoV-2 PCR-test from the end of December 2020 to the end of the study period.

6 CONCLUSIONS

The aim of this thesis was to characterize clinical presentation and outcomes in patients hospitalized with COVID-19 and compare these with other respiratory virus infections and hospital populations. Collectively, the following conclusions were drawn:

Clinical presentation:

I. The patient and clinical characteristics of COVID-19 upon hospital admission were not sufficiently distinct to accurately distinguish it from other respiratory virus infections.
II. The occurrence of detected bacterial co-infection upon hospital admission was substantially lower in SARS-CoV-2 positive CAP compared with influenza or RSV positive CAP.

Acute outcomes:

I. COVID-19 was associated with more severe acute outomes, in particular mortality, compared with other respiratory virus infections and ICU populations. The increased risk of mortality was greatest among the elderly.
II. The VA-LRTI incidence rate was increased for patients metchanically ventilated with COVID-19 compared with other infectious diseases. This was however not the case when compared with most non-infectious diseases.
III. HOB, another hospital-onset infection, was more common in COVID-19 patients compared with pre-pandemic as well as pandemic hospital populations. Furthermore the HOB incidence in non-COVID-19 patients were higher during the pandemic when compared with before the pandemic.

Long-term outcomes:

I. Survivors of COVID-19 critical illness had compared with other critical illness suvivors more days alive and free from further hospitalizations during the next year.
II. The occurrence of PCC diagnosis was substantially higher in individuals hospitalized versus not hospitalized during the acute COVID-19 episode.
III. Associations between health status factors and PCC diagnosis differed by severity of the acute COVID-19 episode, with more and stronger associations among those not hospitalized during the acute infection.
IV. Increases in outpatient healthcare utilization up to one year after the acute infection indicated an incomplete recovery in individuals diagnosed with PCC.

Taken together, patients hospitalized with COVID-19 experienced more severe acute outcomes when compared with other respiratory virus infections and hospital populations, in particular among the elderly. Furthermore, the occurrence and trajectory of PCC varied across different severities of the acute infection. These studies contribute to our understanding of both the acute and long-term clinical epidemiology of COVID-19.

7 FUTURE PERSPECTIVES

As of September 2022 in Sweden, around 85% of the population aged 12 years or more has received at least two doses of COVID-19 vaccine and around 25% of the entire population has had a verified infection [23]. Furthermore, the currently circulating VOC, omicron, has repeatedly been shown to cause less severe disease when compared with previous circulating VOCs [63–65,99]. Contrasting the current situation, the six studies presented in this thesis, primarily covered a period of the pandemic when COVID-19 vaccines were not available, and infections were almost exclusively caused by the primary strain of SARS-CoV-2. As such, the generalizability of our findings over time might be limited. This brings up another important aspect of how research about an unfolding pandemic should best be facilitated and conducted. From a data analysis perspective, almost all results presented in the six studies in this thesis were analysed in such a manner that they could be continuously updated throughout the pandemic to provide continuously updated results and evidence. However, the data sources were not continuously updated, but rather updated in batches with often rather long lead times. If compliant with the legal and ethical requirements, a system with shorter lead times and a more continuous update of data could hopefully facilitate more timely observational research [321].

The gap in global vaccination rates needs to be reduced, in particular among those most at-risk of severe disease, including the elderly and individuals with poorer underlying health status. Furthermore, surveillance, testing, and sequencing are key elements to continue monitoring viral evolution in near real-time. Our finding of patient and clinical characteristic of COVID-19 to not be sufficiently distinct to distinguish it from other respiratory virus infections highlight the need of readily available microbiological testing to distinguish such infections, in particular when different respiratory viruses co-circulate. Whilst many high-income countries now have set up robust systems for SARS-CoV-2 testing, low- and middle-income countries still struggles to access such existing tools [322]. As highlighted by Batista et al, of the 3.2 billion test that had been performed by September 2021 worldwide, only 0.4% were in LMICs [322].

An improved understanding of how the pandemic has caused disruptions and backlogs in healthcare delivery is also necessary. According to a report from England, there were 2.9 million fewer elective inpatient admissions, 1.2 million fewer emergency inpatient admissions, and 17.1 million fewer outpatient appointments between March and December 2020 when compared with the same period in 2019 [323]. Furthermore, a significant increase in antimicrobial use and a lower adherence to infection prevention and control guidance was observed in US hospitals in 2020, leading to an increase in HAIs from antimicrobial-resistant pathogens [324]. More studies and reports on this matter are needed, particularly from low- and middle-income countries where the burden of AMR is known to be disproportionally higher [325]. We found the incidence of HOB and its associated mortality to increase among both COVID-19 and non-COVID-19 patients during the pandemic. Potential implications of such increases were demonstrated in a recent report, which found each event of BSI to lead to an average loss of 6.2 potential life years, with almost 50% of all affected patients dead within one year [326]. As discussed before, several other studies have reported increases of HAIs during the pandemic

and among patients with COVID-19. Much more research is needed to understand the underlying reasons for this, including the effect of structural changes in hospital practices and the effect of healthcare strains on the quality of provided care. Such insights could provide important lessons to be learned for future pandemic preparedness.

At the same time as the number of weekly reported deaths to be near the lowest since the pandemic began, it is estimated that around 17 million people in the WHO European Region may have experienced PCC [327]. Furthermore, protesters outside the White House in the US recently demanded better PCC care [328]. However, as mentioned previously in this thesis, the scientific basis for treatments of PCC currently has a very low reliability [199]. Such a lack of scientific evidence for treatment strategies for a condition estimated to affect or have affected millions of people calls for urgent actions. As pointed out by Xie et al, PCC is not a monolithic entity, and as such the burden of the individual components of the syndrome might be differentially expressed across different population groups [182]. A better understanding of the underlying pathogenesis and pathophysiological hallmarks of PCC is warranted [329]. However, allocation of resources for clinical care and research on PCC must be balanced against other parts of medical research and healthcare. It is for example still not fully understood if and how PCC differs from PICS in such a manner that differential follow-up strategies are warranted following treatments in the ICU with or without COVID-19. Notably, more recent research has shown the risk of PCC to be reduced following COVID-19 caused by omicron when compared with COVID-19 caused by delta [196]. Hopefully this finding will remain consistent over time, with reduced numbers of individuals developing PCC. Larger survey-based studies and prospective cohort studies are warranted to better understand temporal patterns of recovery among patients suffering from PCC.

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