The surveillance of patients hospitalised with COVID-19 in Norway, February 2020 – May 2022

Systems comparisons, risk factors and clinical course

Robert Neil Whittaker

Thesis for the degree of Doctor Philosophiae (dr. philos.)
University of Bergen, Norway
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Summary (English)

Background: In Norway, three systems for the surveillance of patients hospitalised with COVID-19 were set up to monitor pandemic severity. One involved manual, aggregated data collection on hospital bed occupancy, and two were based on national electronic health registry (EHR) data.

Aims: To compare and critically appraise systems for the surveillance of patients hospitalised with COVID-19 in Norway, and to use surveillance data to contribute to ensuring a timely, appropriate and evidence-based public health response in an evolving pandemic setting.

Methods: Observational registry-based cohort studies.

Results: Each system provided a comparable trend in the disease-specific hospital bed occupancy of COVID-19 patients. The EHR had challenges in identifying prevalent patients in intensive care or on invasive ventilatory support. The coverage of COVID-19 patients in each EHR decreased from late 2021 due to high vaccination coverage, spread of the Omicron variant and removal of statutory restrictions. The distribution of diagnosis codes varied by reported main cause of admission, age and time. Vaccination and the Omicron variant were associated with reduced disease severity among hospitalised patients (e.g. reduced length of stay and risk of intensive care). We did not find clear evidence that the Alpha variant (compared to non-variants of concern) was associated with disease severity among hospitalised patients, nor that the risk of hospitalisation among cases of COVID-19 <18 years old varied by infecting variant.

Conclusions and recommendations: Collectively, the three systems provided an accurate picture of hospitalised COVID-19 patients in Norway, but the studies in this thesis also highlight opportunities for improving the use of EHR-data for this surveillance. Surveillance systems for hospital admission in future health crises should ideally be built on data flows from established systems and include detailed disease-specific data. Linked individual national registry data provide a blueprint for robust, integrated and sustainable infectious disease surveillance.

Sammendrag (norsk)

Bakgrunn: I Norge ble tre ulike system for overvåking av pasienter innlagt i sykehus med COVID-19 opprettet for å overvåke alvorligheten av pandemien. Ett var en aggregert, manuell innrapportering om belegg ved sykehusene, og to var basert på data fra nasjonale elektroniske helseregistre (EHR).

Formål: Å sammenligne og kritisk vurdere systemer for overvåking av pasienter innlagt i sykehus med COVID-19 i Norge, og å bruke overvåkingsdata for å bidra til å sikre tidsriktig, hensiktsmessig og evidensbasert håndtering av en utviklende pandemisk situasjon.

Metoder: Registerbaserte kohortstudier.

Resultat: Hvert system ga en sammenlignbar trend i belegg av COVID-19 pasienter ved sykehus. EHR hadde utfordringer med å identifisere pasienter innlagt i intensivavdeling eller på invasiv ventilasjonsstøtte. Dekningsgraden av COVID-19-pasienter i hvert EHR ble redusert fra slutten av 2021 på grunn av høy vaksinasjonsdekning, spredning av Omikron-varianten og opphør av lovpålagte restriksjoner. Fordelingen i diagnosekoder varierte etter rapportert hovedårsak til innleggelse, alder og innleggelsestidspunkt. Vaksinasjon og Omikron-varianten var assosiert med et mildere sykdomsforløp blant innlagte pasienter (f.eks. kortere liggetid og lavere risiko for innleggelse i intensivavdeling). Vi fant ingen assosiasjon mellom Alpha-varianten og sykdomsforløpet blant innlagte pasienter (sammenlignet med ikke-bekymringsvarianter), og heller ikke at risikoen for sykehusinnleggelse blant tilfeller av COVID-19 <18 år gammel varierte med virusvariant.

Konklusjoner og anbefalinger: Sammen ga de tre systemene et nøyaktig bilde av innlagte COVID-19 pasienter i Norge, men studiene i denne avhandlingen viser også muligheter for å forbedre bruken av EHR-data i denne overvåkingen. Overvåkingssystemer for pasienter innlagt i sykehus i fremtidige helsekriser bør ideelt baseres på dataflyt fra etablerte system og inkludere sykdomsspesifikke data. Koblede nasjonale registerdata kan være grunnlaget for robust, integrert og bærekraftig overvåking av infeksjonssykdommer.

Acknowledgements

It is only now that the dust has settled that it feels possible to truly appreciate the uniqueness of the setting and period covered by this thesis. For those of us working in '*Epianalysegruppe*' (the Epidemiology Analysis Group) at the Norwegian Institute of Public Health the COVID-19 pandemic was an endless, erratic and ever-evolving rollercoaster of analyses, requests, discussions, debates, reports, studies, late nights and discarded weekends.

It was completely by chance that I ended up as head of '*Team Overvåking*' (Team Surveillance) in the Emergency Preparedness Register for COVID-19 and as the main contact point for surveillance data on patients hospitalised with COVID-19 in '*Epianalysegruppe*'. The opportunity to work on the papers in this thesis all stemmed from there. While intense and tough at times, I am immensely grateful to have had this fascinating, stimulating and professionally enriching experience. However, what I am most grateful for is all the people I have had the chance to work with and get to know during the pandemic, both digitally and (eventually) in person.

My first thanks go to everyone in '*Epianalysegruppe*' and '*Team Overvåking*'. It is not often that you get the chance to work so closely with and learn from such an engaged, friendly, competent and supportive group. I would especially like to thank Hilde Kløvstad, leader of '*Epianalysegruppe*', for guiding us through and always making us smile when it felt like one had forgotten how. I'll always remember the feeling of excitement to find out what the 'rooster' was going to do each weekend. A big thanks to Hilde as well for encouraging me to write this thesis. During the pandemic it was often not possible to keep track of things beyond your own set of narrow and ever-changing tasks. This thesis has allowed me to properly reflect on this period, not least frame and discuss the research in a wider context and with a broader evidence base and understand what we could have done differently. I also want to specifically thank Elina Marjukka Seppälä, the main colleague I worked with on the surveillance of patients hospitalised with COVID-19, for the daily companionship throughout the pandemic and the pleasure of solving different challenges together.

A huge thanks to all co-authors for their contribution to various elements of the different papers. I would like to specifically mention Anja Bråthen Kristoffersen, Elina Marjukka Seppälä, Lamprini Veneti and Mari Grøsland, who I worked most closely with on different COVID-19 studies throughout the pandemic, including those included in this thesis.

The work in this thesis would not have been possible without good collaboration with external partners, particularly the Norwegian Directorate of Health and Norwegian Intensive Care and Pandemic Registry. I would specifically like to thank Eirik Alnes Buanes, leader of the Norwegian Intensive Care and Pandemic Registry, for his engagement, responsiveness and essential clinical insight. Thanks also to the team at the Emergency Preparedness Register for COVID-19, which made the papers in this thesis possible and has provided the blueprint for enhanced registry-based surveillance of other infectious diseases in Norway.

Furthermore, an enormous thanks to Preben Aavitsland at the Norwegian Institute of Public Health, who gave up his time and expertise to guide me through the process of preparing this thesis, providing constructive, timely and valuable feedback.

Finally, an unquantifiable thanks to Malin, Alvin, 'Apple' and family back home in New Zealand and Sweden. You put up with excessive overtime hours during the pandemic, while the hardest part of this process has been having to forgo even more family time to put this thesis together. Your love and support are invaluable.

List of papers

Paper I

Whittaker R, Grøsland M, Buanes EA, Beitland S, Bryhn B, Helgeland J, Sjøflot OI, Berild J, Seppälä E, Tønnessen R, Telle K. Hospitalisations for COVID-19 – a comparison of different data sources. Tidsskr. Nor. Legeforen. 2020;140(18).

Paper II

Whittaker R, Toikkanen S, Dean K, Lyngstad T, Buanes EA, Kløvstad H, Paulsen TH, Seppälä E. A comparison of two registry-based systems for the surveillance of persons hospitalised with COVID-19 in Norway, February 2020 to May 2022. Euro Surveill. 2023;28(33).

Paper III

Whittaker R, Greve-Isdahl M, Bøås H, Suren P, Buanes EA, Veneti L. COVID-19 hospitalisation among children <18 years by variant wave in Norway. Pediatrics. 2022;150(3).

Paper IV

Whittaker R, Kristofferson AB, Seppälä E, Valcarcel Salamanca B, Veneti L, Storm ML, Bøås H, Aasand N, Naseer U, Bragstad K, Kvåle R, Golestani K, Feruglio S, Vold L, Nygård K, Buanes EA. Trajectories of hospitalisation for patients infected with SARS-CoV-2 variant B.1.1.7 in Norway, December 2020 – April 2021. J. Infect. 2021;83(4):e14-e7.

Paper V

Whittaker R, Kristofferson AB, Valcarcel Salamanca B, Seppala E, Golestani K, Kvåle R, Watle S, Buanes EA. Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a registry-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients. Clin Microbiol Infect. 2022;28(6):871-8.

Paper VI

Stålcrantz J, Kristoffersen AB, Bøås H, Veneti L, Seppälä E, Aasand N, Hungnes O, Kvåle R, Bragstad K, Buanes EA, Whittaker R. Milder disease trajectory among COVID-19 patients hospitalised with the SARS-CoV-2 Omicron variant compared with the Delta variant in Norway. Scand. J. Public Health. 2022;50(6):676-82.

All papers are available open access, except paper VI, for which a preprint under the same title is available on MedRxiv: https://doi.org/10.1101/2022.03.10.22272196.

List of abbreviations

(a)HR	(Adjusted) Hazard Ratio	MIS-C	Multisystem Inflammatory Syndrome in Children
(a)OR	(Adjusted) Odds Ratio	MSIS	Norwegian Surveillance System for Communicable Diseases
(a)RR	(Adjusted) Risk Ratio	NIPaR	The Norwegian Intensive Care and Pandemic Registry
ARI	Acute upper and lower respiratory infection	NIPH	Norwegian Institute of Public Health
Beredt C19	The Emergency Preparedness Register for COVID-19	NIR	Norwegian Intensive Care Registry
CI	Confidence interval	NoPaR	Norwegian Pandemic Registry
COVID-19	Coronavirus disease 2019	NPR	Norwegian Patient Registry
ECDC	European Centre for Disease Prevention and Control	RHA	Regional Health Authorities
EHR	Electronic health registry	RSV	Respiratory Syncytial Virus
Freg	National Population Register	SARI	Severe Acute Respiratory Infection
Hdir	The Norwegian Directorate of Health	SARS-CoV	Severe acute respiratory syndrome coronavirus
ICD-10	International Classification of Diseases, 10th Revision	SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ICU	Intensive Care Unit	SYSVAK	Norwegian Immunisation Registry
IQR	Interquartile range	URI	Acute upper respiratory infection
KUHR	Norwegian Control and Payment of Health Reimbursements Database	VOC	Variant of concern
LoS	Length of Stay	WHO	World Health Organisation
MERS-CoV	Middle East respiratory syndrome coronavirus		

1. Introduction

1.1 Coronavirus disease 2019

1.1.1 The SARS-CoV-2 virus

Family and origins

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China on 7 January 2020 (1). It is a member of the Sarbecovirus subgenus (genus Betacoronavirus, subfamily *Orthocoronavirinae*, family *Coronaviridae*). Coronaviruses are positive-sense single-stranded RNA viruses, with spike proteins protruding from their viral envelope giving them their crown-like appearance (Figure 1). The first coronaviruses were identified in the 1930s and the first human coronaviruses in the 1960s (2). SARS-CoV-2 was the 7th documented coronavirus to infect humans (2) and may have entered the human population between mid-October and mid-November 2019 (3). Betacoronaviruses primarily infect mammals and, while no natural reservoir nor definite intermediate host for SARS-CoV-2 has been identified, a zoonotic origin remains the most plausible explanation (4). SARS-CoV-2 is closely related to bat Betacoronaviruses and more distantly to two other Betacoronaviruses that have caused epidemics of severe respiratory disease in humans, Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (5, 6).

Transmission

SARS-CoV-2 is primarily transmitted directly by respiratory droplets and both short- and long-distance airborne transmission (7, 8). Other routes of transmission, such as vertical transmission and transmission via fomites, may occur but contribute minimally to ongoing transmission (8-10). The basic reproductive rate (the average number of secondary transmissions from one infected person), or R_0, for SARS-CoV-2 prior to the emergence of so-called 'Variants of concern' (VOC, see the paragraph on page 3) was estimated to be around 2.5, similar to that of SARS-CoV (11). However, SARS-

CoV-2 transmission is also heterogenous and most cases may be traced back to a few select 'superspreaders' (8). Unlike for SARS-CoV (12), asymptomatic and presymptomatic individuals can transmit SARS-CoV-2 (13). SARS-CoV-2 viral load and transmission risk peak around the time of symptom onset, with infectious virus able to be isolated up to around 10 days after symptom onset (14).

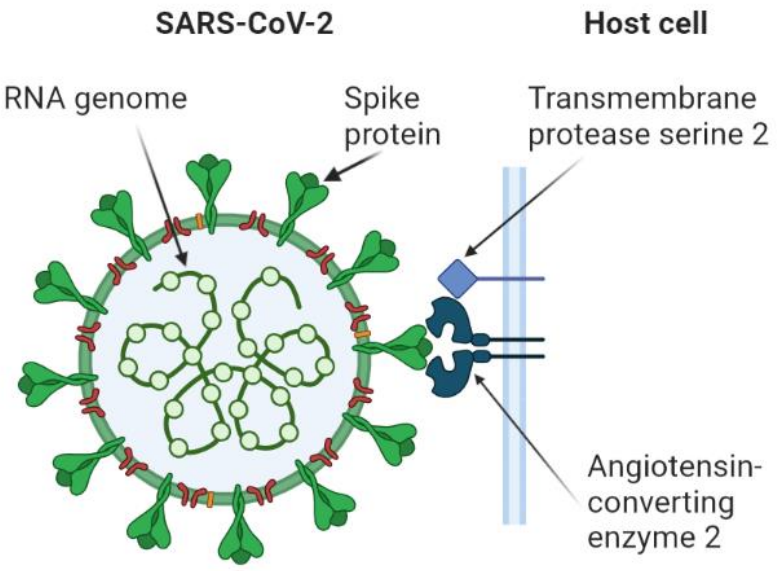

Figure 1: Basic structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and interaction with host cell receptor for angiotensin-converting enzyme 2.

Image created in www.biorender.com.

Infection

As with other coronaviruses, infection with SARS-CoV-2 is mediated through the spike protein (Figure 1). The spike protein is responsible for binding and viral uptake into host cells and therefore determines cell and host specificity (2). The main cell receptor for SARS-CoV-2 is angiotensin-converting enzyme 2, which is expressed on cells in a range of human tissues. This receptor, along with host proteases such as transmembrane protease serine 2, facilitates viral entry into host cells. SARS-CoV-2

has been shown to replicate easily in epithelial cells of the upper and lower respiratory tract, as well as other body sites where angiotensin-converting enzyme 2 and transmembrane proteases serine 2 may be co-expressed, such as the gastrointestinal tract (2, 15, 16). The spike protein also plays a central role in the interaction between SARS-CoV-2 and the host immune system (17). Natural and vaccine-induced immunity may wane over time and reinfection can occur (18, 19).

Variants of concern

While SARS-CoV-2 mutates more slowly than other RNA viruses (20), mutations in the spike protein have resulted in the emergence of different genetic lineages. VOC are lineages of SARS-CoV-2 with mutations that change "*how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures*" (21). They were first defined in December 2020 (21) and have influenced transmission dynamics, viral virulence and immune evasion (14, 17, 22-27).

1.1.2 Disease course and risk factors for severe disease

The disease caused by SARS-CoV-2 infection is called Coronavirus disease 2019 (COVID-19) (28). The spectrum of COVID-19 may range from asymptomatic infection to severe respiratory failure. Early systematic reviews and meta-analyses suggested that 30 – 40 % of SARS-CoV-2 infections may be asymptomatic, with a higher proportion in younger age groups (29, 30). This proportion has likely increased, due for example to vaccination and the emergence of the Omicron VOC (Pangolin designation B.1.1.529) (31-33).

The average incubation period (time from infection to symptom onset) for symptomatic COVID-19 prior to the emergence of VOC was estimated to be 4 – 6 days, with few showing symptoms more than 14 days after exposure. The average incubation period has been reported to have shortened with the emergence of different VOC. For Omicron sublineage BA.1 it was estimated to be just over 3 days (14, 34). The most common symptoms initially described for COVID-19 in the pre-VOC (ancestral strain) and pre-vaccination period included fever, cough and fatigue, with a wide range of other

symptoms also reported including muscle aches, sore throat, runny nose, headaches, diarrhoea and loss of taste or smell (35-37). The reported duration and range of symptoms experienced by symptomatic COVID-19 cases has evolved over time. For example, compared to the Delta VOC (B.1.617.2), Omicron sublineage BA.1 has been associated with milder symptoms of shorter duration, higher frequency of sore throat and lower frequency of loss of smell (38, 39). Also, vaccinated cases have experienced milder symptoms of shorter duration than unvaccinated cases (32, 33).

In mild cases of COVID-19 the infection is generally limited to the upper respiratory tract (15). The onset of acute severe disease is related to a powerful inflammatory response and vascular leakage in the lower respiratory tract. This generally occurs 1 – 2 weeks after initial symptom onset (15, 36, 40), although this time interval may depend on patient factors such as age (41). Dyspnoea and pneumonia can rapidly progress to acute respiratory distress syndrome requiring intensive care and mechanical ventilation. Multi-organ dysfunction and secondary infections may also increase the severity of disease (15, 36, 40).

Age was quickly identified as the most important risk factor for acute severe COVID-19 (42-45). An analysis of seroprevalence surveys from 53 countries in the pre-VOC and pre-vaccination period found an infection-fatality rate of 0.002% among 7-year-olds, increasing to 0.06% among 30-year-olds, 2.9% among 70-year-olds, and 20% among 90-year-olds (46). Other important intrinsic risk factors initially identified in different cohorts included male sex, a wide range of underlying comorbid conditions (such as diabetes, chronic kidney, liver, cardiac or respiratory disease, active cancer, obesity and compromised immune function), pregnancy, certain ethnicities, level of socioeconomic deprivation and patient genetics (42-45, 47-53). In addition to patient factors, setting and healthcare system aspects also influenced healthcare resource use and patient outcomes (41, 54-56). As the COVID-19 pandemic progressed other factors began to further influence the risk of acute severe disease. Natural or vaccine-induced immunity decreased the risk of severe disease (19, 57-61), while the emergence of different VOC was associated with both decreases (23, 62-65) and increases (26, 66-68) in the risk of severe disease, compared to previously circulating variants.

For children, while the risk of acute severe disease is low, a severe post-infectious inflammatory condition named Multisystem Inflammatory Syndrome in Children (MIS-C) had been described by May 2020 (69). It was initially estimated to occur in one in 4,000 cases <18 years in Denmark, a setting with high test activity in younger age groups (59). However, like acute severe COVID-19 this risk has also been drastically reduced by vaccination and the emergence of the Omicron VOC (59, 70, 71). A similar syndrome in adults has also been described (72). Also, for some of those who had a mild acute disease course a range of post-acute sequelae (termed 'Long COVID') have been described (73).

1.1.3 Outbreak and global spread

On 31 December 2019, health authorities in China reported a cluster of cases of pneumonia with unknown cause linked to a seafood market in Wuhan (1). An initial cluster of 41 cases was reported, 27 (66%) of which had been exposed to the seafood market. All were admitted to hospital with pneumonia and six (15%) died (36). On 7 January 2020, SARS-CoV-2 was identified as the causative agent (1). On 8 January, Thailand identified the first case outside China, in a traveller coming from Wuhan (74). Following a field visit to Wuhan on 20 – 21 January, the World Health Organisation (WHO) reported evidence of human-human transmission (75). The first cases in Europe were reported in France on 24 January (76) (with later evidence suggesting cases in France as early as November 2019 (77)). A cluster of 16 cases in Bavaria, Germany a few days later provided the first known example of human-human transmission in Europe (78). By 30 January, almost 20,000 confirmed or suspected cases of COVID-19 and 170 deaths had been reported throughout China, while 83 cases had been reported in 18 other countries. On that day, WHO declared the outbreak a Public Health Emergency of International Concern (79). On 11 February, as the reported number cases in China exceeded 70,000 with over 1,000 deaths (42), WHO announced that the disease was to be named COVID-19 (28). By the end of February, most new cases were being reported from outside of China, with local transmission reported by 17 countries. The Republic of Korea, Japan, Italy and Iran reported the highest number of cases (80). An outbreak on an international cruise ship provided a

unique opportunity to study transmission dynamics (81). On 11 March (118,000 cases in 114 countries and over 4,000 deaths) the WHO declared COVID-19 to be a pandemic (82). On 4 April 2020, with the pandemics' epicentre firmly in Europe, confirmed case numbers topped 1,000,000 globally, with over 50,000 deaths (83).

1.1.4 The COVID-19 pandemic in Norway

First wave: the introduction of SARS-CoV-2 to Norway

In Norway, laboratory diagnostics for SARS-CoV-2 were established on 23 January 2020 and COVID-19 become a notifiable disease on 31 January. The first case was confirmed on 26 February, with the majority of the initial imported cases reported to have been infected in Austria, Spain or Italy during the recent winter holidays (84). Cases were isolated and their close contacts were quarantined. The first person hospitalised with COVID-19 in Norway was admitted on 6 March and the first death was on 12 March (84). Testing initially focussed on travellers returning from countries with widespread transmission and close contacts of confirmed cases. As SARS-CoV-2 began to spread around Norway, the testing policy was shifted to focus on health care workers and those at greatest risk of severe disease (84). Similarly to elsewhere, high age, underlying comorbid conditions and male sex were associated with an increased risk of hospital admission among COVID-19 cases (48). An increasing array of non-pharmaceutical measures to reduce social contact was implemented, culminating in the closure of kindergartens, schools, and hospitality services and businesses with one-on-one contact with customers, cancellation of cultural and sporting activities (12 March), and closing of borders to non-residents (16 March) (84). Hospitals were instructed to reduce normal operations and prepare for an influx of COVID-19 patients. All-cause inpatient admission rates for elective and emergency care decreased (85).

During this first wave there was a peak of 288 new admissions to hospital with COVID-19 as main cause and 77 new admissions to an intensive care unit (ICU) with COVID-19 in week 13 2020 (Figure 2, Figure 3). At the end of March 2020 over 350 people were hospitalised with COVID-19. As the first wave subsided, the non-pharmaceutical measures were revised (for example, kindergartens and schools gradually reopened

from mid-April), a process that would remain continual as the pandemic evolved until 12 February 2022, when all statutory measures were removed (86).

Second wave: increased testing and the start of the vaccination programme

As the second wave started in late summer of 2020, testing capacity and activity for SARS-CoV-2 (and subsequently the number of cases diagnosed) increased. By early 2021 around 200,000 persons were being tested each week (approximately 40 per 1,000 population), compared to less than 25,000 per week in July 2020 (approximately 5 per 1,000) (87). Between week 45 2020 and week 3 2021 there was a relatively stable trend in the weekly number of new admissions to hospital with COVID-19 as main cause, ranging from 78 to 111 (Figure 2, Figure 3). The first dose of the COVID-19 vaccination programme was administered on 27 December 2020 (86). Vaccination was initially offered in a two-dose primary schedule to those at greatest risk of severe disease, with gradual rollout down the age groups and prioritisation of areas with a higher level of SARS-CoV-2 transmission (86, 88).

Third wave: the Alpha VOC

The second wave began to subside at the start of 2021, however the introduction and widespread transmission of the more transmissible and more virulent Alpha VOC (B.1.1.7) (22, 67, 68) led to a renewed increase in hospital admissions from February. The Beta VOC (B.1.351) also circulated, but to a much lesser extent (67). The third wave reached a peak of 229 new admissions to hospital with COVID-19 as main cause in week 11 2021 (Figure 2, Figure 3). Elective surgeries in some regions were postponed, although hospitals functioned within capacity. This wave lasted until late May 2021, initiating a second summer with ongoing low-level transmission (20 or fewer new patients admitted to hospital with COVID-19 as main cause per week).

Fourth wave: the Delta VOC and high coverage of primary vaccination

The Alpha VOC was superseded as the dominant circulating variant by the Delta VOC in week 27 2021 (89), and a fourth wave came gradually with the autumn and winter months as new admissions to hospital with COVID-19 as main cause reached a peak

of 255 in week 51 2021 (Figure 2, Figure 3). Testing was further ramped up, particularly in schools (71) and reached a peak of almost 300,000 persons tested per week (approximately 50 per 1,000) at the end of 2021 (excluding antigen self-tests) (87). Coverage of the primary vaccination series was high (87% among all persons ≥18 years by week 43 2021) (87). Additional primary and booster doses were implemented in the autumn of 2021 (58, 86), on evidence of waning immunity against both infection and severe disease and lower vaccine effectiveness against infection for the Delta VOC, compared to Alpha (19, 58, 90, 91). The cohort of patients hospitalised with COVID-19 as main cause gradually changed with the ongoing rollout of the vaccination programme, with initial decreases in the median age of patients not yet vaccinated (or later having received a booster) being reversed and replaced by elderly vaccinated patients (Figure 4, Figure 5).

Fifth wave: the Omicron VOC and returning to a 'normal every-day'

The Omicron VOC sublineage BA.1 was first identified in Norway in late November 2021 (92) and had outcompeted the Delta VOC by the end of the year (23), driving a fifth wave. New admissions to hospital with COVID-19 as main cause reached a new all-time peak of 557 in week 9 2022. However, with high vaccination coverage and mounting evidence of lower virulence for Omicron, compared to Delta (23, 59, 62-65, 71), testing activity and public health measures were gradually relaxed. This impacted the flow to, and management of, COVID-19 positive patients in hospital, as patients were gradually more spread out across hospitals instead of being treated in specific wards usually under the care of infectious disease physicians. Consequently, for the first time a clear change was observed in the proportion of hospitalised SARS-CoV-2 positive patients being admitted with COVID-19 as main cause (Figure 2). Even as transmission of COVID-19 continued, Norway returned to a 'normal every-day' in the spring of 2022 (86). By early April 2022, over 1.4 million laboratory confirmed cases of COVID-19, 11,500 patients admitted to hospital with COVID-19 as main cause, 1,800 patients admitted to ICU with COVID-19 and 2,600 COVID-19 related deaths had been reported in Norway since the start of the pandemic (87).

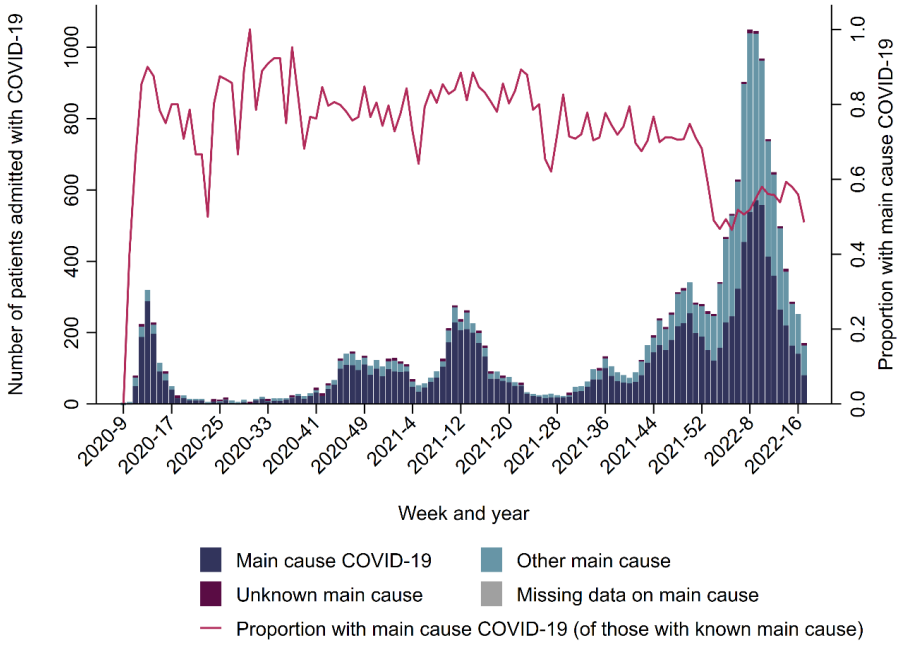

Figure 2: The number of new patients admitted to hospital with COVID-19 by main cause of admission, and the proportion admitted with COVID-19 as main cause, by week, Norway, 24 February 2020 – 1 May 2022.

Data sourced from The Norwegian Intensive Care and Pandemic Registry, updated as of 29 March 2023, and accessed through The Emergency Preparedness Register for COVID-19. Individuals are recounted if there are ≥90 days between the start of two separate hospitalisation periods.

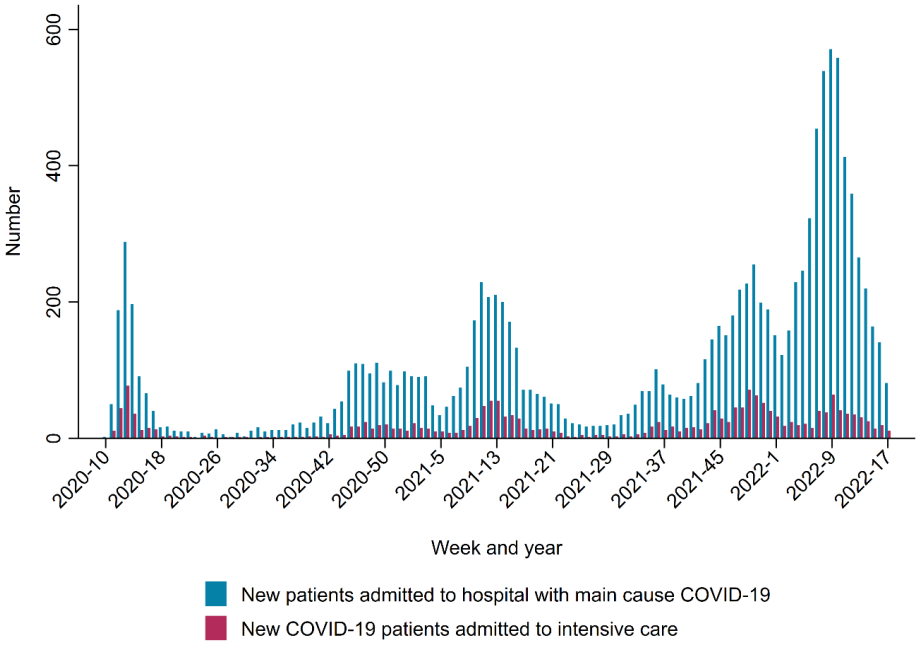

Figure 3: The number of new patients admitted to hospital with COVID-19 as main cause of admission and the number of new COVID-19 patients admitted to intensive care, by week, Norway, 2 March 2020 – 1 May 2022.

Data sourced from The Norwegian Intensive Care and Pandemic Registry, updated as of 29 March 2023, and accessed through The Emergency Preparedness Register for COVID-19. Individuals are recounted if there are ≥90 days between the start of two separate hospitalisation periods.

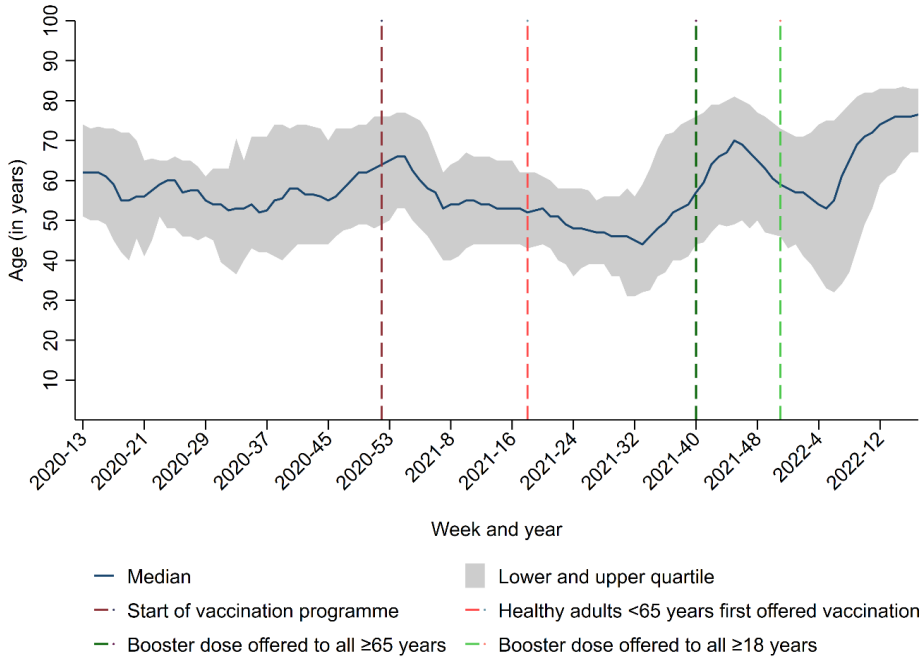

Figure 4: Four-week rolling median age of new patients admitted to hospital with COVID-19 as main cause of admission, by week, and selected milestones in the national COVID-19 vaccination programme, Norway, 23 March 2020 – 1 May 2022.

Data sourced from The Norwegian Intensive Care and Pandemic Registry, updated as of 29 March 2023, and accessed through The Emergency Preparedness Register for COVID-19. Individuals are recounted if there are ≥90 days between the start of two separate hospitalisation periods. Selected milestones in the national COVID-19 vaccination programme are sourced from (86, 88).

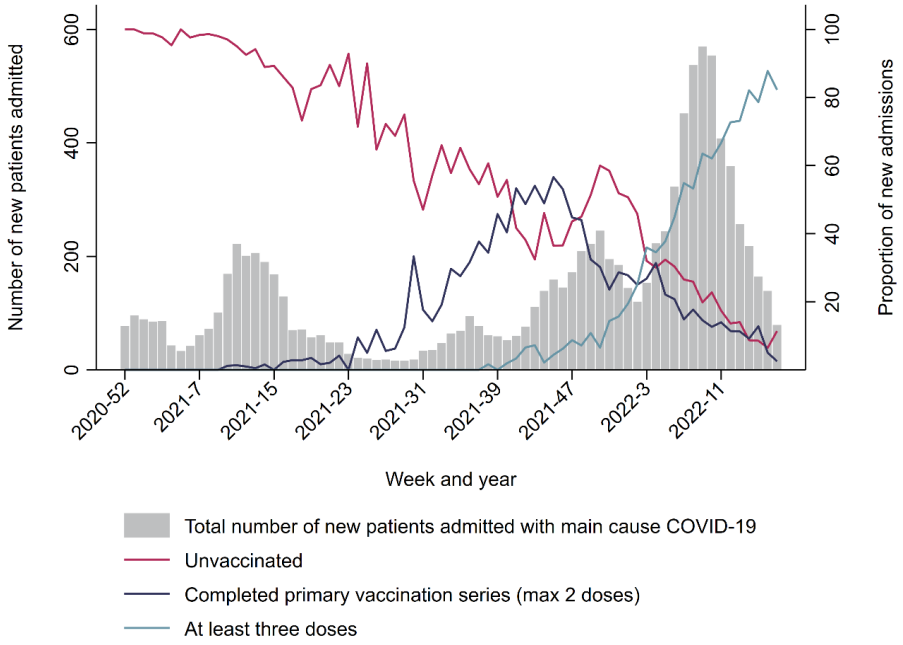

Figure 5: The number of new patients admitted to hospital with COVID-19 as main cause of admission and the proportion by vaccination status, by week, Norway, 21 December 2020 – 1 May 2022.

Data sourced from The Norwegian Intensive Care and Pandemic Registry, the Norwegian Surveillance System for Communicable Diseases laboratory database, the Norwegian Immunisation Registry and the Norwegian Population Register. Data are updated as of 29 March 2023 and accessed through The Emergency Preparedness Register for COVID-19. Individuals are recounted if there are ≥90 days between the start of two separate hospitalisation periods. Only individuals with a national identity number registered in the Norwegian Population Register are included. See the Norwegian Institute of Public Health's weekly report for detailed descriptions of how vaccination status was calculated (87).

1.2 Public health surveillance

1.2.1 Definition and general objectives

Public health surveillance is the ongoing circular process of systematic collection, analysis, interpretation and dissemination of health data for public health action. A simple representation is presented in Figure 6. Broadly speaking, surveillance seeks to answer two key questions about a target health event: 1) what is the distribution in the population? and 2) how does this change over time?, in order to set priorities and plan, implement and evaluate public health practice.

For infectious diseases, surveillance contributes by 1) describing the epidemiology by relevant case characteristics, 2) detecting and investigating outbreaks, and 3) providing a basis for research on the spread and determinants of disease (93).

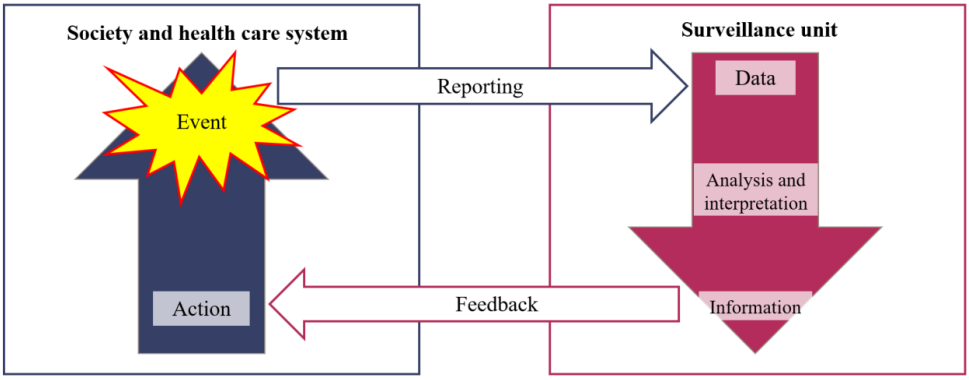

Figure 6: A simple graphical representation of the ongoing circular process of public health surveillance.

1.2.2 Key elements of surveillance systems

Firstly, surveillance systems must be designed around specific objectives for the target health event(s), i.e. what is the purpose of the system. There may be one target health event (a vertical system) or several (an integrated system) (93). For infectious diseases, the system may aim to cover one or several stages of the health event(s). These stages are classically represented as a pyramid (Figure 7), where the narrowing of the pyramid

from bottom to top represents a theoretically decreasing number of people. The shape of the 'pyramid' and relevant stages vary by disease. For some infectious diseases the surveillance of key determinants, independent of infection, is also important. While not represented in Figure 7, for infectious diseases one must not forget elements beyond the pyramid of human infection, under the umbrella of One Health (94).

Surveillance systems also have a range of characteristics, including simplicity, timeliness, data quality (both completeness and accuracy), relevance, acceptability (to all stakeholders), flexibility, sensitivity, specificity, consistency and reliability (93). While one would ideally maximise all these characteristics, it may be necessary to prioritise some over others. Which characteristics are prioritised may change over time.

Once settled, the health event(s), objectives and any prioritised characteristics help determine more specific key system elements. These include the population(s) under surveillance, case definitions (what is the 'event' in Figure 6) and necessary indicators (measurable outcomes), data items (e.g. clinical, laboratory, epidemiological data) and data sources (e.g. hospitals, physicians, laboratories, health surveys, registry data, news reports) (95). One must also consider how the system will operate, including plans for data collection, analysis, interpretation and dissemination, and system evaluation. For data collection, a variety of attributes may be considered (93, 95):

- comprehensive (all reporting units) or sentinel (selected reporting units),
- national or subnational,
- passive (no prompting), active (prompting data providers) or automated reporting,
- passive or active (e.g. contact tracing, screening) case finding,
- reporting at diagnosis/recognition or another time interval (daily, weekly, …),
- indicator-based (predefined, structured) or event-based (ad-hoc, unstructured),
- voluntary or mandatory (i.e. the legal basis for reporting),
- year-round or vary in temporal continuity,
- electronic (web-based or otherwise) or paper-based,
- case-based (i.e. individual-level data) or aggregated data.

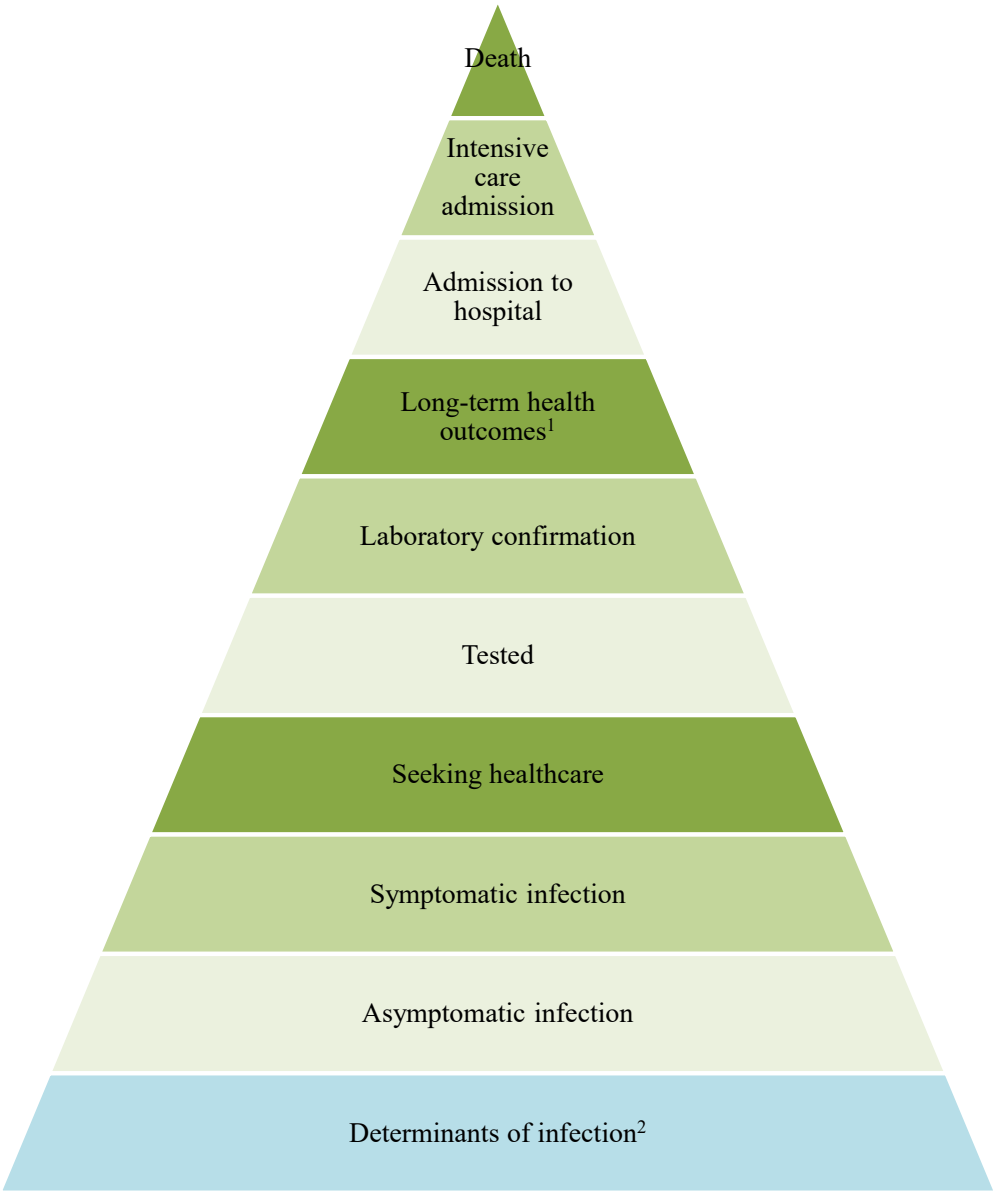

Figure 7: Pyramid of stages of infection that may be targeted by surveillance systems for infectious diseases.

[1] For example, Long COVID or quality of life for people living with HIV.

[2] Determinants worthy of surveillance independent of infection, for example, risk behaviour and vaccination coverage.

1.2.3 A brief history of infectious disease surveillance with a Norwegian focus

While several historical figures and events provided preceding and concurrent milestones, as described elsewhere (93), the modern concept of public health surveillance has been credited to British physician William Farr (1807 – 1883) (93, 96). As the Compiler of Abstracts at the Registrar General's Office, where he worked from 1837 – 1879, Farr instigated the annual compilation, analysis, interpretation and reporting of data on vital statistics, including cause of death and mortality by occupation, to describe the impact of diseases on different populations (93, 96). Simultaneously, important innovations for infectious disease surveillance were being developed in Norway. Notably, the world's first national patient registry, The Leprosy registry (or '*Lepra-registret*' in Norwegian), was established in 1856. Leprosy was one of the major public health challenges of the time and the registry informed the local and national assessment of the spread of the disease, research on disease aetiology, the evaluation of implemented control measures, patient management and trajectories, and hospital capacity needs (97, 98). This paved the way for future patient registries for other diseases, such as tuberculosis in 1900 (98). Legislation to support the development of disease surveillance was also evolving. All doctors in Norway were first required to report epidemic diseases to authorities in 1847 and the first descriptions of the epidemiology of infectious diseases were published in 1853. The Health Act of 1860 and the Medical Act of 1927 brought with them more systematic data collection on infectious diseases (99). Surveillance systems for infectious diseases were also developing in other European countries, with several instigating the mandatory reporting of some infectious diseases by 1890 (93). In 1965 the WHO established an epidemiological surveillance unit and in 1968 declared public health surveillance an essential function of public health practice (93).

In 1975, the Norwegian Surveillance System for Communicable Diseases (MSIS) was implemented nationwide, compiling cases of notifiable infectious diseases from clinicians and laboratories (99). While the overarching principle has remained unchanged, development of MSIS has been ongoing, including updated regulations, initiation of reporting for new diseases, transition to nominative reporting for diseases

previously reported anonymously and transition from paper-based to electronic reporting (99). While test activity for some diseases had been monitored previously (100), the establishment of electronic reporting to the MSIS-laboratory database in late 2020, following the outbreak of COVID-19, first made this possible for all diseases (101). MSIS data have been provided to European networks since the early-2000s (102), an example of the ongoing international integration between national systems.

Alongside developments in specific reporting systems for notifiable infectious diseases, there have been rapid advances in supplementary surveillance methodologies in recent decades. These have often been driven by technological advances like the digitalisation of health information (93, 103). For example:

- Event-based surveillance, where potential events are detected and investigated through ad-hoc, unstructured signals from formal or informal sources, has supplemented structured and pre-defined indicator-based surveillance (104).
- Syndromic surveillance systems (surveillance of clinical signs and symptoms, not defining of one specific disease) have emerged since the mid-1990s, enabling earlier detection and a better understanding of the size and severity of epidemics, particularly those where cases presenting to health care will not always be tested for or diagnosed with a specific disease, such as acute respiratory or gastrointestinal infections (105-107). '*Sykdomspulsen*' (Disease Pulse) is a Norwegian example (108).
- The linkage of data from different electronic registries not specifically designed for infectious disease surveillance. In Norway, other central administrative and health registries, and national clinical registries that can support the surveillance of infectious diseases include the National Population Register (Freg, established in 1964 (109)), the Norwegian Immunisation Registry (SYSVAK, 1995 (110)), the Norwegian Patient Registry (NPR, 1997 (111)) and the Norwegian Intensive Care Registry (NIR, 1998 (112)).
- The surveillance of phenotypic and genotypic characteristics of pathogens has further deepened our capacity to understand the source of outbreaks and how

different strains of a pathogen can vary in virulence, drug resistance, risk factors for transmission and the effectiveness of public health interventions (113, 114).

- Second generation surveillance, first proposed in 2000, combines biological and behavioural surveillance to better understand the drivers of epidemics (115). Infectious disease surveillance has also branched into health-related quality of life (116). In Norway, both concepts have been integrated into the monitoring of risk groups for, and people diagnosed with, chronic, often asymptomatic infections like HIV (117, 118).
- The use of advanced statistical methods, such as modelling all-cause and influenza-attributable mortality, or 'nowcasting' of outbreaks (107, 119).
- The internet has enabled more automated and timely dissemination of surveillance data (120, 121).

For an infectious disease, a modern surveillance system therefore now often comprises a collection of different complementary systems with methods and data sources tailored to different objectives and stages of infection (Figure 7). This is exemplified by the surveillance system for influenza in Norway at the outbreak of the COVID-19 pandemic in 2020. This system included national syndromic surveillance in primary care, sentinel surveillance of laboratory-confirmed cases in primary and secondary care, national surveillance of intensive care admissions, outbreaks, seroepidemiology, excess mortality, antiviral resistance, genetic sequencing, vaccine distribution and vaccination coverage (122).

1.2.4 Lessons from past health crises: the importance of the surveillance of disease severity

Global lessons

Experiences from notable epidemics and pandemics prior to COVID-19, such as SARS (2002 – 2004), influenza A(H1N1)pdm09 (2009) and Ebola virus disease (2014 – 2016), have provided important lessons for the planning, implementation and operation of surveillance systems during a health crisis. Recurring themes include the need for effective early warning systems, tailored and tested surveillance plans that can be

rapidly implemented to ensure the timely assessment of early cases, systems that ensure accurate and timely data collection, analysis and dissemination, are flexible to changing surveillance needs and minimise reporting burden, and international collaboration and data sharing (123-128).

Severity is an essential element to inform the shape of the surveillance pyramid (Figure 7) for accurate risk assessment. Following the influenza A(H1N1)pdm09 pandemic, WHO concluded a lack of preparedness "*to rapidly assess the severity of a pandemic*" (129). One key lesson learnt was that "*severity … needs to be monitored throughout a pandemic*" (124). WHO encouraged hospital-based surveillance for the assessment of pandemic influenza severity (129). Surveillance systems were gradually established and by the outbreak of the COVID-19 pandemic the European Centre for Disease Prevention and Control (ECDC) was receiving data on cases of Severe Acute Respiratory Infection (SARI) from 18 countries, hospitalised influenza patients from 7 countries and influenza patients admitted to an ICU from 11 countries (130).

Lessons in Norway

Prior to COVID-19, the last major public health emergency in Norway was the influenza A(H1N1)pdm09 pandemic. Similarly to global findings, shortcomings of national surveillance highlighted a need to update national legislation, establish surveillance plans before the outbreak of a health crisis, and develop systems that did not entail an unnecessary reporting burden, had the flexibility and capacity to fulfil changing needs and enabled epidemiological research (131). For the surveillance of hospitalised patients, the system took several months to be set up, collected aggregated data that risked double reporting and could not be used for research, and was not coordinated with regional health authorities (RHA) (131). In the subsequent revision of the national health preparedness plan, a key action that strengthened surveillance during a future health crisis was the 2017 revision of the Health Preparedness Act ('*Helseberedskapsloven*'). This revision allowed the establishment of a preparedness registry ('*Beredskapsregistre*'), where case-based data from different registries could be linked in order to respond to a health crisis (132).

1.2.5 The surveillance of patients hospitalised with COVID-19

Surveillance systems around the world

The surveillance of disease severity during a pandemic is essential (see chapter 1.2.4). As the COVID-19 pandemic hit, countries scrambled to fill this rapidly pressing need. A variety of systems to monitor both the incidence (number of new admissions in a defined period) and prevalence (number admitted at a given point in time) of patients hospitalised with COVID-19 evolved. Some examples are described below. Some systems were based on pre-existing data collection infrastructure and practices, others newly established.

For the surveillance of incidence (new admissions), Germany (133) and Portugal (45) provide examples of data collection integrated into the national surveillance system for cases of infectious diseases. Similarly, in Norway data on hospitalisation among notified COVID-19 cases were collected in MSIS, but never formally used in the ongoing surveillance of hospitalised COVID-19 patients as alternative systems were available (as described in chapter 3.2). Denmark (134), Scotland (135) and Sweden (136) established systems based on pre-existing national patient and/or intensive care registries. England set up a system integrated with the surveillance of influenza and respiratory syncytial virus (RSV), with voluntary sentinel reporting for hospital admission and mandatory comprehensive reporting for ICU admission (137). In the United States, a sentinel system for hospitalisation due to influenza and RSV was expanded to collect clinical data on new admissions to hospital with COVID-19 (138). Germany (133, 139), Ireland (140) and Slovenia (141) are examples of countries who established or built on existing hospital surveillance for SARI, with laboratory testing of SARI patients for SARS-CoV-2. Belgium implemented a mandatory aggregated and voluntary patient-level clinical survey on hospitalised COVID-19 patients (142).

For prevalence (number admitted), in Denmark twice daily patient-level data on patients admitted to hospital, ICU or on ventilatory support who were diagnosed with, or under observation for, COVID-19 were provided by the five Danish regions (143). In Scotland, the 14 health boards reported the number of COVID-19 patients in hospital

and ICU beds once daily. For some health boards data collection was a manual process, whereas others set up automated reports (personal communication, John Wood, Public Health Scotland). Similarly, in Belgium (142), England (144) and the United States (145) hospitals reported daily aggregated data to national authorities. In Sweden, data on hospital bed occupancy were provided by each region, while data on ICU bed occupancy came from the intensive care registry (136). In Germany, Australia and New Zealand, ICUs reported daily on total and COVID-19 bed occupancy (146, 147).

Surveillance systems in Norway

In Norway, the establishment of a preparedness registry under the Health Preparedness Act (see chapters 1.2.4 and 3.2.2) facilitated the set-up of two separate electronic health registry[1] (EHR)-based systems with the potential to conduct surveillance of patients admitted to hospital with COVID-19 (including ICU/need for ventilatory support):

1) The Norwegian Intensive Care and Pandemic Registry (NIPaR)
2) Linking of NPR and MSIS (NPR-MSIS).

Also, the Norwegian Directorate of Health (Hdir) set up daily data collection on the bed occupancy of COVID-19 patients in hospital, ICU and on invasive ventilatory support (i.e. prevalence indicators). These new systems formed the backbone of the surveillance of patients hospitalised with COVID-19 in Norway during the first two years of the pandemic and the basis for this thesis. Detailed system descriptions are presented in chapter 3.2.

[1] *"EHRs consist of longitudinal data in electronic format concerning a patient's health that are generated during routine medical care" (148).*

2. Study objectives

2.1 Study setting

In 2020, Norway had a population of 5.37 million people (149). National hospital capacity under normal circumstances was approximately 11,000 (2.0 per 1,000) somatic beds (150) and 260 (4.8 per 100,000) ICU beds with mechanical ventilation (151). Secondary and tertiary healthcare is predominantly provided by public hospitals, organised into over 20 health trusts, which in turn are organised into four RHA; South-East, West, Mid-Norway and North (152).

2.2 General research aims

At the outbreak of the COVID-19 pandemic, systems for the surveillance of patients hospitalised with COVID-19 in Norway were newly established and untested. Also, as the pandemic evolved it was unknown how novel factors, such as patient and virus characteristics, would affect the epidemiology and clinical course of COVID-19.

The research in this thesis therefore comprises key studies conducted during the first two years of the COVID-19 pandemic in Norway (February 2020 – May 2022), assessing or using surveillance data to fill these knowledge gaps. The general research aims were:

1) to compare and critically appraise systems for the surveillance of patients hospitalised with COVID-19 to contribute to the further development of these systems.
2) to contribute to ensuring a timely, appropriate and evidence-based public health response in an evolving pandemic setting.

2.3 Specific study aims

2.3.1 Part I: Comparison of surveillance systems for hospitalised COVID-19 patients (papers I – II)

Paper I: To compare the daily number of new admissions (incidence) and the daily number of hospitalised patients and the number of patients on ventilatory support (prevalence) reported from Hdir, NIPaR and NPR-MSIS to see whether they retrospectively[2] provided a comparable picture of the bed occupancy of COVID-19 patients in hospitals in Norway.

Paper II: To compare hospitalised COVID-19 patients registered in NIPaR and NPR-MSIS with regards to system coverage[3] and explore the use of International Classification of Diseases, 10th Revision, (ICD-10) codes from NPR for the surveillance of hospitalisation due to COVID-19.

[2] *Results from an unpublished prospective follow-up study are also presented in this thesis.*

[3] *Meaning the proportion of 'cases' (patients hospitalised with laboratory-confirmed COVID-19) reported in the system, not geographical coverage.*

2.3.2 Part II: Use of surveillance data to study risk factors for hospitalisation due to COVID-19 and the clinical course of hospitalised COVID-19 patients (papers III – VI)

Risk factors for hospitalisation due to COVID-19

Paper III: To compare the risk of hospitalisation among unvaccinated persons <18 years infected with SARS-CoV-2 during waves of the Alpha, Delta and Omicron VOC in Norway.

Clinical course of hospitalised COVID-19 patients

Paper IV: To estimate the time from symptom onset to hospitalisation, length of stay (LoS) in hospital and ICU, and odds of ICU admission and death (in-hospital and post discharge) among hospitalised COVID-19 patients in Norway infected with the Alpha VOC, compared to patients infected with the ancestral strain.

Paper V: To estimate the LoS in hospital, and risk of ICU admission and in-hospital death among hospitalised COVID-19 patients aged ≥18 years in Norway who had completed their primary vaccination series with an mRNA vaccine, compared to unvaccinated patients.

Paper VI: To estimate the LoS in hospital, and risk of ICU admission and in-hospital death among hospitalised COVID-19 patients in Norway infected with the SARS-CoV-2 Omicron VOC, compared to patients infected with the Delta VOC.

3. Materials and methods

3.1 Study design

All studies in this thesis are registry-based observational cohort studies.

3.2 Study population, period and data sources

The population, period and data sources of the studies in the thesis are described in Table 1. A detailed description of each data source is presented in chapters 3.2.1 – 3.2.5. Also, a summary of core attributes of the three surveillance systems for patients admitted to hospital with COVID-19 in Norway is presented in Table 2. The core attributes of the EHR-based systems were similar, although the data flow for NPR-MSIS was more automated than NIPaR, while NIPaR contained more disease-specific clinical data. For Hdir, system attributes were generally similar to the two EHR-based systems, although the data were aggregated and limited to a few key variables.

Table 1: Population, period and data sources of the studies in the thesis.

Paper number	Study population[1]	Study period	Date of data extraction (minimum number of follow-up days)	Data sources
I	Patients admitted to hospital with COVID-19	1 March 2020 – 28 June 2020	29 June 2020 (1 day) for NIPaR, NPR and MSIS. Prospective data collection for Hdir.	**NIPaR**, **NPR**, **MSIS**, **Hdir**
II	Patients admitted to hospital with COVID-19	17 February 2020 – 1 May 2022	12 May 2022 (11 days)	**NoPaR**, **NPR**, MSIS-laboratory database, Freg
III	Unvaccinated diagnosed cases of COVID-19 aged <18 years	15 March 2021 – 30 January 2022	12 April 2022 (72 days)	NIPaR, NPR, **MSIS**, MSIS-laboratory database, Freg, SYSVAK, KUHR

Table 1 continued.

Paper number	Study population[1]	Study period	Date of data extraction (minimum number of follow-up days)	Data sources
IV	Unvaccinated patients admitted to hospital with COVID-19	21 December 2020 – 25 April 2021	2 June 2021 (36 days)	**NIPaR**, MSIS, MSIS-laboratory database, Freg, SYSVAK
V	Patients aged ≥18 years admitted to hospital with COVID-19 as the main cause of admission	1 February – 30 November 2021	14 December 2021 (13 days)	**NIPaR**, MSIS, MSIS-laboratory database, Freg, SYSVAK
VI	Patients admitted to hospital with COVID-19 as the main cause of admission	6 December 2021 – 6 February 2022	15 February 2022 (8 days)	**NIPaR**, MSIS, MSIS-laboratory database, Freg, SYSVAK

Freg: Norwegian Population Register. Hdir: Norwegian Directorate of Health. KUHR: Norwegian Control and Payment of Health Reimbursements Database. MSIS: Norwegian Surveillance System for Communicable Diseases. NIPaR: Norwegian Intensive Care and Pandemic Registry. NoPaR: Norwegian Pandemic Registry. NPR: Norwegian Patient Registry. SYSVAK: Norwegian Immunisation Registry. Bold text: data source used to define the study cohort. [1] For all data analyses requiring the linkage of different registries, the study population was restricted to those with a national identity number ('Fødselsnummer') registered in Freg. Paper IV also included 12 patients registered with a D-number (1.1% of study cohort). Patients with D-numbers were excluded from later linkage studies (papers II, III, V and VI) due to uncertainty of their COVID-19 vaccination status (persons with a D-number vaccinated in their home country may not have had this registered in SYSVAK) and to maximise the correct linkage of individual data between several registries.

Table 2: Core attributes of the surveillance systems for patients admitted to hospital with COVID-19 in Norway.

Attribute[1]	**Norwegian Directorate of Health**	**Norwegian Intensive Care and Pandemic Registry**	**NPR-MSIS**
Population under surveillance	General population	General population	General population
Case defintion[2]	Patients hospitalised with laboratory-confirmed COVID-19	Patients hospitalised with laboratory-confirmed COVID-19	Patients hospitalised with laboratory-confirmed COVID-19
Data source	Hospitals	Registry data	Registry data
Case-based or aggregated data	Aggregated	Case-based	Case-based
Active or passive case finding	Active[3]	Active[3]	Active[3]
Active, passive or automated reporting	Active	Active, automated data transfer from the registry to Beredt C19	Automated (data flow from established reporting systems)
Electronic or paper-based reporting	Electronic (not web-based)	Electronic	Electronic
Reporting frequency	Daily	At time of registration, but data in Beredt C19 updated once daily	At time of registration, but data in Beredt C19 updated once daily
Temporal continuity	Year-round, except on weekends in periods with few patients admitted to hospital with COVID-19	Year-round	Year-round

NPR-MSIS: Linkage Norwegian Patient Registry (NPR)-Norwegian Surveillance System for Communicable Diseases (MSIS). Beredt C19: The Emergency Preparedness Register for COVID-19, described in chapter 3.2.2. [1] As described in chapter 1.2. In addition to the attributes presented, all three systems were vertical, diagnosis-based, comprehensive, national and indicator-based with a mandatory basis for reporting. [2] Small differences between systems are detailed in chapters 3.2.1, 3.2.3 and 3.2.4, and chapter 3.5. [3] Widespread community testing, contact tracing, screening at hospitals (either all patients or those with indications for testing).

3.2.1 The surveillance of hospital bed occupancy by Hdir

On 11 March 2020, Hdir requested that the four RHA as well as three private hospitals in Oslo and Bergen started reporting daily prevalence on the number of patients admitted to hospital with laboratory-confirmed COVID-19 and the number of admitted patients with laboratory-confirmed COVID-19 on invasive ventilatory support (intubated or tracheostomised) in each hospital within each respective region (153). All laboratory-confirmed patients were counted, independent of the laboratory, test method or date of diagnosis. Patients that were admitted to hospital for something other than COVID-19 were counted if they were considered to be contagious. Reporting started on 12 March 2020. Data were reported (by email) as presented in Table 3 each day by midday, except on weekends in periods with few COVID-19 patients admitted to hospital. Data reflected the status at hospitals as of 0800 that morning and were made publicly available around 1300 (154). Each hospital identified a contact person for the reporting. Missing daily reports were followed up by Hdir. The number of COVID-19 patients admitted to ICU was added as an additional indicator in early April 2020 (155). Data were also collected on the daily prevalence of the total number of patients admitted to ICU and number of deaths among hospitalised COVID-19 patients the previous day (Table 4). Data on these two indicators were never published publicly and not included in the analyses in this thesis.

Table 3: Table for reporting of data on each hospital by the regional health authorities to the Norwegian Directorate of Health, March 2020.

Name of hospital	*Enter name*
Date	*Enter date*
Number of hospitalised patients with confirmed COVID-19	*Enter the number of patients who fulfil the criteria*
Number of patients on invasive ventilatory support with confirmed COVID-19	*Enter the number of patients who fulfil the criteria*

Table 4: Table for reporting of data on each hospital by the regional health authorities to the Norwegian Directorate of Health, September 2020.

Hospital	Number of hospitalised patients with confirmed COVID-19	Of those, the number in intensive care	Of those, the number on invasive ventilatory support	Total number of patients in intensive care	Deaths among COVID-19 patients the previous day (0800 – 0800)
A					
B					
C …					

In early January 2022, Hdir also started to publish daily prevalence data on the total number of patients admitted to hospital (using data from NPR) and total number of patients admitted to ICU (reported by the RHA) (156). The RHA also started to report the number of new COVID-19 patients and the number of urgent care ('*øyeblikkelig hjelp*' in Norwegian) patients admitted to hospital the previous day (incidence) to Hdir, although these data were never published publicly and not included in the analyses in this thesis. Data reporting from the RHA to Hdir ended on 23 March 2022.

3.2.2 The Emergency Preparedness Register for COVID-19

The Norwegian Institute of Public Health (NIPH) established The Emergency Preparedness Register for COVID-19 (Beredt C19) in March 2020, pursuant to the Health Preparedness Act (see chapter 1.2.4). The aim of the registry was "*to provide a rapid overview and knowledge of how the pandemic and implemented measures affect the population's health, use of healthcare services and health-related behaviour*" (157). In Beredt C19, individual-level data from different central health registries, national clinical registries and other national administrative registries in Norway were housed and able to be linked using unique national identity numbers. Initially, Beredt C19 contained data from MSIS, NPR and NIPaR, with other data sources added or removed over time according to knowledge and analysis needs (157).

Aside from data from the surveillance of hospital bed occupancy by Hdir (see chapter 3.2.1), all other data sources included in the different studies in this thesis were accessed through Beredt C19.

3.2.3 The Norwegian Patient Registry

NPR is a central health registry established in 1997 that contains patient-level data on hospital stays for all patients who are referred to or have received specialist healthcare at a hospital, outpatient clinic or contracted specialist in Norway (111, 158). NPR is housed at Hdir. All Norwegian hospitals report to NPR and reporting is mandatory, through electronic patient journals (159). National identity numbers are registered. A full variable list for NPR is available at (160).

ICD-10 diagnosis codes are registered at discharge at the latest and related to hospitals' reimbursement claims. During the thesis period, national guidelines recommended the use of the ICD-10 code U07.1 (COVID-19, virus identified) when COVID-19 was laboratory-confirmed, regardless of the patient's clinical presentation. The code was to be registered in addition and secondary to relevant codes for the patient's clinical presentation (e.g. pneumonia). National guidelines recommended PCR to confirm patients who sought healthcare for COVID-19 and in all cases where confirmation was important for differential diagnosis and choice of treatment. Hospitalised patients who recently tested positive for COVID-19 could also be identified by linking hospital stays in NPR to notified COVID-19 cases in MSIS or the MSIS-laboratory database (see chapter 3.2.5). The ICD-10 code U10.9 (Multisystem inflammatory syndrome associated with COVID-19, unspecified) was registered for cases of MIS-C.

During the thesis period clinical procedure codes could be used to distinguish stays on invasive and non-invasive ventilatory support, but not ICU admission independent of ventilatory support.

Data from NPR were first available in Beredt C19 in April 2020 and were updated each morning around 0900. During the thesis period the data were predominantly used for research and modelling, but also for SARI surveillance (established in late 2021) and, when linked to MSIS or the MSIS-laboratory database, to indicate potential underreporting and reporting delays in NIPaR. Owing to the principle of data minimisation, researchers in Beredt C19 were only given access to full ICD-10 codes that were necessary to perform required analyses.

3.2.4 The Norwegian Intensive Care and Pandemic Registry

NIPaR was the primary data source used in Norway for the surveillance of new patients admitted to hospital or ICU with COVID-19 during the period covered by the studies in this thesis. NIPaR is managed by the Bergen Hospital Trust. It consists of two arms: NIR and the Norwegian Pandemic Registry (NoPaR).

NIR is a national clinical registry and was established in 1998 (112). Patient-level data are registered for stays in ICU for patients that fulfil one of five categories:

1. LoS over 24 hours in intensive care
2. Require ventilatory support
3. Are transferred between intensive care wards
4. Persistent administration of vasoactive medication
5. LoS under 24 hours, but passed away during stay in intensive care

NIR has collected data on patients admitted to ICU with influenza since 2016, using a separate reporting form (electronic since 2018). A similar form for suspected and laboratory-confirmed COVID-19 had been implemented by 10 March 2020, as the first COVID-19 patients were being admitted to ICU in Norway (161, 162). Within two weeks, the data were first reported in the NIPHs national weekly COVID-19 reports (87). Each ICU has a coordinator who ensures data collection and maintains close contact with NIR. Data collected include national identity numbers, demographic characteristics (age, sex, underlying risk factors), admission and discharge times, diagnosis (confirmed or suspected COVID-19), treatment during stay (e.g. ventilatory support) and status at discharge. Children admitted to ICU with MIS-C are registered.

Simultaneously, NoPaR was established as an expansion of NIR (163). NoPaR is a national clinical registry and collects patient-level data on hospital stays for patients who test positive for SARS-CoV-2 by PCR. Data collection started on 30 March 2020 and data were first reported in the national weekly COVID-19 reports in mid-April (87). Separate stays are registered if a patient is discharged and readmitted, or transferred between wards or hospitals. For patients who were already admitted at the time of positive test, admission dates are set to the date of symptom onset or, if

asymptomatic, to the date of positive test. Patients admitted with sequelae of COVID-19 are registered if they tested positive within 3 months before admission. Patients readmitted for causes other than COVID-19 are not registered if they do not require isolation. Outpatient visits are not registered (164). All Norwegian hospitals report to NoPaR and reporting is mandatory with consistent reporting criteria during the period covered by this thesis. Each hospital has a registry coordinator. Coordinators may use different methods to identify SARS-CoV-2 positive patients. For example, prior to the emergence of the Omicron variant in late 2021, when COVID-19 patients received treatment in specific wards, many hospitals kept internal lists of COVID-19 patients. Patients who fulfilled the inclusion criteria could then be registered in NoPaR. After the emergence of Omicron, searches for relevant diagnosis codes in electronic patient journals became more common. During the thesis period, coordinators had close contract with NoPaR, particularly in periods with a high number of new admissions. Notable discrepancies with the publicly available data published by Hdir and new admissions to hospital with COVID-19 in NPR-MSIS (identified in Beredt C19) were followed up as indicators of potential underreporting.

Data are registered in NoPaR in two electronic forms, one at admission (165) and one at discharge (166). Data collected include national identity numbers, demographic characteristics (age, sex, underlying risk factors), admission and discharge times, the main cause of admission, clinical condition and treatment, and status at discharge. Tailored COVID-19 treatment variables (e.g. steroids and specific antivirals) were gradually added from May 2021. ICD diagnosis codes are not registered. The reported main cause of admission (COVID-19 or other) is based on the physicians' clinical assessment. For patients with underlying risk factors, COVID-19 is reported as the main cause of admission if it contributed to worsening the underlying condition so that hospitalisation was necessary. The admitting physician in the emergency department would often determine the main cause of admission. However, there was not one uniform method used across all hospitals and over time, with other examples including searches in electronic patient journals, or physician or nurse notes, or assessment by the discharging physician. In any case, validation visits by NoPaR to hospitals found that the main cause of admission was predominantly correctly registered.

Initially, registrars were asked to register forms in NIPaR within 24 hours of admission/discharge. The timeliness of reporting to NoPaR and NIR throughout the pandemic is presented in Figure 8, Figure 9 and Figure 10. In NoPaR, following a period of delayed registration during the establishment of the registry, most new admissions were registered within 1 – 2 days (week 21 2020 – week 17 2022, median: 1.1 days, interquartile range (IQR): 0.7 – 3.1). Reporting in the same period was similarly timely for the registration of completed hospital admission forms (median: 1.2 days, IQR: 0.7 – 3.4) and discharge from hospital (median: 1.0 days, IQR: 0.6 – 2.9), and slightly slower for admission to ICU (median: 1.9 days, IQR: 0.6 – 7.1). Registration of completed hospital discharge forms took a median of 6.0 days (IQR: 3.2 – 12.0). Data on time from discharge from ICU to registration are not available.

From April 2022, the necessity for timely and detailed reporting diminished with the widespread transmission of the Omicron variant and high COVID-19 vaccination coverage (see chapter 1.1.4). In NoPaR, mandatory data items were thus limited and deadlines for registration have been gradually relaxed to 1500 every Tuesday for national reporting purposes (164). Timeliness consequently decreased.

Initially, the NIPH had access to aggregated data from NIPaR through an online dashboard. Patient-level data were first available in Beredt C19 from 27 May 2020 and were updated each morning around 0600. Not all variables in the NoPaR and NIR COVID-19 forms were transferred to Beredt C19, e.g. some variables on clinical condition (for example level of acute respiratory failure and vital signs) and treatment at admission and during stay were not transmitted from NoPaR to Beredt C19 as they were considered to fall outside the aim of the preparedness registry (see chapter 3.2.2).

Using data from NIPaR, also linked to other registries in Beredt C19, daily and weekly reports were published on patients admitted to hospital or ICU with COVID-19 by a range of factors, including time, age, sex, vaccination status, county of residence, country of birth, virus variant and underlying comorbid conditions and risk factors (87). The data were also used for research and modelling.

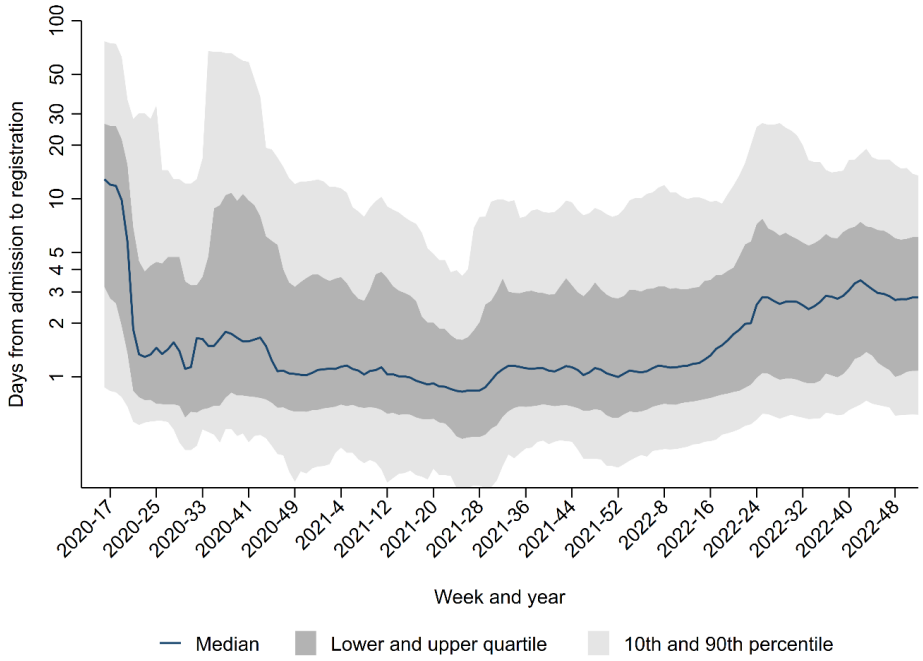

Figure 8: Eight-week rolling median number of days from first admission to hospital with COVID-19 to registration of admission in The Norwegian Pandemic Registry (log scale), by week, Norway, 13 April 2020 – 1 January 2023.

Data sourced from The Norwegian Pandemic Registry, updated as of 29 March 2023, and accessed through The Emergency Preparedness Register for COVID-19. Individuals are recounted if there are ≥90 days between the start of two separate hospitalisation periods. n=30,555.

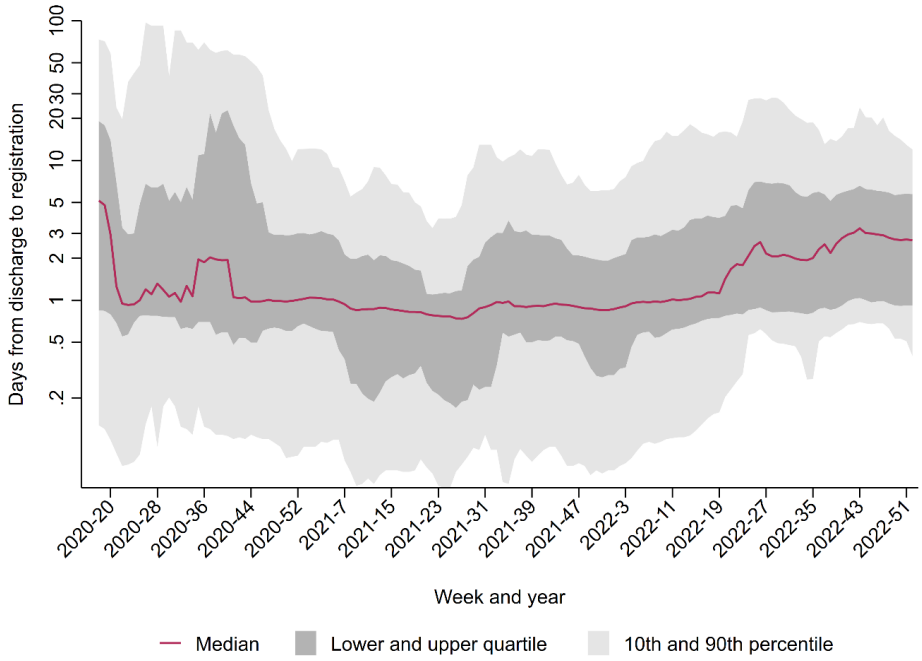

Figure 9: Eight-week rolling median number of days from last discharge from hospital with COVID-19 to registration of discharge in The Norwegian Pandemic Registry (log scale), by week, Norway, 27 April 2020 – 1 January 2023.

Data sourced from The Norwegian Pandemic Registry, updated as of 29 March 2023, and accessed through The Emergency Preparedness Register for COVID-19. Individuals are recounted if there are ≥90 days between the start of two separate hospitalisation periods. n=23,071. The discrepancy in the number of patients compared to Figure 8 relates to some hospitals registering discharge forms prior to patient discharge, thus for these patients it is not possible to accurately calculate the time from discharge to form registration. The first eight-week period is two weeks later than Figure 8, as the first registered discharge was in week 11 2020, two weeks following the first registered admission (week 9 2020).

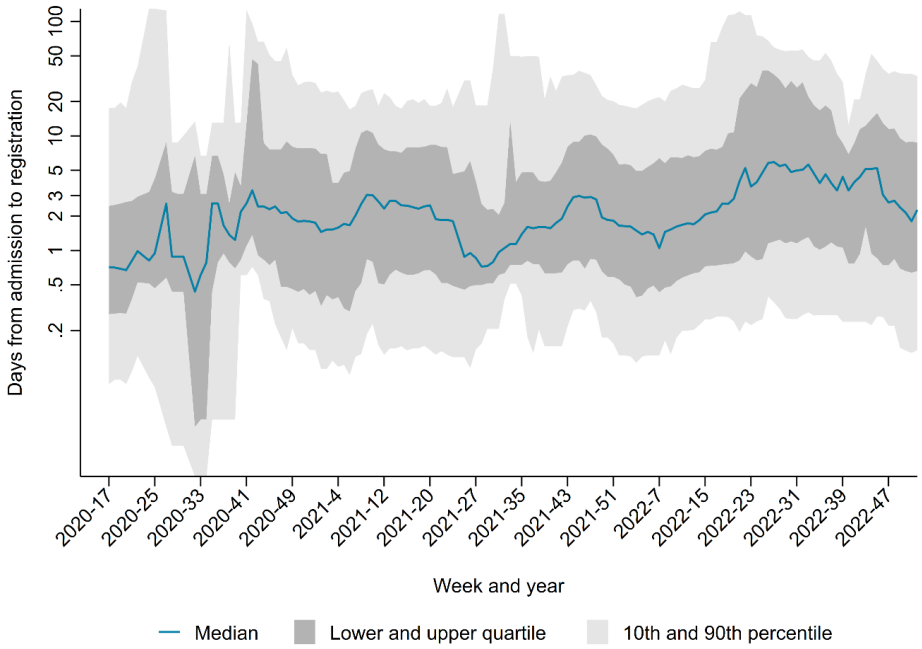

Figure 10: Eight-week rolling median number of days from admission to intensive care with COVID-19 to registration of admission in The Norwegian Intensive Care Registry (log scale), by week, Norway, 20 April 2020 – 1 January 2023.

Data sourced from The Norwegian Intensive Care Registry, updated as of 29 March 2023, and accessed through The Emergency Preparedness Register for COVID-19. Individuals are recounted if there are ≥90 days between the start of two separate hospitalisation periods. n=2,546. The first eight-week period is one week later than Figure 8, as the first registered admission to intensive care was in week 10 2020, one week following the first registered admission to hospital (week 9 2020).

3.2.5 Other data sources

Beyond those described above, other data sources included in the analyses for the studies in this thesis were MSIS, MSIS-laboratory database, Freg, SYSVAK and the Norwegian Control and Payment of Health Reimbursements Database (KUHR). All these data sources were accessed through Beredt C19.

MSIS provided data on all notified cases of confirmed COVID-19 in Norway. Up to 23 January 2022, COVID-19 reinfections were registered in MSIS if there was ≥6 months between two positive sampling dates for an individual. This definition was thereafter changed to ≥60 days, or when the national reference laboratory had identified the case as a reinfection (based on variant identification). MSIS was the data source used to define the study cohort in paper III and to determine COVID-19 hospital admissions in linkage with NPR in paper I (and the prospective follow-up study). Also, in paper IV deaths were defined using MSIS data (deaths where COVID-19 was reported as the underlying cause of death through linkage to the Cause of Death Registry, or deaths within 30 days of sampling through linkage to Freg). Furthermore, MSIS provided data on the date of positive test and previous COVID-19 diagnoses for determining immunity status in papers III – VI.

The MSIS-laboratory database contains results for microbiological samples analysed for SARS-CoV-2 in all medical microbiological laboratories in Norway (101). It is housed at the NIPH, which is the national reference laboratory for COVID-19. The MSIS-laboratory database provided data on positive COVID-19 tests in article II and the variant of SARS-CoV-2 that the study populations of COVID-19 cases or hospitalised patients were infected with in papers III – VI. In Norway, SARS-CoV-2 variants were determined based on the results of whole genome sequencing, Sanger partial S-gene sequencing or PCR screening targeting specific single nucleotide polymorphisms, insertions or deletions. The laboratory testing and notification for variants of SARS-CoV-2 in Norway has been described in detail elsewhere (167).

As personally identifiable data in Beredt C19 was encrypted, data from Freg provided information on whether persons registered in the different registries had a national

identity number. The national identity number was essential to link data from different registries and understand why some persons may not have been able to be linked. Freg was also used to identify cases' country of birth in papers III – VI, parents' country of birth in papers III, V and VI, and all deaths during the study period in paper III (and for sensitivity analyses in paper V). In paper II, birth date from Freg was used to calculate patients' age at admission to hospital.

Data from SYSVAK provided information on the vaccination status of the study cohorts in papers III – VI based on the type of vaccine and number of doses received, time since last dose and/or previous SARS-CoV-2 infection (based on MSIS), according to the definition of vaccination status at the time of each study.

In paper III, MSIS was the data source used to define the study cohort. However, MSIS had incomplete data on underlying comorbid conditions. Therefore, data from KUHR and NPR were used to define medium- and high-risk medical comorbid conditions, as stipulated by the national COVID-19 vaccination program. This was based on ICD-10 from NPR and International Classification of Primary Care, 2nd edition, codes from KUHR. In papers IV, V and VI, where NoPaR was the data source used to define the study cohort, we used the data registered directly in NoPaR on underlying risk factors for severe COVID-19 diagnosed before admission.

3.3 Methodological considerations

3.3.1 Studies based on national registry data

The studies in this thesis are observational cohort studies based on data from central health registries, national clinical registries and other national administrative registries. Some of the registries were long-standing and others were established at the outbreak of the COVID-19 pandemic. While the data provide nationally representative cohorts, data collection was not controlled by the researchers. Completeness and accuracy of data registration may impact data linkage or bias data analyses. Data completeness was generally very high for all variables included in the studies, except for virus variant in MSIS-laboratory database. To account for this, in studies where virus variant was the

key exposure of interest we assessed the representativeness of cases with known virus variant among all COVID-19 cases in the study period (papers IV and VI) or used testing date as a proxy for virus variant (paper III). Also, information on some potential confounders may not be available in studies based on registry data (for example treatment received by hospitalised patients in papers IV – VI), while the observational nature has the potential for residual confounding (168). We partially accounted for this by linking a wide range of different registries together in Beredt C19, conducting a broad range of sensitivity analyses and restricting our study population by factors such as time, age and vaccination status.

3.3.2 Studies based on diagnosed cases of COVID-19

Infection with SARS-CoV-2 may be asymptomatic (29, 30). Also, reinfection can occur and previous infection may reduce the risk of subsequent infection and severe disease (57). Therefore, studies of factors related to disease severity based on cohorts of diagnosed cases of COVID-19 may be biased by sampling effects if there are systematic differences between diagnosed and undiagnosed cases, or a difference in the proportion of undiagnosed previous infections between key exposure groups. As described in 1.1.4, during the period covered by the studies in this thesis there was high testing activity for SARS-CoV-2 in the general population in Norway, especially among children (71). However, the testing strategy, capacity and activity changed over time, and one cannot rule out bias due to undiagnosed cases, particularly in paper III, where diagnosed COVID-19 cases constitute the study cohort.

3.3.3 Studies based on hospitalised patients

Studies on the clinical course of hospitalised patients provide essential information for patient management and capacity planning in hospitals. A conceptual framework for COVID-19 developed by colleagues in Belgium demonstrates the range of factors that may influence hospitalisation periods, including host (e.g. age, comorbid conditions), viral (e.g. variants) and healthcare organisational characteristics (e.g. change in hospital capacity, admission criteria, treatment) (169). Controlling for these factors is important to minimise confounding. Compared to studies based on diagnosed cases of

COVID-19, under ascertainment of patients hospitalised with COVID-19 is less likely to be an important source of bias, especially when the study population is those admitted due to COVID-19 where confirmation is important for differential diagnosis and choice of treatment. However, like studies on diagnosed cases, previous infections that were undiagnosed may still introduce bias. Also, selection bias may be introduced if a sub-cohort of patients is studied, for example only those with known variant. Another important potential limitation in analyses on hospitalised cohorts when assessing the association of an explanatory variable with severe disease is collider bias (170). Contrary to confounders, colliders may introduce bias if they are controlled for.

3.3.4 Regression models

Papers III – VI in this thesis use multivariable logistic, log-binomial or Cox regression to analyse differences in study outcomes by explanatory variables and control for potential confounders. These models assume independent observations, which may not be able to be assumed for studies on risk of infection (171) but would be expected to hold true for the studies on disease severity presented here. For a binary outcome variable logistic regression estimates odds ratios (OR) and log-binomial regression estimates risk ratios (RR). Cox regression considers the time to an outcome and estimates hazard ratios (HR). Data on the outcomes in papers III – VI (risk of admission to hospital, LoS in hospital and ICU, risk of admission to ICU, risk of death) allowed a time-dependent analysis (e.g. time from testing date to hospital admission). Thus, Cox regression would be the preferred statistical model (172). However, in paper III the key exposure of interest (variant wave) violated the proportional hazards assumption, thus log-binomial regression was used. Given the short time from exposure to some outcomes and sufficient follow-up time for all outcomes, it is unlikely that the choice of regression model affected the associations observed, as demonstrated in similar studies of the risk of hospitalisation by SARS-CoV-2 virus variant (64, 89).

3.4 Ethical considerations

For paper I, no approval by the Regional Committee for Medical and Health Research Ethics was required for the use of the publicly available data from Hdir. For NIPaR

and NPR-MSIS, the Regional Committee for Medical and Health Research Ethics South East Norway concluded that analyses of health service use fell outside the scope of the Health Research Act (reference number 153204).

For paper II, Beredt C19 was established under the Health Preparedness Act §2-4 in response to the COVID-19 pandemic. Under the Infectious Disease Control Act §7-9, the NIPH is responsible for the surveillance of infectious diseases in Norway. Approval by an ethical review board was not considered necessary.

For papers III – VI, ethical approval was granted by Regional Committee for Medical and Health Research Ethics South East Norway (reference number 249509). The study protocol is available in the appendix, chapter 9.2.

3.5 Data analysis

3.5.1 Part I: Comparison of surveillance systems for hospitalised COVID-19 patients (papers I – II)

Paper I: Hospital bed occupancy

We linked NPR to MSIS (NPR-MSIS) and included inpatient admissions in the period two days before until 14 days after SARS-CoV-2 sampling date and/or where the patient was registered with the ICD-10 code U07.1. We defined periods on invasive ventilatory support using the relevant code from the Norwegian clinical procedure coding system (GXAV01). We defined periods on non-invasive ventilatory support using codes for treatment with continuous positive and/or biphasic positive airway pressure (GAXV10 and GAXV20, respectively). We included all stays registered in NIPaR (except those in NIR with only suspected COVID-19).

In NIPaR and NPR-MSIS, stays in hospitals with <24 hours between discharge and subsequent admission were considered to be part of the same hospitalisation period. For stays on ventilatory support a 12-hour time limit was applied. We defined a patient as hospitalised or on ventilatory support starting from the date after admission up to and including the last discharge date for the period. In NPR, we defined the end of

periods on ventilatory support using the discharge date from the ward where ventilatory support was used, due to incomplete data on the time when ventilatory support ended.

The data analysis was descriptive. We compared the number of new admissions to hospital (excluding readmissions) in NIPaR and NPR-MSIS and the number of hospitalised patients (Hdir, NIPaR, NPR-MSIS), patients on ventilatory support (NIPaR, NPR-MSIS) and patients on invasive ventilatory support (Hdir, NPR-MSIS) per day and RHA. The data set provided by NIPaR to the NIPH did not distinguish between invasive and non-invasive ventilatory support. Hdir did not collect data on non-invasive ventilatory support.

Paper II: Comparison of EHR-systems

For paper II, we considered individual stays in NoPaR (all stays) and NPR (inpatient admissions) for the same patient with <2 days between discharge and subsequent admission to be part of the same hospitalisation period. We defined four age groups (0 – 17, 18 – 54, 55 – 74 and ≥75 years) and four time periods based on changes in the dominant circulating variant and progress of the COVID-19 vaccination programme[4].

For patients with a national identity number in Freg, we linked overlapping hospitalisation periods and described the overlap between patients registered in NoPaR and COVID-19 patients in NPR (defined as: 1) patients with any diagnosis code in NPR and a positive PCR test in the MSIS-laboratory database from 14 days before admission until discharge, 2) patients registered with U07.1 in NPR and 3) a combination of 1) and 2)). Among U07.1 patients we also described positive PCR tests >14 days before admission and positive rapid antigen tests up to 14 days before

[4] *Week 9/2020 – 6/2021: ancestral strain dominant, COVID-19 vaccination programme started week 52/2020. Week 7/2021 – 26/2021: Alpha variant dominant, second dose vaccination coverage reached 95% among persons ≥75 years, first dose coverage reached 66% among persons ≥18 years, few hospitalised COVID-19 patients vaccinated. Week 27/2021 – 51/2021: Delta variant dominant, second dose vaccination coverage reached 89% among persons ≥18 years, increasing proportion of hospitalised COVID-19 patients vaccinated with at least two doses. Week 52/2021 – 17/2022: Omicron variant dominant, third dose vaccination coverage reached 90% among persons ≥75 years and 66% among persons ≥18 years, majority of hospitalised COVID-19 patients vaccinated with three doses.*

admission until discharge. We chose 14 days to ensure we identified all patients with recent positive tests that could reasonably be expected to be registered with U07.1 or in NoPaR. Fourteen days was also the cut-off used in similar registry-based surveillance systems in other countries (134, 173) and studies on variant severity (63).

To study the association between ICD-10 diagnosis codes (registered in NPR) and the clinically assessed main cause of admission (registered in NoPaR) we analysed overlapping hospitalisation periods in NPR and NoPaR for each patient. We only included the first overlapping period, as the similarity of multiple hospitalisations for a particular patient could distort the distribution. The ICD-10 codes available included full codes on acute upper and lower respiratory infections (ARI). For other codes only the first letter was available. For J codes (diseases of the respiratory system) we grouped codes for pneumonia (J12 – J18), other acute lower respiratory infections (J20 – J22 and J80) and acute upper respiratory infections (URI; J00 – J06). We grouped RSV codes for pneumonia (J12.1) and acute lower respiratory infections (J20.5 and J21.0) separately, as RSV was of specific interest in a potential integrated surveillance system for respiratory infections. We also grouped codes for influenza (J09 – J11). The remaining J codes (i.e. excluding J00 – J22 and J80) were grouped according to the first letter of the diagnosis code (J (non-ARI)). We calculated the prevalence of all different ICD-10 codes and their combinations by reported main cause of admission (COVID-19 or other), age group and period. For efficiency, we used an apriori algorithm (R package arules (174)). For each age group or period, we calculated the sensitivity and specificity of selected diagnosis code combinations for identifying U07.1 patients' main cause of admission. We also presented the trend in new admissions over time for patients with main cause COVID-19 in NoPaR and selected diagnosis code combinations in NPR using unlinked data.

Supplementary analyses beyond published papers

Paper I was a retrospective study, not able to discern if NPR-MSIS or NIPaR would be suitable for the surveillance of the bed occupancy of COVID-19 patients in hospitals in real-time. To investigate this, we also conducted a prospective follow-up study. Data

were extracted daily from the three data sources each morning from 1 September 2020 – 30 June 2021. These data have so far not been published, although are relevant to present here, as they answer a critical question that could not be answered in paper I and may further inform the design of similar surveillance systems in the future.

We defined hospitalisation periods in NIPaR and NPR-MSIS in the same way as in paper I. Our outcomes were the daily number of 1) COVID-19 patients in hospital (Hdir, NIPaR, NPR-MSIS); 2) COVID-19 patients in ICU (Hdir, NIPaR); 3) COVID-19 patients on invasive ventilatory support (Hdir, NPR-MSIS). For NIPaR and NPR-MSIS, each outcome was calculated based on identifying COVID-19 patients for which a relevant discharge date had not been registered. The data analysis was descriptive. For each outcome, we compared the daily number of admitted patients in the two EHR with corresponding data from Hdir. To describe differences over time, we categorised the number of hospitalised patients into eight time periods (1a – 8a), based on changes in the trend in the number of hospitalised patients. Intensive care patients and patients on invasive ventilatory support were categorised into five time periods (1b – 5b).

Data are described on a national level, although data on the number of hospitalised COVID-19 patients from NIPaR and NPR-MSIS by health trust are available in the appendix, chapter 9.3. Equivalent data from Hdir are publicly available (155).

3.5.2 Part II: Use of surveillance data to study risk factors for hospitalisation due to COVID-19 and the clinical course of hospitalised COVID-19 patients (papers III – VI)

Paper III: Relationship between virus variant and the risk of hospitalisation due to COVID-19 among children and adolescents

For paper III we defined the Alpha dominant wave as week 11 to 20 (March 15 to May 23) 2021, the Delta dominant wave as week 35 to 48 (August 30 to December 5) 2021 and the Omicron dominant wave as week 2 to 4 (10 to 30 January) 2022. Our severity outcomes were: 1) admission to hospital with acute COVID-19 (regardless of main cause of admission) ≤14 days after positive test, 2) admission to hospital ≤14 days after

positive test in which acute COVID-19 was the reported main cause of admission and 3) admission to hospital with MIS-C, defined as patients registered with the ICD-10 diagnosis code U10.9. We described the study cohort by variant wave, severity outcome, demographic characteristics and underlying comorbid conditions. We also described other outcomes among hospitalised patients including LoS in hospital and admission to an ICU, and all deaths in the study cohort.

For our three severity outcomes, we calculated adjusted risk ratios (aRR) with 95% confidence intervals (CI) using multivariable log-binomial regression. Explanatory variables to analyse differences in our outcomes included variant wave, age (as continuous or categorical variable), sex, country of birth, region of residence and underlying comorbid conditions. Explanatory variables were checked in univariable models. Those with $p < 0.2$ were further explored in multivariable models. Explanatory variables were further categorised in some models to best fit the data, for example a dichotomous variable for underlying comorbid conditions (yes or no). We maintained the variant wave variable in each multivariable analysis, even if not significant. We used Akaike Information Criteria and the likelihood ratio test to check model fit. We ran models for each variant combination (Delta vs. Alpha, Omicron vs. Alpha, Omicron vs. Delta) for the whole study cohort and for the age subgroups <3 months, 3 – 11 months, 1 – 11 years and 12 – 17 years. For infants <3 months we also described severity outcomes 1) and 2) among those with unvaccinated mothers.

We conducted sensitivity analyses among cases 12 – 17 years including vaccinated cases and cases with a reported previous SARS-CoV-2 infection and controlling for vaccination status. We explored the impact of analysing variant waves instead of cases with known variant in models unrestricted by age.

Papers IV – VI: Relationship between virus variant, vaccination and the clinical course of patients hospitalised with COVID-19

The data analyses in papers IV, V and VI were similar, yet tailored to the specific research question and study period in each paper. The inclusion criteria are presented in Table 5 (see also Table 1). We did not restrict admissions by LoS in any study. We

did not restrict the time since positive test based on MSIS data in paper VI, as in papers IV and V, as the definition of reinfection in MSIS at the time (≥6 months between two positive sampling dates for an individual) could have unduly excluded patients reinfected with Omicron (24). We did in any case explore the time since positive test for all patients in paper VI (also using data on date of positive test that NIPaR had recently started to submit to Beredt C19) and excluded one Delta patient with a date of positive test two months before hospitalisation. In all three papers, we present the median number of days with IQR from positive test to admission in the study cohorts.

Table 5: Inclusion criteria for papers IV – VI.

	Paper IV	**Paper V**	**Paper VI**
By time since positive test	Patients hospitalised ≤2 days before and ≤28 days after a positive SARS-CoV-2 test	Patients hospitalised ≤2 days before and ≤28 days after a positive SARS-CoV-2 test	No restriction
By main cause of admission	No restriction	Patients hospitalised with COVID-19 as main cause of admission	Patients hospitalised with COVID-19 as main cause of admission
By exposure of interest	Infected with the SARS-CoV-2 Alpha variant or ancestral strain	Unvaccinated[1] or fully vaccinated[2] with a COVID-19 vaccine	Infected with the SARS-CoV-2 Omicron BA.1 sublineage or Delta variant
By age	No restriction	Patients ≥18 years	No restriction
Other inclusion criteria	Had not been vaccinated with a COVID-19 vaccine before sampling or hospitalisation	No additional criteria	No additional criteria

[1] Unvaccinated: Also excludes those with a reported previous SARS-CoV-2 infection. [2] Fully vaccinated: Positive test ≥7 days after second dose with at least the absolute minimum interval between doses depending on vaccine type, or ≥7 days after first dose if previously diagnosed with a SARS-CoV-2 infection ≥21 days before vaccination. 'Fully vaccinated' was later re-termed 'Completed primary vaccination series', see the results for paper VI.

The outcomes in papers IV, V and VI included discharge from hospital (with and without ICU admission), admission to ICU, discharge from ICU (papers IV and V) and in-hospital death (or up to 30 days post discharge, as in paper IV). In paper VI we also analysed a composite outcome of admission to ICU or death in-hospital. In paper IV we also analysed the time between symptom onset and hospitalisation, for patients with known date of symptom onset in MSIS. Given the low completeness (49% in paper IV) and uncertainty over the quality of the data on symptom onset in MSIS, we did not analyse this outcome in papers V and VI.

We calculated LoS as the time between first admission and last discharge. For patients with >1 registered hospital stay, we included the time between consecutive stays if <24 hours. For LoS in ICU, we included the time between consecutive stays if <12 hours. Patients with unknown date of discharge from their last stay were considered still hospitalised. Patients who additionally had an unknown date of discharge from ICU were considered still admitted to ICU. In-hospital death was registered at discharge. Death following discharge came from Freg. In paper IV we calculated the number of days between symptom onset and hospitalisation using the reported date of symptom onset and time of first admission.

In each paper we present the frequency distribution of characteristics of patients in the study cohort by key exposure of interest (paper IV: Alpha vs. ancestral strain; paper V: fully vaccinated (i.e. completed primary vaccination series) vs. unvaccinated; paper VI: Omicron vs. Delta). Characteristics included demographic characteristics (age, sex, county of residence, country of birth, regional health authority), underlying risk factors, vaccination status (papers V and VI), virus variant, date of admission, main cause of admission (paper IV), ICU admission and deaths. In paper V and VI we used $\chi 2$ tests or Wilcoxon rank sum tests as appropriate to test differences in the distribution of these characteristics by exposure of interest. For all LoS outcomes and the time between symptom onset and hospitalisation we present the median number of days with an IQR.

To estimate differences between our outcomes by exposure of interest we used a Cox proportional hazards model (except the difference in the proportion of patients admitted

to ICU or that died in paper IV). Outcomes were explored univariably and by calculating Kaplan-Meier curves, with right censoring of patients still admitted to hospital. Crude log HR with medians and IQR for LoS were obtained. Explanatory variables with $p < 0.2$ were further explored in multivariable models. Forward model selection was performed based on the Akaike Information Criterion. Only variables with a correlation of <0.5 were used in the same model. The key exposure of interest was maintained in all models regardless of significance. Continuous variables (date of admission and age) were tested as linear, categorical, or with a spline. The multivariable model was checked for the assumption of proportional hazards by checking Schoenfeld residuals and some explanatory variables were stratified to satisfy the assumption. We also checked for interactions between variables included in multivariable models. Adjusted log HR (aHR) obtained in the multivariable models were reported with 95% CI. For LoS outcomes in papers V and VI, because hazard rates are not explicitly estimated in Cox regression, we also estimated a proxy for the expected difference in LoS as 1 – (1/aHR) by assuming a constant baseline hazard rate, i.e. an exponential survival distribution (175).

In paper V we conducted subgroup analyses for the age subgroups 18 – 64, 65 – 79 and ≥80 years. LoS in ICU was not analysed by age subgroup due to the small number of vaccinated ICU patients in each subgroup (≤50). In paper VI we conducted subgroup analyses by age group and vaccination status for subgroups with ≥50 omicron patients, ≥50 delta patients and ≥10 outcomes.

To estimate the difference in the proportion of patients that were admitted to ICU or died in paper IV we used logistic regression and adjusted OR (aOR) with 95% CI were reported. For death, we included patients who had been discharged by 30 April 2021 to ensure at least 30 days of follow-up post discharge for all patients. We included admission to ICU as an additional explanatory variable in this analysis.

In all studies we conducted sensitivity analyses by changing the study population and/or period to check if our results were robust. For example, only including patients with COVID-19 as main cause of admission in paper IV and, conversely, not restricting

by main cause of admission in paper V. In papers IV and V we also conducted sensitivity analyses by changing our outcome definitions, e.g. excluding all time between hospital stays in the calculation of LoS.

In papers IV and VI, we assessed the representativeness of our study population by describing the frequency distribution of characteristics of patients with known and unknown SARS-CoV-2 variant and testing differences in these distributions using $\chi 2$ tests or Wilcoxon rank sum tests as appropriate. We conducted a similar analysis in paper IV to assess the representativeness of patients with known date of symptom onset, compared to our study cohort.

Supplementary analyses beyond published papers

In paper III, NoPaR was the data source used to define outcomes 1) and 2). Results in paper II suggested that an increasing proportion of hospitalised patients with a recent positive PCR test for SARS-CoV-2 were not registered in NoPaR during the Omicron wave in paper III. Therefore, in order to investigate the impact of the decreasing coverage in NoPaR on the analysis in paper III, a supplementary analysis where the outcome was admission to hospital ≤14 days after a positive test for COVID-19 (outcome 1) as registered in NPR (data extracted 24 May 2022) is also presented.

In paper IV we included admission to ICU as an additional explanatory variable in the analysis of the outcome death in hospital or up to 30 days post discharge. This may have introduced overcontrol bias, as ICU admission is often on the path between hospital admission and death (176). We have therefore reanalysed the outcome death in hospital or up to 30 days post discharge without controlling for ICU admission. Furthermore, in paper IV we used logistic regression to estimate the difference in the proportion of patients that were admitted to ICU or died. Here I present the results from a supplementary analysis for these outcomes instead using a Cox proportional hazards model, as in articles V and VI. In the Cox proportional hazards model for death, the cohort was not restricted to patients who had been discharged by 30 April 2021 and follow-up time was calculated as admission until death, date of data extraction or 30 days post discharge.

3.5.3 Statistical programs for data analysis

Data analyses were conducted using Microsoft Excel (paper I), STATA version 16.0 (papers I, II and III) and R version 3.6.2 or higher (papers II, IV, V and VI).

4. Summary of results

Key results from papers I – VI are presented below. For the results of all analyses described in the methods, please see the published manuscripts (appendix chapter 9.1).

4.1 Part I: Comparison of surveillance systems for hospitalised COVID-19 patients (papers I – II)

4.1.1 Paper I: Hospital bed occupancy

The cumulative number of new admissions to hospital (incidence) reported by NPR-MSIS (n=1,260) was higher than in NIPaR (n=1,153) throughout the study period. The discrepancy was high at the early stage of the epidemic (93 as of 29 March). The trend in the number of hospitalised patients each day (prevalence) was consistent in all three data sources throughout the study period, with some daily variations. There were on average 16 more hospitalised patients per day in NPR-MSIS than in NIPaR and 21 more in NPR-MSIS than reported to Hdir. The trend in the number of hospitalised patients on ventilatory support followed a similar pattern, with NPR-MSIS averaging 21 more patients on ventilatory support than NIPaR and 15 more patients on invasive ventilatory support than Hdir from early April to late May, but with minimal difference between the data sources at the start and end of the study period.

In the prospective follow-up study to paper I, the study period consisted of 303 days. Data were available from Hdir on 279 days (92%), with no data collection during weekends in periods with few patients. Of these 279 days, data were available on 276 from NIPaR (99%) and 252 from NPR-MSIS (90%, of which 244 with data on invasive ventilatory support). Days with missing data from the two registries were due to irregular data extraction at the start of the study period for NPR-MSIS and rare failures in the data transfer to, or data extraction from, Beredt C19. For NIPaR, data for the number of hospitalised COVID-19 patients was affected by an artefact in the estimation of patients at the start of the study period (discharge determined by registration of discharge form, not registration of discharge date, see the appendix, chapter 9.3). Thus,

comparison of this indicator for NIPaR is limited to time periods from 19 December 2020 (183 days). Had we maintained our original definition for discharge (registration of discharge form) NIPaR would have estimated a mean of 57 fewer patients per day nationally than Hdir in the period 19 December 2020 – 30 June 2021, compared to a mean of 7 more patients based on registered discharge dates. Data completeness in NIPaR was also affected by patients being reported with unknown data on the health trust where they were admitted (range 0 – 7 per day). These patients had been admitted to hospital units (generally within drug and psychiatric treatment) with incomplete data in the system NIPaR used to identify health trusts. While such patients are included in the national data, they were not able to be assigned to a health trust or RHA.

Both registries estimated a higher number of hospitalised COVID-19 patients than Hdir, except for NIPaR during a period with a rapidly increasing trend (6a) (Table 6, Table 7, Figure 11). The absolute and proportional difference between both registries and Hdir, increased towards the end of the study period. For NPR-MSIS this may have been due to long-stay patients. From 11 May 2021 we additionally defined patients in NPR-MSIS as those without a registered date of discharge for their last COVID-19-related stay (a stay at some point in the period two days before until 14 days after a positive COVID-19 test or an admission where the patient received the ICD-10 code U07.1), not their whole hospitalisation period as defined throughout the whole study period. After excluding long-stay patients that were unlikely to still be being treated for COVID-19, the mean difference between Hdir and NPR-MSIS decreased from 37 to 17 patients in the period 11 May 2021 – 30 June 2021.

The trend in patients admitted to ICU was relatively comparable between Hdir and NIPaR, but NIPaR had fewer patients when the trend was increasing, smaller peaks (highest peak on 4 April 2021: 88 patients in NIPaR vs. 101 reported to Hdir) and more patients when the trend was decreasing (Table 6, Figure 12). The trend in patients on invasive ventilatory support in NPR-MSIS often deviated from Hdir and NPR-MSIS regularly had fewer patients, especially when the trend was increasing. For example, on 4 April 2021, NPR-MSIS reported 36 patients on invasive ventilatory support, compared to 65 reported to Hdir (Table 7, Figure 13).

Table 6: Prevalence of the daily number of COVID-19 patients admitted to hospital or to an intensive care unit in NIPaR compared to Hdir, per time period and data source, prospective data collection, Norway, 1 September 2020 – 30 June 2021.

Number of patients admitted to hospital[1]						
Time period and date	**Trend**	**Number of days with data in period**	**Min – max difference to Hdir**	**Number of days the difference to Hdir was ≥10% (%)**	**Number of days the difference to Hdir was ≥20% (%)**	**Average difference to Hdir**
4a: 19.12.2020 – 24.1.2021	Stable	34 (94%)	-3 – 31	14 (41%)	2 (6%)	12
5a: 25.1.2021 – 17.02.2021	Decreasing	24 (100%)	-7 – 19	8 (33%)	1 (4%)	6
6a: 18.2.2021 – 7.4.2021	Increasing	49 (100%)	-47 – 9	19 (39%)	6 (12%)	-14
7a: 8.4.2021 – 10.5.2021	Decreasing	33 (100%)	-3 – 59	19 (58%)	8 (24%)	20
8a: 11.5.2021 – 30.6.2021	Decreasing	43 (84%)	6 – 33	41 (95%)	32 (74%)	18
Whole period	-	183 (95%)	-47 – 59	101 (55%)	49 (27%)	7
Number of patients admitted to an intensive care unit						
1b: 1.9.2020 – 2.11.2020	Increasing	45 (71%)	-3 – 4	37 (82%)	31 (69%)	1
2b: 3.11.2020 – 24.11.2020	Increasing	22 (100%)	-11 – -1	22 (100%)	18 (82%)	-7
3b: 25.11.2020 – 6.3.2021	Stable	101 (99%)	-7 – 10	26 (26%)	7 (7%)	0
4b: 7.3.2021 – 4.4.2021	Increasing	29 (100%)	-18 – 5	17 (59%)	0 (0%)	-7
5b: 5.4.2021 – 30.6.2021	Decreasing	79 (91%)	-12 – 14	47 (59%)	39 (49%)	5
Whole period	-	276 (91%)	-18 – 14	149 (54%)	95 (34%)	0

Hdir: Norwegian Directorate of Health. NIPaR: Norwegian Intensive Care and Pandemic Registry. [1] For NIPaR, data for the number of hospitalised COVID-19 patients was affected by an artefact in the estimation of patients at the start of the study period, thus comparison of this indicator for NIPaR is limited to time periods 4a – 8a.

Table 7: Prevalence of the daily number of COVID-19 patients admitted to hospital or on invasive ventilatory support in NPR-MSIS compared to Hdir, per time period and data source, prospective data collection, Norway, 1 September 2020 – 30 June 2021.

Number of patients admitted to hospital						
Time period and date	**Trend**	**Number of days with data in period**	**Min – max difference to Hdir**	**Number of days the difference to Hdir was ≥10% (%)**	**Number of days the difference to Hdir was ≥20% (%)**	**Average difference to Hdir**
1a: 1.9.2020 – 19.10.2020	Increasing	26 (53%)	-5 – 7	13 (50%)	7 (27%)	2
2a: 20.10.2020 – 18.11.2020	Increasing	17 (57%)	-12 – 7	2 (12%)	0 (0%)	-2
3a: 19.11.2020 – 18.12.2020	Stable	30 (97%)	-8 – 23	11 (37%)	1 (3%)	9
4a: 19.12.2020 – 24.1.2021	Stable	36 (100%)	-6 – 19	9 (25%)	0 (0%)	8
5a: 25.1.2021 – 17.02.2021	Decreasing	19 (79%)	0 – 27	9 (47%)	7 (37%)	13
6a: 18.2.2021 – 7.4.2021	Increasing	48 (98%)	-4 – 39	18 (38%)	3 (6%)	16
7a: 8.4.2021 – 10.5.2021	Decreasing	33 (100%)	30 – 62	33 (100%)	14 (42%)	40
8a: 11.5.2021 – 30.6.2021	Decreasing	43 (84%)	25 – 48	43 (100%)	43 (100%)	37
Whole period	-	252 (83%)	-12 – 62	138 (55%)	75 (30%)	18
Number of patients on invasive ventilatory support						
1b: 1.9.2020 – 2.11.2020	Increasing	34 (54%)	-4 – 2	31 (91%)	31 (91%)	-1
2b: 3.11.2020 – 24.11.2020	Increasing	15 (68%)	-15 – -2	15 (100%)	15 (100%)	-9
3b: 25.11.2020 – 6.3.2021	Stable	87 (85%)	-15 – 3	64 (74%)	52 (60%)	-5
4b: 7.3.2021 – 4.4.2021	Increasing	29 (100%)	-29 – -1	28 (97%)	27 (93%)	-15
5b: 5.4.2021 – 30.6.2021	Decreasing	79 (91%)	-31 – 9	54 (68%)	30 (38%)	-1
Whole period	-	244 (81%)	-31 – 9	192 (79%)	155 (64%)	-5

Hdir: Norwegian Directorate of Health. NPR-MSIS: Linkage Norwegian Patient Registry-Norwegian Surveillance System for Communicable Diseases.

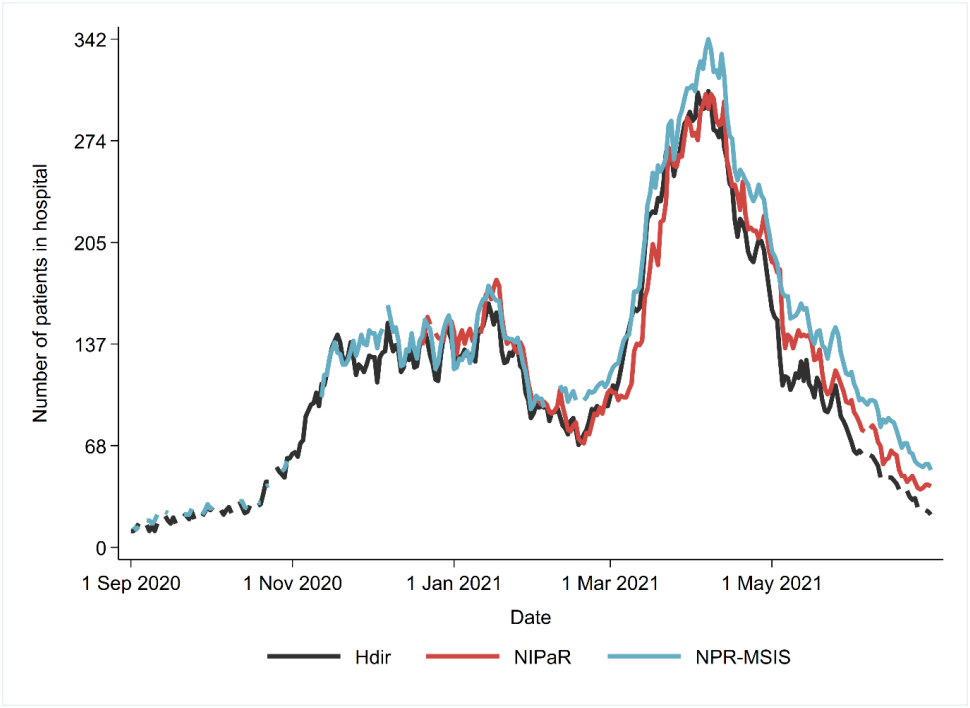

Figure 11: Prevalence of the number of COVID-19 patients admitted to hospital, per day and data source, prospective data collection, Norway, 1 September 2020 – 30 June 2021.

Hdir: Norwegian Directorate of Health. NIPaR: Norwegian Intensive Care and Pandemic Registry. NPR-MSIS: Linkage Norwegian Patient Registry-Norwegian Surveillance System for Communicable Diseases.

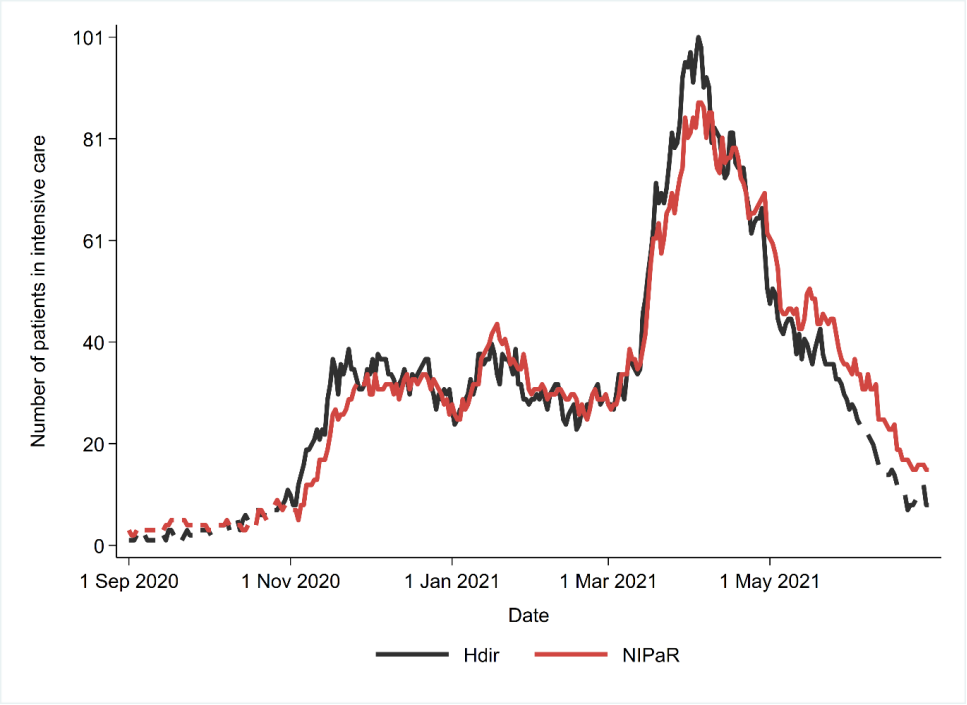

Figure 12: Prevalence of the number of COVID-19 patients admitted to an intensive care unit, per day and data source, prospective data collection, Norway, 1 September 2020 – 30 June 2021.

Hdir: Norwegian Directorate of Health. NIPaR: Norwegian Intensive Care and Pandemic Registry.

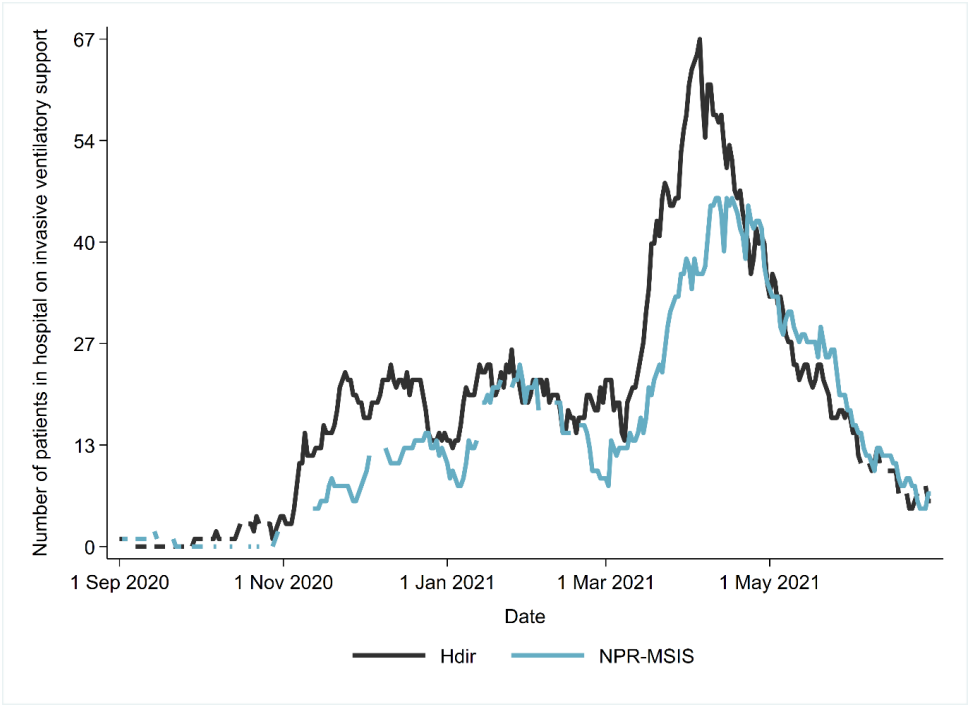

Figure 13: Prevalence of the number of COVID-19 patients on invasive ventilatory support, per day and data source, prospective data collection, Norway, 1 September 2020 – 30 June 2021.

Hdir: Norwegian Directorate of Health. NPR-MSIS: Linkage Norwegian Patient Registry-Norwegian Surveillance System for Communicable Diseases.

4.1.2 Paper II: Comparison of EHR-systems

During the study period, 90% – 100% of new hospitalisation periods each week overlapped between NoPaR and NPR until late 2021, after which the overlap gradually decreased to <75% as the number of registered new admissions in both registries increased (Figure 14, Figure 15). Of the 20,815 admissions registered with U07.1 (COVID-19, virus identified) in NPR, 1,620 (7.8%) could not be linked to a positive PCR from ≤60 days before admission until discharge, the vast majority of which were admitted from week 52/2021. Of all admissions in NPR with a positive PCR from ≤14 days before admission until discharge (n=26,506), the proportion registered with U07.1 decreased from late 2021 (87% up to week 51/2021, 61% from week 52/2021). The proportion registered in NoPaR followed a similar pattern (85% up to week 51/2021, 55% from week 52/2021) (Figure 15).

U07.1 was the most common diagnosis code registered for both admissions with COVID-19 as main cause (11,380/11,803, 96%) and main cause 'other' (5,143/6,206, 83%). For admissions with COVID-19 as main cause, 7,976 (68%) were registered with a pneumonia code and 4,244 (36%) with a J (non-ARI) code. For admissions with another main cause than COVID-19, there was more variation in the registered diagnosis codes. For patients ≥75 years, pneumonia followed by J (non-ARI) codes were most common among those admitted with COVID-19 as main cause across all periods, although less prominent from week 52/2021. A similar pattern was observed among patients 18 – 54 and 55 – 74 years, with increased prominence of R (symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified) and Z codes (factors influencing health status and contact with health services) in later periods. Among patients 0 – 17 years, R codes were prominent in all periods regardless of main cause, while the proportion of URI codes increased over time, particularly among those admitted with COVID-19 as main cause. Consequently, the sensitivity and specificity of selected ICD-10 codes for representing patients' main cause of admission varied by age group and period (Table 8).

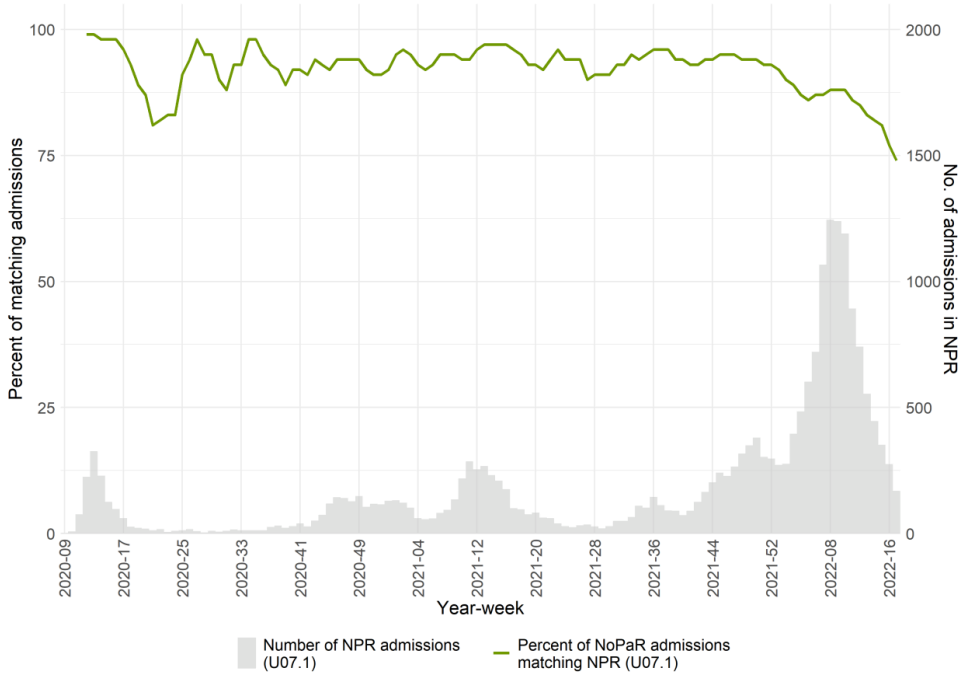

Figure 14: Four-week moving average of the proportion of weekly admissions with confirmed COVID-19 in the Norwegian Pandemic Registry (NoPaR) that overlapped with admissions with confirmed COVID-19 (U07.1) in the Norwegian Patient Registry (NPR), and weekly number of admissions in NPR, Norway, 17 February 2020 – 1 May 2022.

U07.1: International Classification of Diseases, Tenth Revision, code for COVID-19, virus identified.

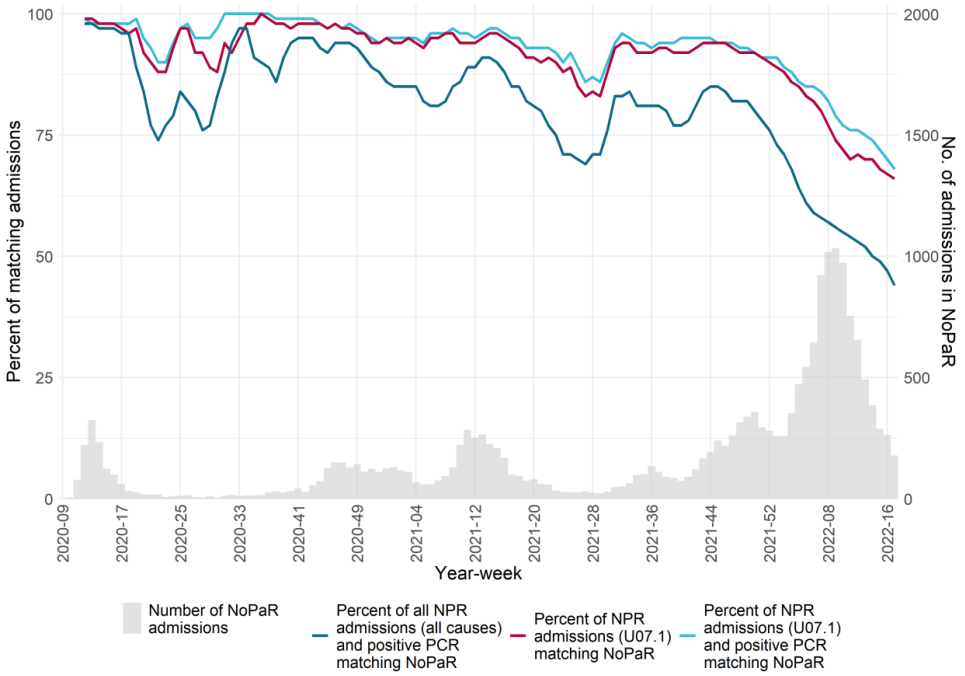

Figure 15: Four-week moving average of the proportion of weekly admissions in the Norwegian Patient Registry (NPR) with confirmed COVID-19 (U07.1) and/or positive PCR test for SARS-CoV-2 ≤14 days before admission until discharge in the Norwegian Surveillance System for Communicable Diseases laboratory database that overlapped with admissions with confirmed COVID-19 in the Norwegian Pandemic Registry (NoPaR), and weekly number of admissions in NoPaR, Norway, 17 February 2020 – 1 May 2022.

U07.1: International Classification of Diseases, Tenth Revision, code for COVID-19, virus identified.

Table 8: The sensitivity and specificity of selected ICD-10 diagnosis code combinations for representing U07.1 patients' main cause of admission, by age and period, Norway, 17 February 2020 – 1 May 2022.

ICD-10 code combination among NPR admissions with U07.1		No. of admissions with COVID-19 as main cause in NoPaR	No. of admissions with other main cause in NoPaR	Sensitivity (%)	Specificity (%)
Overall					
Pneumonia	Yes	7,857	1,436	69	72
	No	3,523	3,707		
Pneumonia or J (non-ARI)	Yes	8,665	1,785	76	65
	No	2,715	3,358		
URI or R	Yes	2,829	1,545	25	70
	No	8,551	3,598		
Pneumonia or J (non-ARI) or URI or R	Yes	10,149	2,910	89	43
	No	1,231	2,233		
By age group (years)					
0 – 17					
Pneumonia	Yes	38	17	8	94
	No	413	269		
Pneumonia or J (non-ARI)	Yes	63	27	14	91
	No	388	259		
URI or R	Yes	267	125	59	56
	No	184	161		
Pneumonia or J (non-ARI) or URI or R	Yes	320	145	71	49
	No	131	141		
≥18					
Pneumonia	Yes	7,819	1,419	72	71
	No	3,110	3,438		
Pneumonia or J (non-ARI)	Yes	8,602	1,758	79	64
	No	2,327	3,099		
URI or R	Yes	2,562	1,420	23	71
	No	8,367	3,437		
Pneumonia or J (non-ARI) or URI or R	Yes	9,829	2,765	90	43
	No	1,100	2,092		

Table 8 continued.

ICD-10 code combination among NPR admissions with U07.1		No. of admissions with COVID-19 as main cause in NoPaR	No. of admissions with other main cause in NoPaR	Sensitivity (%)	Specificity (%)
By period (weeks)					
9/2020 – 51/2021					
Pneumonia	Yes	5,508	779	81	56
	No	1,270	1,011		
Pneumonia or J (non-ARI)	Yes	5,760	882	85	51
	No	1,018	908		
URI or R	Yes	1,342	505	20	72
	No	5,436	1,285		
Pneumonia or J (non-ARI) or URI or R	Yes	6,327	1,180	93	34
	No	451	610		
52/2021 – 17/2022					
Pneumonia	Yes	2,349	657	51	80
	No	2,253	2,696		
Pneumonia or J (non-ARI)	Yes	2,905	903	63	73
	No	1,697	2,450		
URI or R	Yes	1,487	1,040	32	69
	No	3,115	2,313		
Pneumonia or J (non-ARI) or URI or R	Yes	3,822	1,730	83	48
	No	780	1,623		

ICD-10: International Classification of Diseases, Tenth Revision. U07.1: ICD-10 code for COVID-19, virus identified. Pneumonia: ICD-10 codes J12 – J18, excluding J12.1. J (non-ARI): respiratory diseases other than acute respiratory infections; ICD-10 codes from group J excluding J00 – J22 and J80. URI: upper respiratory infections; ICD-10 codes J00 – J06. R: ICD-10 codes for symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified. NPR: Norwegian Patient Registry. NoPaR: Norwegian Pandemic Registry. The breakdown for the age groups 18 – 54, 55 – 74 and ≥75 years, and periods week 9/2020 – 6/2021, week 7/2021 – 26/2021 and week 27/2021 – 51/2021, is available in the published manuscript.

4.2 Part II: Use of surveillance data to study risk factors for hospitalisation due to COVID-19 and the clinical course of hospitalised COVID-19 patients (papers III – VI)

4.2.1 Paper III: Relationship between virus variant and the risk of hospitalisation due to COVID-19 among children and adolescents

The risk of hospitalisation with acute COVID-19 as main cause was lower in the Delta (aRR: 0.53, 95% CI: 0.30 – 0.93) and Omicron wave (aRR: 0.40, 95% CI: 0.24 – 0.68), compared to the Alpha wave (Table 9). Among infants <3 months, the proportion hospitalised with acute COVID-19 decreased from 15% in the Alpha wave to 5.9% in the Delta wave and 7.8% in the Omicron wave. A similar difference between these outcome proportions was observed in the Alpha and Delta waves, when restricting the analysis to infants whose mothers were unvaccinated up to four weeks after the child's birth. We did not observe a difference in the adjusted risk of hospitalisation with acute COVID-19 as main cause in the Omicron wave, compared to the Delta wave (Table 9).

Results for the outcome admission to hospital ≤14 days after positive test (regardless of main cause) were largely consistent with those for acute COVID-19 as main cause, although we did observe a decreased risk in the Omicron wave compared to the Delta wave (aRR: 0.67, 95% CI: 0.48 – 0.94). In the supplementary analysis for this outcome using data from NPR (see chapter 3.5.2), the number of outcomes in the Delta and Omicron waves increased two-fold. Increases were observed in all age subgroups. The observed decreased risk for admission to hospital in the Omicron wave, compared to the Alpha and Delta waves, was no longer statistically significant. However, the observed decreased risk for Omicron, compared to Alpha, was sustained in a model additionally adjusting for sex and region of residence (Table 10).

The risk of MIS-C was lower in the Omicron wave, compared to the Alpha (aRR: 0.09, 95% CI: 0.03 – 0.27) and Delta waves (aRR: 0.26, 95% CI: 0.10 – 0.63). We did not observe a significant difference in the risk of MIS-C in the Delta wave, compared to the Alpha wave (Table 11).

Table 9: Number of reported COVID-19 cases <18 years admitted to hospital with COVID-19 as main cause of admission ≤14 days after positive test and adjusted risk ratios from log-binomial regression in paper III, by age group and variant wave.

	Alpha wave		**Delta wave**			**Omicron wave**			
Age group	**Number admitted/ reported cases**	**%**	**Number admitted/ reported cases**	**%**	**Adjusted risk ratio, compared to Alpha (95% CI)**	**Number admitted/ reported cases**	**%**	**Adjusted risk ratio, compared to Alpha (95% CI)**	**Adjusted risk ratio, compared to Delta (95% CI)**
<3 months	8/55	14.6	7/118	5.9	0.41 (0.16 – 1.07) [1]	17/218	7.8	0.50 (0.23 – 1.09) [5]	1.31 (0.56 – 3.08) [1]
3 – 11 months	3/212	1.4	3/518	0.6	0.41 (0.08 – 2.01) [1]	10/1,395	0.7	0.51 (0.14 – 1.82) [1]	1.23 (0.34 – 4.47) [1]
1 – 11 years	6/5,928	0.1	10/27,999	<0.1	0.72 (0.26 – 2.01) [2,3,4]	18/70,288	<0.1	**0.32 (0.13 – 0.83)** [2,3]	0.62 (0.28 – 1.35) [2,3,4]
12 – 17 years	4/4,343	<0.1	8/13,727	<0.1	0.63 (0.19 – 2.10) [1]	3/11,006	<0.1	0.30 (0.07 – 1.32) [1]	0.47 (0.12 – 1.76) [1]
All <18 years	21/10,538	0.2	28/42,362	<0.1	**0.53 (0.30 – 0.93)** [2,3]	48/82,907	<0.1	**0.40 (0.24 – 0.68)** [2,3]	0.76 (0.47 – 1.23) [2,3]

95% CI: 95% confidence interval. Results in bold text: statistically significant result. [1] The crude model was the best model. [2] Adjusted for age. [3] Adjusted for underlying comorbid conditions. [4] Adjusted for country of birth. [5] Adjusted for region of residence.

Table 10: Number of reported COVID-19 cases <18 years admitted to hospital ≤14 days after positive test for COVID-19 and adjusted risk ratios from log-binomial regression, by variant wave and data source for hospital admission.

	Alpha wave		**Delta wave**			**Omicron wave**			
Data source for hospital admission	**Number admitted/ reported cases**	**%**	**Number admitted/ reported cases**	**%**	**Adjusted[1] risk ratio, compared to Alpha (95% CI)**	**Number admitted/ reported cases**	**%**	**Adjusted[1] risk ratio, compared to Alpha (95% CI)**	**Adjusted[1] risk ratio, compared to Delta (95% CI)**
Norwegian Pandemic Registry	30/10,538	0.3	58/42,362	0.1	0.70 (0.46 – 1.08)	86/82,907	0.1	**0.48 (0.31 – 0.72)**	**0.67 (0.48 – 0.94)**
Norwegian Patient Registry[2]	37/10,538	0.4	107/42,362	0.2	0.96 (0.66 – 1.37)	172/82,907	0.2	0.73 (0.51 – 1.05) [3]	0.78 (0.61 – 1.00)

95% CI: 95% confidence interval. Results in bold text: statistically significant result. [1] Risk ratios are adjusted for age and underlying comorbid conditions, as in the published manuscript. Adjusted estimates did not noticeably change in a sensitivity analysis considering patients admitted ≥2 days before positive test as not hospitalised (n=20 in the Norwegian Patient Registry, n=5 in the Norwegian Pandemic Registry). [2] Total number of outcomes by the age subgroups <3 months, 3 – 11 months, 1 – 11 years and 12 – 17 years: Alpha: 11, 3, 12 and 11; Delta: 18, 8, 47 and 34; Omicron: 27, 25, 101 and 19. For equivalent data when the Norwegian Pandemic Registry was the data source for hospital admission, see Table 9. Although not shown in Table 10, adjusted results by age subgroup when the Norwegian Patient Registry was the data source for hospital admission were consistent with the published manuscript. The one exception was in the age group <3 months, where the observed decrease in risk in the Delta wave, compared to Alpha (aRR: 0.43, 95% CI: 0.20 – 0.97), was no longer statistically significant (aRR: 0.69, 95% CI: 0.35 – 1.36). [3] When also adjusting for sex and region of residence, the estimate was aRR: 0.66, 95% CI: 0.45 – 0.96. The likelihood ratio test indicated that this model was a better fit (p = 0.001).

Table 11: Number of reported COVID-19 cases <18 years admitted to hospital with Multisystem Inflammatory Syndrome in Children and adjusted risk ratios from log-binomial regression in paper III, by age group and variant wave.

	Alpha wave		**Delta wave**			**Omicron wave**			
Age group	**Number admitted/ reported cases**	**%**	**Number admitted/ reported cases**	**%**	**Adjusted risk ratio, compared to Alpha (95% CI)**	**Number admitted/ reported cases**	**%**	**Adjusted risk ratio, compared to Alpha (95% CI)**	**Adjusted risk ratio, compared to Delta (95% CI)**
<3 months	0/55	0.0	0/118	0.0	-	0/218	0.0	-	-
3 – 11 months	0/212	0.0	0/518	0.0	-	0/1,395	0.0	-	-
1 – 11 years	6/5,928	0.1	11/27,999	<0.1	0.39 (0.14 – 1.05) [1]	7/70,288	<0.1	**0.10 (0.03 – 0.29)** [1]	**0.25 (0.10 – 0.65)** [1]
12 – 17 years	1/4,343	<0.1	3/13,727	<0.1	0.95 (0.10 – 9.12) [1]	0/11,006	0.0	-	-
All <18 years	7/10,538	<0.1	14/42,362	<0.1	0.50 (0.20 – 1.23) [1]	7/82,907	<0.1	**0.09 (0.03 – 0.27)** [2,3]	**0.26 (0.10 – 0.63)** [1]

95% CI: 95% confidence interval. Results in bold text: statistically significant result. [1] The crude model was the best model. [2] Adjusted for age. [3] Adjusted for region of residence.

4.2.2 Paper IV: Clinical course of patients hospitalised with COVID-19, Alpha vs. ancestral strain

The study cohort included 946 (86%) Alpha and 157 (14%) ancestral strain patients hospitalised in the period 21 December 2020 – 25 April 2021. At the end of follow-up, 16 patients (1.5%) were still hospitalised. Of the 946 Alpha patients, 175 had been admitted to ICU (18%) compared to 25 (16%) of the 157 patients infected with the ancestral strain. The median overall LoS in hospital among all patients, regardless of ICU admission, was 5.0 days (IQR: 2.6 – 10.0) for Alpha patients and 5.1 days (IQR: 2.5 – 9.9) for patients infected with the ancestral strain. Of the 1,103 patients, 1,037 (94%) were discharged by 30 April 2021; 880 Alpha patients and 157 patients infected with the ancestral strain. Fifty Alpha patients died in hospital (6%), one died less than seven days post discharge (0.1%) and three died 7 – 30 days post discharge (0.3%). Ten patients infected with the ancestral strain died in hospital (6%), two died less than seven days post discharge (1.3%) and two died 7 – 30 days post discharge (1.3%).

In both the univariable and multivariable models, we did not observe a statistically significant difference in any outcome for Alpha patients, compared to patients infected with the ancestral strain.

In the supplementary analyses for death, not controlling for ICU admission did not notably change the estimates (aOR: 1.32, 95% CI: 0.67 – 2.70, compared to aOR: 1.39, 95% CI: 0.68 – 3.01 in the published manuscript). Using a Cox proportional hazards model instead of logistic regression did not notably change the estimates for ICU admission (aHR using Cox: 1.24, 95% CI: 0.84 – 1.90, aOR using logistic regression: 1.37, 95% CI: 0.86 – 2.26) or death (aHR using Cox: 1.11, 95% CI: 0.60 – 2.01, aOR using logistic regression: 1.32, 95% CI: 0.67 – 2.70).

4.2.3 Paper V: Clinical course of patients hospitalised with COVID-19, fully vaccinated vs. unvaccinated

The study cohort included 2,487 (78%) unvaccinated and 716 (22%) fully vaccinated (i.e. completed primary vaccination series) patients ≥18 years who were hospitalised in the period 1 February – 30 November 2021. Age and the frequency of certain underlying risk factors, such as cancer, chronic lung disease, heart disease, immunosuppression (due to illness or treatment) and kidney disease, were higher among fully vaccinated patients. Of the 716 fully vaccinated patients, 666 (93%) had received two doses, 47 (6.6%) three doses and three (0.4%) one dose with a previous SARS-CoV-2 infection. Most patients (658, 92%) received a homologous Comirnaty (BioNTech-Pfizer, Mainz, Germany/New York) regimen. At the end of follow-up, 75 (2.3%) patients were still hospitalised. Of the 716 fully vaccinated patients, 103 (14%) were admitted to ICU and 86 (13%) died in hospital. Of the 2,487 unvaccinated patients, 480 (19%) were admitted to ICU and 102 (4.1%) died in hospital.

Our multivariable models suggested that fully vaccinated patients had a shorter overall LoS in hospital (aHR for discharge: 1.61, 95% CI: 1.24 – 2.08) and shorter LoS without ICU admission (aHR: 1.28, 95% CI: 1.07 – 1.52) compared to unvaccinated patients. Assuming exponential distribution of the survival data, an aHR of 1.61 translates into an expected 38% (95% CI: 19% – 52%) shorter LoS. Fully vaccinated patients also had a 50% lower risk of ICU admission (aHR: 0.50, 95% CI: 0.37 – 0.69) compared to unvaccinated patients. We did not observe a difference in the LoS in ICU or risk of in-hospital death between vaccinated and unvaccinated patients (Table 12).

By age subgroup, fully vaccinated patients aged 18 – 64 years and 65 – 79 years had an expected shorter overall LoS and lower risk of ICU admission, compared to unvaccinated patients. Fully vaccinated patients 18 – 64 years also had a shorter LoS without ICU admission. There was no difference in the adjusted risk of in-hospital death between vaccinated and unvaccinated patients in any age subgroup. We did not observe a difference between vaccinated and unvaccinated hospitalised patients aged ≥80 years in adjusted estimates for any outcome (Table 12).

Table 12: Adjusted hazard ratios for fully vaccinated hospitalised COVID-19 patients, compared to unvaccinated patients, from a Cox proportional hazards model for different outcomes in paper V, by age group.

Age group	Number of unvaccinated patients	Number of fully vaccinated[2] patients	Adjusted hazard ratios[1] for fully vaccinated patients[2], compared to unvaccinated patients				
			Discharge from hospital – all patients (95% CI)	Discharge from hospital – patients not admitted to ICU (95% CI)	ICU admission (95% CI)	Discharge from ICU (95% CI)	Death in hospital (95% CI)
18 – 64 years	1,952	180	**1.91 (1.37 – 2.66)**	**1.46 (1.11 – 1.91)**	**0.53 (0.32 – 0.88)**	[3]	1.35 (0.64 – 2.87)
65 – 79 years	453	260	**1.29 (1.09 – 1.52)**	1.22 (0.94 – 1.58)	**0.64 (0.46 – 0.89)**	[3]	1.43 (0.89 – 2.28)
≥80 years	82	276	1.08 (0.84 – 1.39)	1.00 (0.77 – 1.29)	0.91 (0.36 – 2.30)	[3]	0.77 (0.44 – 1.34)
All patients	2,487	716	**1.61 (1.24 – 2.08)**	**1.27 (1.07 – 1.52)**	**0.50 (0.37 – 0.69)**	1.03 (0.80 – 1.31)	1.00 (0.54 – 1.85)

ICU: Intensive care unit; 95% CI: 95% confidence interval. Results in bold text: statistically significant result. [1] Adjusted for age, sex, county of residence, regional health authority, date of admission, country of birth, virus variant and underlying risk factors. The variables included in the final multivariable models were obtained by forward model selection based on Akaike Information Criterion. [2] Later termed 'Completed primary vaccination series', see results for paper VI. [3] Not analysed for age subgroups due to the small number of fully vaccinated patients admitted to ICU in each age subgroup (≤50).

4.2.4 Paper VI: Clinical course of patients hospitalised with COVID-19, Omicron vs. Delta

The study cohort included 409 Omicron (38%) and 666 Delta (62%) patients hospitalised in the period 6 December 2021 – 6 February 2022. At the end of follow-up, 65 patients (6.0%) were still hospitalised. Of the 409 Omicron patients, 31 (7.6%) were admitted to ICU and 16 (4.0%) died in hospital. Of the 666 Delta patients, 165 (25%) were admitted to ICU and 63 (10%) died in hospital.

Omicron patients had a 48% lower risk of ICU admission (aHR: 0.52, 95% CI: 0.34 – 0.80) and a 56% lower risk of in-hospital death (aHR: 0.44, 95% CI: 0.24 – 0.79), compared to Delta patients. By age subgroup, Omicron patients 18 – 79 years had a lower risk of ICU admission than Delta patients. Patients ≥80 years were infrequently admitted to ICU, but Omicron patients had a lower risk of death than Delta patients (Table 13). Omicron patients vaccinated with three doses had an 80% lower risk of ICU admission and a 70% lower risk of in-hospital death, compared to Delta patients. Results tended in the same direction for unvaccinated patients (aHR for ICU admission or death: 0.51, 95% CI: 0.26 – 0.98). We did not observe a difference in the risk of ICU admission or death between hospitalised Omicron and Delta patients who had completed primary vaccination with maximum two doses (Table 14).

The median overall LoS was 2.8 days (IQR: 1.5 – 6.2) for Omicron patients and 5.9 days (IQR: 3.0 – 11.2) for Delta patients. In the multivariable models including all patients, the variable ‘variant’ did not satisfy the proportional hazards assumption for either LoS outcome. However, subgroup analysis suggested a shorter LoS (with or without ICU stay) for Omicron patients, compared to Delta patients, in the age subgroups 18 – 79 years and those who had completed at least primary vaccination (Table 13, Table 14). For example, for Omicron patients vaccinated with three doses the aHR for discharge overall was 1.58 (95% CI: 1.16 – 2.17). Assuming exponential distribution of the survival data, this translates into an expected 37% (95% CI: 14% – 54%) shorter overall LoS for Omicron patients, compared to Delta patients.

Table 13: Adjusted hazard ratios for hospitalised COVID-19 patients infected with the Omicron variant, compared to patients infected with the Delta variant, from a Cox proportional hazards model for different outcomes in paper VI, by age group.

Age group	Number of Delta patients	Number of Omicron patients	Adjusted hazard ratios[1] for Omicron patients, compared to Delta patients				
			Discharge from hospital – all patients (95% CI)	**Discharge from hospital – patients not admitted to ICU (95% CI)**	**ICU admission (95% CI)**	**Death in hospital (95% CI)**	**ICU admission or death in hospital (95% CI)**
<18 years	15	44	[2]	[2]	[2]	[2]	[2]
18 – 44 years	150	99	**1.98 (1.44 – 2.71)**	**2.40 (1.80 – 3.19)**	**0.31 (0.11 – 0.90)**	[2]	**0.31 (0.11 – 0.90)**
45 – 64 years	236	107	**1.56 (1.14 – 2.13)**	1.26 (0.92 – 1.72)	**0.38 (0.17 – 0.83)**	[2]	**0.37 (0.17 – 0.78)**
65 – 79 years	177	91	1.19 (0.87 – 1.64)	**1.13 (1.00 – 1.78)**	**0.47 (0.24 – 0.90)**	0.67 (0.24 – 1.88)	0.73 (0.37 – 1.14)
≥80 years	88	68	1.20 (0.86 – 1.67)	1.05 (0.72 – 1.52)	0.31 (0.09 – 1.13)	**0.26 (0.11 – 0.61)**	**0.31 (0.15 – 0.64)**
All patients	666	409	[3]	[3]	**0.52 (0.34 – 0.80)**	**0.44 (0.24 – 0.79)**	**0.46 (0.32 – 0.67)**

ICU: Intensive care unit. 95% CI: 95% confidence interval. Results in bold text: statistically significant result. [1] Adjusted for age, sex, regional health authority, country of birth, vaccination status and underlying risk factors. The variables included in the final multivariable models were obtained by forward model selection based on Akaike Information Criterion. [2] Subgroup analysis not conducted due to small sample size (<50 omicron and/or <50 delta patients and/or <10 outcomes). [3] Adjusted estimates not presented as the variable 'variant' had to be stratified in this model to satisfy the proportional hazards assumption.

Table 14: Adjusted hazard ratios for hospitalised COVID-19 patients infected with the Omicron variant, compared to patients infected with the Delta variant, from a Cox proportional hazards model for different outcomes in paper VI, by vaccination status.

Vaccination status[2]	Number of Delta patients	Number of Omicron patients	Adjusted hazard ratios[1] for Omicron patients, compared to Delta patients				
			Discharge from hospital – all patients (95% CI)	Discharge from hospital – patients not admitted to ICU (95% CI)	ICU admission (95% CI)	Death in hospital (95% CI)	ICU admission or death in hospital (95% CI)
Unvaccinated	401	99	[3]	[3]	0.53 (0.24 – 1.14)	0.41 (0.16 – 1.44)	**0.51 (0.26 – 0.98)**
Completed primary vaccination series with maximum two doses 7 – 179 days before positive test	63	77	1.46 (0.99 – 2.14)	**1.63 (1.10 – 2.42)**	0.73 (0.25 – 2.12)	[4]	0.89 (0.32 – 2.47)
Completed primary vaccination series with maximum two doses ≥180 days before positive test	111	69	1.34 (0.98 – 1.83)	**1.41 (1.01 – 1.97)**	1.17 (0.51 – 2.67)	0.50 (0.14 – 1.74)	0.66 (0.31 – 1.39)
Vaccinated with three doses ≥7 days before positive test	71	152	**1.58 (1.16 – 2.17)**	1.22 (0.88 – 1.68)	**0.20 (0.08 – 0.47)**	**0.30 (0.11 – 0.83)**	**0.28 (0.15 – 0.54)**
All patients	666	409	[3]	[3]	**0.52 (0.34 – 0.80)**	**0.44 (0.24 – 0.79)**	**0.46 (0.32 – 0.67)**

ICU: Intensive care unit. 95% CI: 95% confidence interval. Results in bold text: statistically significant result. [1] Adjusted for age, sex, regional health authority, country of birth, vaccination status and underlying risk factors. The variables included in the final multivariable models were obtained by forward model selection based on Akaike Information Criterion. [2] Some vaccination status groups (e.g. 'Partially completed primary vaccination series ≥21 days before positive test') are not presented due to small numbers (n=32 for all other groups and both variants). [3] Adjusted estimates not presented as the variable 'variant' had to be stratified in this model to satisfy the proportional hazards assumption. [4] Subgroup analysis not conducted due to small sample size (<50 omicron and/or <50 delta patients and/or <10 outcomes).

5. Discussion

5.1 Part I: Comparison of surveillance systems for hospitalised COVID-19 patients (papers I – II)

This thesis presents findings from studies that compare three newly established systems for the surveillance of patients hospitalised with COVID-19 during the first two years of the pandemic in Norway. One involved manual, aggregated data collection and two were based on patient-level EHR-data. These three systems were collectively a marked improvement on equivalent surveillance during the influenza A(H1N1)pdm09 pandemic (131) and have also outdated the sentinel, manual, weekly reporting Norway had for influenza hospitalisation before the COVID-19 pandemic (122).

Ideally, the surveillance of hospitalised patients should be sensitive and timely for public health action, representative, accurate, sustainable year-round, collect relevant data on the patient cohort, integrated with, but able to distinguish between, different pathogens and not entail an unnecessary reporting burden. A diverse landscape of surveillance systems for hospital admission with COVID-19 has emerged around the world (see chapter 1.2.5), with designs naturally tailored to the local setting, resource availability and existing data collection infrastructure and practices. The COVID-19 pandemic has driven a digital revolution in infectious disease surveillance (177). Routine healthcare data are now forming the backbone of the surveillance of hospital admission with COVID-19 and other respiratory illnesses in many countries (87, 133, 134, 136, 173, 178) and will likely do so in future health crises (177, 179). In light of this, the findings in this thesis provide clear examples of advantages and disadvantages with different surveillance systems for COVID-19 hospitalisations and during a health crisis. These are discussed below and presented in Table 15.

The daily hospital and ICU bed occupancy of COVID-19 patients (prevalence) remains a recommended surveillance indicator (180) but has not been under surveillance in

Norway since March 2022 (155). The surveillance of total bed occupancy is ongoing (156). The system best suited to monitoring disease-specific hospital bed occupancy depends on the disease, how quickly the system can be established, how quickly the patient flow can change and what indicators are needed. The daily aggregated collection by Hdir was similar to that conducted in other countries like Belgium, England, Scotland and the United States (see chapter 1.2.5) and had many ideal characteristics for such surveillance for COVID-19 (e.g. quickly established, timely, simple, national, comprehensive, flexible, reliable, consistent). However, the system also placed an additional reporting burden on hospitals and was limited to key variables.

Paper I and the prospective follow-up suggest that the EHR-based systems could have monitored the daily hospital bed occupancy of COVID-19 patients in Norway precisely and timely enough for appropriate public health action, including on a regional and hospital level (see (155) and appendix chapter 9.3). However, there were delays in the detection of increasing trends in NIPaR, which also adds an additional reporting burden with the registration of detailed patient-level data. Also, there were challenges in identifying patients on invasive ventilatory support in NPR-MSIS, likely linked to registration practices for procedure codes in NPR (e.g. registration first at discharge). We also had to adjust how the number of patients in hospital was calculated in both registries and there were rare failures in the data transfer to, or data extraction from, Beredt C19. These vulnerabilities emphasise that an EHR-based system for monitoring daily disease-specific bed occupancy would likely require validation at hospitals, especially during start of a health crisis when the disease is novel, disease-specific definitions untested and the systems themselves may need to be established.

While both EHR-based systems had national, comprehensive and mandatory reporting, these attributes do not guarantee full coverage by default. Despite different registration criteria in each registry, paper II found high coverage of patients with a recent positive PCR test for SARS-CoV-2 in NoPaR and with U07.1 in NPR, and a high degree of overlap between patients in NoPaR and with U07.1 in NPR, until late 2021. This is a particularly commendable result for a new manual reporting system for patient-level

data like NoPaR. However, from late 2021 the overlap gradually decreased to <75% and an increasing proportion of recently PCR positive patients were not registered with U07.1 in NPR, nor registered in NoPaR. Furthermore, 1,620 (7.8%) U07.1 patients in NPR did not have a recent positive PCR test registered, the vast majority admitted from late 2021. This suggests increasing registration of U07.1 for non-PCR positive patients from early 2022, contrary to national guidelines.

The decreasing overlap between the registries coincided with the Delta variant being superseded by the milder Omicron variant (23, 59, 62-65, 71), increasing vaccination coverage (87) and the gradual scaling back of non-pharmaceutical interventions and SARS-CoV-2 testing in Norway. This consequently impacted the flow to, and management of, COVID-19 positive patients in hospital, with patients gradually becoming more spread out across hospitals, instead of being treated in specific wards usually under the care of infectious disease physicians. Our results suggest that this impacted the registration of new patients in NoPaR and ICD-10 codes in NPR, such that the two registries were identifying increasingly different cohorts of patients and a decreasing proportion of all COVID-19 patients with a recent positive PCR test.

Norway was one of a limited number of countries who disaggregated hospital admissions due to COVID-19 from the start of the pandemic. The benefit of this was clearly illustrated in late 2021. More sustained vaccine effectiveness against severe disease than infection (19, 91), the spread of Omicron and the scaling back of non-pharmaceutical interventions and testing strategies increased community transmission and reduced the proportion of cases diagnosed. However, these factors also reduced the proportion of COVID-19 cases who developed severe disease. Thus, positive tests for SARS-CoV-2 became incidental in a larger proportion of hospitalised patients and the proportion of COVID-19 patients hospitalised due to COVID-19 fell markedly (Figure 2). Denmark (134), England (181) and Scotland (182) observed similar trends.

In paper II, while certain ICD-10 code combinations closely followed the trend in new admissions with COVID-19 as main cause, the distribution of ICD-10 codes varied by age and time. From late 2021 the frequency of pneumonia codes decreased in the age

groups ≥18 years, potentially related to the increasing proportion of vaccinated patients (183-186). In the same period, the proportion of patients 0 – 17 years admitted with COVID-19 as main cause who were registered with a URI code increased, in line with findings from the United States during a period of increasing Omicron dominance (187). From week 52/2021 the sensitivity of all code combinations including pneumonia for determining the main cause of admission was lower, compared to earlier periods. Statens Serum Institut in Denmark has developed an algorithm defining patients admitted to hospital a) due to COVID-19, b) where COVID-19 may have played a role or c) other causes of admission, using data from their national patient registry. Clinical validation of the algorithm by reviewing ca. 1,600 journals from patients ≥18 years found sensitivity of 95% in the Delta period and 87% in the Omicron period and specificity of 75% in the Delta period and 89% in the Omicron period (134). This highlights that using diagnosis codes for the surveillance of patients hospitalised 'due to COVID-19' requires consideration of temporal changes in patient and disease characteristics. It also underlines the importance of a surveillance system that is sensitive to changes in disease characteristics during a health crisis.

Other definitions of 'due to COVID-19' have also been proposed. Public Health Scotland now defines hospitalisation due to COVID-19 as community-acquired hospital admissions with a positive PCR test from emergency admissions to medical specialties, excluding surgical and mental health specialties and emergency admissions for injuries (173). SARI surveillance, either EHR- or questionnaire-based, is an alternative standardised approach established in several European countries (180). However, in the context of the surveillance of patients hospitalised due to COVID-19, one must consider how the definition of SARI may influence the sensitivity of the system. For example, in the EHR-based sentinel system in Germany SARI is defined as patients admitted with ICD-10 codes J09 – J22 (139). This will miss patients admitted with an URI (J00 – J06), which we observed in an increasing proportion of younger patients hospitalised due to COVID-19 since Omicron emerged.

NIPaR was the primary data source used in Norway for the surveillance of new patients admitted to hospital or ICU with COVID-19 (incidence) during the period covered by

this thesis. Data quality in both NoPaR and NIR was high (including COVID-19-specific clinical data (188)) and data reporting consistent, reliable and timely (Figure 8, Figure 9 and Figure 10). The main cause of admission was particularly valuable for surveillance. Also, the addition of new variables (e.g. on COVID-19 treatment) and extending registration deadlines and limiting mandatory data items from April 2022 in NoPaR indicate flexibility in an evolving pandemic setting and to sustain system acceptability among data providers (188). However, data registration in NIPaR entailed an additional reporting burden. Also, currently NoPaR only collects data on SARS-CoV-2 positive patients and system coverage waned from late 2021.

Utilising existing data flows in established EHR like NPR can provide the basis for a simple and acceptable, yet comprehensive, integrated and automated hospital-based surveillance system, encompassing both syndromic and diagnosis-based components. Prominent changes in disease characteristics may be detected (e.g. decrease in admissions with pneumonia among ≥18-year-olds and admission with an URI among <18-year-olds during the Omicron period in paper II). Indicators for both total and disease-specific hospital bed occupancy may be calculated. However, data collection is not designed for disease-specific surveillance and coding practices may change over time or be influenced by the degree of reimbursement. In this regard, linkage to laboratory results (e.g. the MSIS-laboratory database) may be critical to ensure high system coverage and consistency. Also, the timeliness of a system based on codes that may be registered at discharge is intrinsically linked to LoS. This appeared to be a notable issue for indicators of greater severity, like ventilatory support. LoS may also vary in an evolving pandemic setting (61, 62). This could be somewhat compensated for if data on the time to registration of ICD-10 codes were available, or by nowcasting while adjusting for LoS. Linkage to laboratory results can also improve system timeliness if positive test results are registered quicker than diagnosis codes (as was the case during COVID-19).

Table 15: Advantages and disadvantages of the systems used for the surveillance of patients hospitalised with COVID-19 in Norway.

Data source	Norwegian Directorate of Health	Norwegian Intensive Care and Pandemic Registry	NPR-MSIS
Data collection method	• Manuel daily counting and aggregated reporting of hospital-level data.	• Registration of patient-level data on COVID-19 patients in hospital.	• Linkage of patient-level data from patient journals in NPR to COVID-19 cases in MSIS.
Data content	• Prevalence of COVID-19 patients in hospital, ICU and on invasive ventilatory support.	• Detailed patient-level data from COVID-19 patients in hospital.	• Detailed patient-level data from COVID-19 patients in hospital.
Advantages	• National coverage • Simpler design easier and quicker to establish during early stages of the pandemic. • No delay in registration. • Quick and simple registration procedure. • May quickly incorporate new hospitals and ICUs. • Registrars do not need to be healthcare personnel.	• National coverage • Provides detailed, COVID-19-specific data on patients admitted to hospital. • Potential to monitor total bed occupancy in ICU and ventilatory support. • Data can be updated several times a day (if direct access to registry given). • Data suitable for research purposes, including disease-specific data.	• National coverage • Well-established routine reporting process through linkage of pre-existing registries. • Provides detailed data on patients admitted to hospital. • Potential to monitor total bed occupancy in hospital, ICU and ventilatory support. • Data can be updated several times a day (if direct access to registry given). • Data suitable for research purposes.

Table 15 continued.

Data source	Norwegian Directorate of Health	Norwegian Intensive Care and Pandemic Registry	NPR-MSIS
Advantages continued.		• Can be linked to other registries to achieve integration between surveillance systems and health-care levels, and for research. • Data suitable for epidemiological modelling.	• Can be linked to other registries to achieve integration between surveillance systems and health-care levels, and for research. • Data suitable for epidemiological modelling.
Disadvantages	• Additional manual reporting procedures. • Data only updated once daily. • Limited to a few indicators. No patient identifiers. • Cannot be linked to other national registries. • Data not suitable for research purposes. • Data not suitable for epidemiological modelling.	• Additional and time-consuming manual reporting procedures. • Some delay in registration linked to manual reporting procedures. • Registrars must be healthcare personnel, or personnel trained in reporting to the registry. • Incorporation of new hospital and ICU wards dependent on their registration in the national patient journal system.	• Some delay in registration, particularly of certain data items that may not be registered at the start of a patients stay in hospital e.g. diagnosis and procedure codes. • Data collection not tailored to specific disease. • Registrars must be healthcare personnel. • Incorporation of new hospitals and ICU wards dependent on their registration in the national patient journal system.

NPR-MSIS: Linkage Norwegian Patient Registry (NPR)-Norwegian Surveillance System for Communicable Diseases (MSIS). ICU: Intensive Care Unit. Each system is described in chapter 3.2.

5.2 Part II: Use of surveillance data to study risk factors for hospitalisation due to COVID-19 and the clinical course of hospitalised COVID-19 patients (papers III – VI)

As the pandemic progressed, studies on factors associated with the risk of hospitalisation with COVID-19 and clinical course among hospitalised COVID-19 patients, such as in papers III – VI, were essential to ensure a timely and appropriate public health response. In Norway, these studies were facilitated by the daily updated, individual-level surveillance data in Beredt C19. Numerous examples of other studies using Beredt C19 have been published (23, 48, 58, 67, 89). Other countries also used linked national registry data for surveillance and to conduct similar studies (64, 189).

When comparing results between studies, discrepancies in observed associations for comparable measures and study populations are not unexpected, nor just consigned to the examples below for papers III – VI (26, 89, 190, 191). While discrepancies could reflect biases, it is important to keep in mind that each study has been conducted in a different population, health care system and potentially epidemic phase.

In paper III we did not find clear evidence that different SARS-CoV-2 variants influenced the risk of hospitalisation with acute COVID-19 among children and adolescents in Norway. There was no difference in the risk of hospitalisation due to acute COVID-19 among <18-year-olds between the Omicron and Delta waves. We found a lower risk of hospitalisation due to acute COVID-19 in the Delta and Omicron waves, compared to the Alpha wave. For the outcome hospitalisation regardless of main cause, we found a lower risk for Omicron, compared to Delta and Alpha. The supplementary analysis presented in Table 10 suggests underreporting in NoPaR during the Delta and Omicron waves, which affected the observed decrease in the risk of this outcome for Omicron, compared to Delta. It was not possible to conduct a similar sensitivity analysis for the outcome hospitalisation due to acute COVID-19 using available data from NPR. While one would expect a lower degree of

underreporting for patients admitted due to COVID-19 as opposed to those admitted for non-COVID-19-related causes, I cannot rule out that the observed associations for this outcome were also affected by underreporting in NoPaR, particularly for Delta and Omicron, compared to Alpha. For Omicron compared to Delta, it is unlikely that any underreporting led to erroneous conclusions, given the wide confidence intervals.

Omicron has been comprehensively shown to decrease the risk of severe disease in adults, compared to Delta (23, 62-65). However, studies on the association between SARS-CoV-2 variants and the risk of hospitalisation among children with acute COVID-19 are less conclusive. For Omicron compared to Delta, our results are in line with some national cohort studies analysing overlapping exposure periods. In England, unvaccinated children <10 years infected with Omicron had a similar risk of hospitalisation ≤14 days after positive test, compared to children infected with Delta (aHR: 1.10, 95% CI: 0.85 – 1.42). This finding was sustained when breaking down the age group into <1, 1 – 5 and 5 – 9 years. Unvaccinated 10 – 19-year-olds may have had a small decrease in risk (aHR: 0.78, 95% CI: 0.60 – 1.00) (63). In Denmark, 3 – 19-year-olds infected with Omicron and Delta also had a similar risk of hospitalisation ≥12 hours (aRR Omicron vs. Delta: 1.41, 95% CI: 0.75 – 2.66) (64). Conversely, a propensity matched case-control study from Qatar among 985 matched pairs <18 years who were unvaccinated and did not have prior infection reported a substantially decreased risk of hospitalisation with Omicron, compared to Delta (aOR: 0.12, 95% CI: 0.07 – 0.19) (192). In a matched cohort study among children <5 years with no known prior infection in the United States, Omicron has been associated with a reduced risk of visiting an emergency department (aHR: 0.84, 95% CI: 0.80 – 0.87) and hospitalisation (aHR: 0.66, 95% CI: 0.58 – 0.74), compared to Delta (193). A study from Germany reported lower risks of COVID-19-related hospitalisation and ICU admission among PCR-positive <5-, 5 – 11- and 12 – 17-year-olds in the Omicron period, compared to Delta (194).

Studies including all age groups have found an increased risk of hospitalisation in persons infected with Delta, compared to Alpha (26, 190, 191). Similar studies in children and adolescents appear to still be limited. The study in Germany used

seroprevalence data to endeavour to account for undiagnosed cases and reported an approximate two-fold decrease in risk for COVID-19-related hospitalisation and ICU admission among <18-year-olds in the Delta period, compared to Alpha (194). However, these estimates were unadjusted and based on aggregated data with incomplete reporting on outcomes. Therefore, this study alone does not provide convincing evidence of a real difference in disease severity.

We found a lower risk of MIS-C in the Omicron wave, compared to the Delta wave, as reported elsewhere (59, 71, 195-197). This high degree of agreement between studies may be due to a greater strength of association for the outcome MIS-C for Omicron compared to Delta, compared to the outcome hospitalisation due to acute COVID-19. For Delta compared to Alpha (or earlier strains), studies on the difference in the risk of MIS-C are less conclusive (70, 71, 195).

The most important potential source of bias in severity studies based on diagnosed cases is systematic differences in undiagnosed cases between groups, as well as undiagnosed prior infections. This may affect outcome proportions and the observed association between exposure and outcome. Such differences may be related to temporal changes in testing guidelines, capacity and activity. For example, in our study the testing strategy was further enhanced after the Alpha wave. A higher proportion of school-age children and adolescents with asymptomatic and mild COVID-19 may therefore have been diagnosed in the Delta and Omicron waves, even if experiences from previous waves suggest that the proportion of children diagnosed was high before routine biweekly screening of school children was recommended. This may explain why we observed a lower risk of hospitalisation due to acute COVID-19 among persons <18 years in the Delta and Omicron waves, compared to the Alpha wave.

Also, changes in viral characteristics may play a role, for example increased rates of asymptomatic infection, changes in symptom profile and increased risk of reinfection with the emergence of Omicron (24, 31, 38, 39). The magnitude of the estimated decrease in risk for Omicron compared to Delta in Qatar (192) is particularly intriguing, compared to other literature. The authors report that approximately 16% of Delta and

2% of Omicron cases were admitted to hospital, significantly higher than other studies, including those with screening of school children (64, 71). This may suggest notable underdiagnosis of previous infections in the cohort in Qatar, which may have biased the association towards a reduced risk for Omicron. Interestingly, among adult age groups the authors also report a similar proportion of hospitalised cases and a 10-fold reduction in the risk of hospitalisation with Omicron, compared to Delta. This is a notably larger reduction than in other studies (23, 63, 64). Furthermore, matching on age 0 – 5 years may not precisely adjust for the differing risk of hospitalisation for infants and young children.

Other unmeasured confounders like coinfection with other respiratory viruses (198), or changes in health care seeking behaviour and admission practices may also play a role. For example, maternal vaccination against COVID-19 has been reported to protect infants from severe COVID-19 (199, 200). Maternal vaccination was first recommended in Norway before the start of the Delta wave. However, the decrease in the proportion of hospitalised infants <3 months old between the Alpha and Delta waves was also observed in infants born to unvaccinated mothers. Thus, other factors, such as differences in physicians' decisions on whether to hospitalise an infant, may also have influenced our outcomes. These points are especially relevant in studies with non-overlapping exposure periods. However, analyses on overlapping exposure periods have been more restricted for younger age groups than adults, given the low incidence of severe outcomes among children and adolescents.

Furthermore, changes in clinical presentation related to disease severity may be masked when the outcome is hospitalisation. Tissue-based studies have shown that Omicron infects bronchial cells more efficiently and lung alveolar cells less efficiently, compared to the Delta variant (201, 202). Children have smaller airways than adults, thus it is perhaps unsurprising that both our analysis in paper II and a study from the United States found increases in URI among SARS-CoV-2 positive hospitalised children and adolescents during the initial Omicron surge (187). This and other studies in the United States and South Africa also reported decreased rates or risks of other severity outcomes, like ICU admission, ventilatory support or death, among

hospitalised children infected with Omicron compared to Delta (187, 193, 198, 203). This may indicate lower disease severity, even if the observed risk of hospitalisation remains unchanged in some studies. For Delta compared to Alpha, these studies have not suggested a difference in disease severity in hospitalised cohorts (198, 203).

The discussion above highlights some of the inherent challenges with studies of SARS-CoV-2 variant severity among diagnosed cases, even during periods of high testing activity. The gradual down-scaling of community-based surveillance (87) may now put more emphasis on studies of non-overlapping exposure periods, studies of hospitalised cohorts and studies with bespoke data collection beyond the registry data used in such studies thus far in Norway (23, 67, 89) (such as indication for testing). In Norway, a recently established enhanced surveillance system aims to sequence all hospitalised COVID-19 patients for infecting variant (204).

Papers IV, V and VI all studied factors associated with the clinical course for hospitalised SARS-CoV-2 patients. In paper IV, we found no difference in any of our outcomes for persons infected with the Alpha variant, compared to ancestral SARS-CoV-2. These findings are in line with some other small studies among hospitalised cohorts (205-207), despite comprehensive evidence in community studies on diagnosed cases that Alpha increased the risk of hospitalisation, ICU admission and death, compared to the ancestral strain (66-68). This could suggest an increased risk of hospitalisation due to Alpha, but not a subsequent increased rate of the inflammatory phase and critical disease once hospitalised.

However, a study in England on 4,910 hospitalised patients found an increased risk of death among patients infected with Alpha, compared to the ancestral strain (aHR: 1.44; 95% CI: 1.11 – 1.87) (66). A study in Belgium on 3,919 hospitalised patients found an increased risk of a composite measure of severe disease (acute respiratory distress syndrome, ICU admission or in-hospital death, aRR: 1.55, 95% CI: 1.15 – 1.97) and ICU admission alone (aRR: 1.69, 95% CI: 1.21 – 2.17) among patients aged <65 years infected with Alpha, compared to the ancestral strain (189). Another study among 2,341 patients at eight hospitals in England found an increased risk of ICU admission

among women infected with Alpha (aHR: 1.82, 95% CI 1.15 – 2.90), but not men. This effect was sustained in analyses of age subgroups, and they reported no interaction between infecting variant and age for ICU admission (208).

The three larger studies suggest some increase in disease severity for certain groups of hospitalised patients infected with Alpha, compared to ancestral SARS-CoV-2. This may indicate that our study (only 157 patients infected with the ancestral strain) and others (205-207) were underpowered, especially as the change in risk of severe disease for Alpha compared to ancestral SARS-CoV-2 appears to have been more modest than for the key exposures in papers V and VI (see chapters 4.2.3 and 4.2.4 and related discussion below). The Alpha patient cohorts in ours and other small studies (205-207) were generally younger, had fewer comorbid conditions and had a higher frequency of ICU admission. This could be consistent with more severe disease.

Furthermore, an important potential limitation in analyses of hospitalised cohorts is collider bias (170). Both the SARS-CoV-2 variant and our outcomes independently influenced the likelihood of hospitalisation. This may have masked the association between the Alpha variant and increased disease severity consistently reported in community studies (66-68). The study in England demonstrates how the association between the Alpha variant and death weakened as the study population was conditioned on more severe outcomes, like ICU admission (66).

Selection bias may also have played a role. This is difficult to assess in studies that do not provide a comparison of patients with and without known variant (66, 208). The study in Belgium did report an increased proportion of ICU patients with known variant, compared to non-ICU patients, as we observed in papers IV and VI (see chapter 5.4). However, their sensitivity analyses did not suggest that this had resulted in a false positive association (189). Finally, unmeasured confounders must also be considered, such as changes in bed occupancy and patient management over time (169), although hospitals in Norway functioned within capacity during the study period and criteria for hospitalisation and treatment guidelines of COVID-19 patients were consistent.

In paper V, hospitalised COVID-19 patients aged 18 – 64 and 65 – 79 years, that were 'fully vaccinated' (at least completed primary vaccination series) with an mRNA vaccine had a shorter LoS in hospital (both with and without ICU admission) and lower risk of ICU admission, compared to unvaccinated patients. There was no difference in the risk of in-hospital death. This suggests that, once hospitalised, the risk of death among fully vaccinated and unvaccinated patients in Norway was similar, but that for survivors the clinical course in fully vaccinated patients was milder. For patients not admitted to ICU, the observed reduction in LoS may even have been attenuated by vaccinated patients, who may have ended up in ICU if unvaccinated, instead spending more time in regular wards. For all outcomes, we observed no difference between vaccinated and unvaccinated patients aged ≥80 years. Treatment limitations (for example, less frequent admission to ICU) may confound vaccine effects in the elderly, while the small number of unvaccinated patients aged ≥80 years in our cohort should also be considered.

Our results are generally consistent with others. Studies with hospitalised COVID-19 patient cohorts ranging from smaller to up to almost 10-times larger than ours from Canada (209), Slovenia (210), South Korea (183) and the United States (211-213) all reported that patients who were fully vaccinated with predominantly or exclusively an mRNA COVID-19 vaccine had reduced risks for different severity outcomes, such as LoS, ICU admission, pneumonia, need for ventilatory support, clinical severity score and death, compared to unvaccinated patients. Examples of similar vaccine effects among hospitalised cohorts have also been described for other infectious diseases (214, 215) and results further support comprehensive evidence of high COVID-19 vaccine effectiveness against severe disease from community studies (19, 57-60). The study in Canada also reported a dose-response relationship between number of COVID-19 vaccine doses and size of the risk reduction (209). Contradictory findings have also been published. A study in Michigan did not find a statistically significant difference in the risk of ICU admission, ventilatory support or death among hospitalised COVID-19 patients by vaccination status. However, this study may have been limited by small cohort of fully vaccinated patients (216).

Common to all studies was that vaccinated patients were generally older, had a higher prevalence of underlying comorbid conditions and had predominantly or exclusively received an mRNA vaccine. Our study was conducted in a period of Alpha and Delta dominance. Some studies suggest lower disease severity among fully vaccinated COVID-19 patients in hospital, also after the emergence of Omicron (209, 211, 213).

While the general trend in the literature indicates decreased disease severity among vaccinated hospitalised patients, the associations for some outcomes or subgroups differ and warrant further disentanglement of the study designs and settings. For example, we observed no difference in the risk of in-hospital death between fully vaccinated and unvaccinated patients, in contrast to other studies (209, 211). One important difference between our study and others is that we only included patients with COVID-19 as their clinically assessed main cause of admission. In sensitivity analyses we did observe a lower risk of death among fully vaccinated patients compared to unvaccinated patients in the age group 18 – 64 years, when including all SARS-CoV-2 positive patients regardless of main cause of admission, which may be more in line with the cohorts in other studies.

We also observed a lower risk of death in the age group 18 – 64 years when excluding patients who had received three vaccine doses or two doses with >180 days between date of last dose and positive test. This is understandable as at the time it was likely only 18 – 64-year-olds in high-risk groups who had received a third dose or received their last dose >180 days previously. This sensitivity analysis also highlights an interesting difference in comparable subgroup analyses between studies. In (211) the authors generally report less protection among those who had received a second dose <150 days ago compared to patients with ≥150 days since last dose, including for the risk of death among patients 18 – 64 years during the Delta dominant period. This appears to be contrary to the results in our sensitivity analysis, although the authors note that recent vaccinees in their cohort may have been at higher risk to present later to medical services or have had reduced treatment access, which could explain the observed trend in their data. This demonstrates the importance of considering the local

epidemiology in comparing studies from different settings and the benefit of analysing local datasets where possible to best inform public health action.

We did not observe a difference in LoS in ICU between fully vaccinated and unvaccinated patients. A report from Switzerland found a shorter LoS among vaccinated ICU patients who survived (a subgroup analysis we did not conduct) but no difference in death, compared to unvaccinated patients (217). Discrepancies in results for this indicator between studies are perhaps not surprising. Conditioning on ICU admission selects a cohort of already severely ill patients, while ICU cohorts between settings may vary by admission criteria and patient management.

In paper VI, hospitalised COVID-19 patients infected with the Omicron BA.1 variant had a milder clinical course than Delta patients, with a shorter LoS and lower risk of ICU admission and in-hospital death. This is in line with studies in hospital cohorts from elsewhere (65, 203, 213, 218-223) and supports substantial evidence of reduced disease severity among those infected with Omicron from community studies (23, 63-65, 71). As described earlier, tissue-based studies provide a plausible clinical mechanism (201, 202), as well as evidence of a decreased inflammatory response (222, 224). Our subgroup analyses generally supported the main results, although we did not observe a difference in the risk of ICU admission or death between two-dose vaccinated Omicron and Delta patients. Similar results for the outcome death ≤30 days after admission were reported in a study from Denmark (222). This would be in line with evidence of reduced two-dose mRNA vaccine effectiveness against severe disease with Omicron, compared to Delta (213, 225). However, we did not observe an interaction between variant and vaccination status and two-dose vaccinated Omicron patients had a shorter LoS than Delta patients. Also, the size of each subgroup must be considered.

5.3 Strengths

Collectively, papers I – VI have a range of strengths. All data sources had comprehensive and national coverage. The daily updated data from each registry available in Beredt C19 allowed the analyses in these studies to be conducted in a timely manner for appropriate public health action. Analyses were updated regularly

and results efficiently shared internally and externally (e.g. in reports and pre-prints). By linking registries using unique identity numbers, a wide range of potential confounders were able to be controlled for and adapted over time (e.g. time since last vaccination dose). Selection bias was able to be assessed in variant severity studies. Also, criteria for the hospitalisation and isolation of COVID-19 patients were not related to key exposures, including virus variant and vaccination status.

The studies also provide novel perspectives so far not described elsewhere. For papers I and II, Norway was in the relatively unique position of being able to compare two EHR-based systems for the surveillance of hospital bed occupancy (prevalence) and new patients admitted (incidence) since the start of the pandemic, as well as being able to disaggregate data on the main cause of admission based on a clinical assessment. Such comparisons will contribute to the further development of surveillance systems for hospitalised patients, both with COVID-19 and for future health crises.

For papers III – VI, results were relatively consistent in different sensitivity analyses, providing evidence of internal validity. Most results were also in line with studies conducted elsewhere, highlighting the external validity of the findings. As discussed above, discrepancies between studies are not unexpected and provide a basis for better understanding of results and further improvement in study design and data analysis.

Paper III was conducted in a setting with high testing capacity and activity, essential for studies on cohorts of diagnosed cases. In papers IV – VI, although we did not have access to treatment data, there were no major changes in treatment guidelines for COVID-19 patients in hospital or ICU in Norway during the study periods. In these studies, we also had minimal censoring (1.5% – 6.0% of patients still hospitalised at the end of follow-up).

5.4 Limitations

Despite notable strengths, the research conducted in this thesis has several limitations. General theoretical limitations are presented in chapter 3.3 and the discussion, such as the potential for residual confounding, selection bias and use of registry data with

collection not controlled by the researchers. While being able to conduct the studies in this thesis in a timely manner for appropriate public health action is a strength of the surveillance of patients hospitalised with COVID-19 in Norway, the rapidly evolving nature of the pandemic left limited capacity to analyse the data more comprehensively. For example, I would have liked to at least have attempted to assess residual confounding, as done by others (189, 211). However, I have no reason to believe that residual confounding has led to erroneous conclusions.

Also, speed may increase the risk for methodological and analytical errors. Paper IV provides an example of this, where we initially may have induced overcontrol bias in our analysis of in-hospital death by controlling for ICU admission. However, supplementary analyses not controlling for ICU admission did not notably affect the estimates.

In paper I (and the prospective follow-up), we cannot conclude how well the registries would have performed for the prospective surveillance of hospital bed occupancy around the time of system implementation and later in the pandemic, for example when Omicron was the dominant circulating variant. We also do not know how much of the discrepancy between the data sources may be due to subtle differences in how COVID -19 patients were defined. Finally, we also do not know whether data quality and timeliness for NIPaR would have been better if there had been fewer reporting sources.

In paper II, some ICD-10 code combinations were registered among patients in both main cause categories. This highlights that clinicians may assess the main cause of admission differently for patients with similar diagnostic codes, leading to non-differential misclassification. This could potentially have been alleviated by including more main cause categories beyond COVID-19/other (134). Also, we cannot rule out that the decreasing overlap between U07.1 patients in NPR and patients in NoPaR towards the end of the study period affected our analysis of hospitalisation due to COVID-19 and the precision of our sensitivity and specificity estimates. Furthermore, we did not have access to full ICD-10 codes for all diagnostic categories. This limited the exploration of whether more detailed code combinations could more precisely

represent patients hospitalised due to COVID-19. We also only considered the distribution of ICD-10 codes in this analysis, however other parameters could additionally inform more precise proxies. For example, in Denmark, the proportion of admission time related to certain diagnosis codes is considered (134).

In paper III, the small number of infants <3 months old, small number of vaccinated mothers in the Delta wave and lack of data on important confounders, such as breastfeeding and preterm birth, limited more in-depth analysis on how maternal vaccination may have influenced our outcomes. Another general limitation with our study was that the small number of outcomes restricted further exploration of the results, for example through additional severity outcomes like ICU admission. Also, we analysed an Omicron wave when the sublineage BA.1 was the dominant circulating variant, thus our results are not generalisable to other Omicron sublineages.

A limitation common to papers IV – VI is that some reported risk factors in NoPaR did not distinguish between well-regulated or treated conditions and unregulated or untreated conditions, for example asthma, while 40% – 46% of patients had unknown body mass index. Therefore, our models likely did not fully adjust for certain risk factors. Also, papers IV – VI generally did not include care home residents, who in Norway were recommended to receive treatment for severe COVID-19 in their care home, not in hospital, thus results are not necessarily generalisable to this population. Also, for paper V our fully vaccinated cohort was predominantly representative of patients who received a homologous two-dose Comirnaty regimen. This may limit the generalisability of the findings to patient cohorts who were vaccinated with another vaccine type.

Regarding selection bias in papers IV and VI, a higher proportion of patients admitted to ICU had known variant. In paper VI, this may mean we oversampled severely ill Delta patients, given their increased risk of ICU admission compared to Omicron patients. We may therefore have overestimated the reduction in LoS and risk of ICU admission and in-hospital death for Omicron patients. In paper VI we could also not distinguish sublineage BA.1 and BA.2 for all Omicron patients. Furthermore, for paper

VI, I cannot rule out an increased risk of underreporting of patients with COVID-19 as main cause of admission in NoPaR during the Omicron period, based on results in paper II.

In papers V and VI, our estimated proportional differences in LoS are likely slightly underestimated for some age groups where up to 10% of patients did not follow an exponential distribution.

Finally, as for paper III, although we dropped or controlled for previously diagnosed SARS-CoV-2 infection in papers V and VI, other previously undiagnosed infections may have been unevenly distributed between key exposure groups. This would most likely cause us to overestimate the reduction in risk of our outcomes for fully vaccinated patients (vs. unvaccinated) and Omicron patients (vs. Delta). This is less likely a limitation in paper IV, which was conducted earlier in the pandemic.

6. Main Conclusions

The general aims of this research were to compare and critically appraise systems for the surveillance of patients hospitalised with COVID-19 and to contribute to ensuring a timely, appropriate and evidence-based public health response in an evolving pandemic setting.

Papers I – II and the prospective follow-up to paper I demonstrated that EHR-data provided an accurate picture of patients hospitalised with COVID-19 in Norway, both in terms of bed occupancy (prevalence) and number of new admissions (incidence). However, they also highlight challenges with different the EHR-system designs for the surveillance of these indicators. These comparisons have allowed more comprehensive understanding of the data in each EHR through different phases of the pandemic and can inform the ongoing development of surveillance systems for patients hospitalised with COVID-19 and in preparation for future health crises.

Papers III – VI used COVID-19 surveillance data to study the association between vaccination or virus variant and the risk of hospitalisation among COVID-19 cases or clinical course among hospitalised COVID-19 patients. These analyses were essential to help provide timely and ongoing support for patient management and capacity planning in hospitals in Norway, as well inform the wider public health response. Results were generally in line with comparable studies in other settings and provide important lessons for conducting similar studies in future health crises.

7. Reflections and future perspectives

Despite the scaling back of community surveillance for COVID-19, SARS-CoV-2 continues to circulate around the world. Now in this post-acute pandemic phase, surveillance systems for COVID-19 and respiratory infections, and in advance of future health crises, need strengthening. In 2022, the ECDC noted "*an urgent need to establish robust, integrated surveillance systems that are sustainable and resilient should a new pandemic arrive"* (180). Guidelines are evolving, building on the many lessons for surveillance provided by the COVID-19 pandemic. Positive developments include linked registry-based systems (e.g. Beredt C19), participatory surveillance (e.g. '*Symptometer*' in Norway (226)), wastewater surveillance (227) and increased capacity for self-testing and genomic surveillance (228, 229). Conversely, system weaknesses have been revealed. Data from Europe (130, 230) and the Middle East (231) demonstrated how the COVID-19 pandemic interrupted data reporting and/or reduced testing for influenza in different countries. This underlined a need to ensure systems can be scaled up in health crises, without negatively impacting the surveillance of other diseases. Furthermore, the need for a more holistic, "*collaborative*" and One Health approach to surveillance, spanning environmental factors and animal and human populations, has been made even more apparent by the pandemic (94, 232, 233).

The WHO has set out a vision where "*all countries develop well-coordinated mosaics of multiple fit-for-purpose surveillance approaches that address priority surveillance objectives for influenza, SARS-CoV-2, and other respiratory viruses of epidemic and pandemic potential according to country context*" (228). Hospital admissions remain a central indicator in this mosaic. WHO guidelines from July 2022 list "*monitoring trends in morbidity and mortality*" and "*monitoring burden of disease on health care capacity*" as two of four core surveillance objectives for COVID-19 (234). In pursuit of developing "*robust, integrated, … sustainable and resilient*" (180) surveillance systems, my key reflections on our experience with the surveillance of patients hospitalised with COVID-19 and recommendations in advance of similar health crises (and for ongoing routine surveillance) are summarised in the box below and described in more detail in the subsequent text. These reflections are directly related to the

Norwegian setting and naturally most applicable to the surveillance of novel, high-impact infectious diseases. However, the underlying lessons may also have relevance for similar surveillance in other types of health crises.

Key reflections on the surveillance of patients hospitalised with COVID-19 and recommendations for similar health crises

1. The system should ideally incorporate the strengths of NPR (data flow from established systems) and NIPaR (disease-specific, timely and accurate reporting for indicators of greater severity). Datasets and data flows could be adapted and plans for scale up developed to ensure timely and high-quality data collection when a crisis occurs.
2. Indicators that disaggregate the main cause of hospital admission are essential. They should contain >2 categories and be regularly compared to patient characteristics and other disease-specific data to better understand any changes in disease characteristics and reporting practices over time.
3. More detailed disease-specific clinical data can help ensure more precise assessment of factors associated with severe disease and a system that is sensitive to changes in disease characteristics over time.
4. EHR-data can underpin the surveillance of total and disease-specific hospital bed occupancy, but validation of disease-specific indicators at hospitals is advised, especially at the start of a health crisis.
5. Potential solutions to improve the accuracy and timeliness of an EHR-based system for the surveillance of bed occupancy for indicators of greater severity beyond hospitalisation could be explored.
6. A more permanent version of a registry like Beredt C19 should be established to ensure robust, integrated and sustainable infectious disease surveillance, both in advance and independent of future health crises.

Looking forward, the most straight-forward solution to the disease-specific surveillance of new hospital admissions and bed occupancy in Norway, both for the routine surveillance of COVID-19 and in a similar health crisis, is a system based on data flows from established EHR-systems like NPR. NPR can provide the basis for simple and acceptable, yet comprehensive, national, integrated and automated surveillance. An integrated SARI surveillance system based on NPR data is currently operating in Norway (87). Further linkage to daily updated data from the MSIS-laboratory database can ensure high system coverage, consistency and timeliness. However, the surveillance system would ideally also incorporate the strengths NIPaR displayed throughout the pandemic, with disease-specific data collection (particularly during the acute phase of a health crisis) and timely and accurate reporting for greater severity indicators like ICU admission.

Regarding disease-specific data, experience in Norway and elsewhere demonstrated the value of indicators disaggregating hospital admissions due to, not just with, a disease. Regardless of whether based on a clinical assessment, diagnosis code algorithms or another measure, these indicators should be clearly defined and disaggregated into categories beyond yes/no/unknown (134). In NPR, diagnosis codes (other than the disease-specific diagnosis code) provide some nuance of patients' clinical presentation. For routine surveillance, further exploration of more detailed code-based algorithms, beyond the analysis in paper II, could provide a more sensitive and specific indicator for hospitalisation due to COVID-19 in Norway. Data from Denmark have shown that this is feasible (134). In this post-acute phase of COVID-19, NIPaR have already limited mandatory data items in NoPaR to reduce reporting burden (188) and in June 2023 only required the registration of patients with COVID-19 as their main cause of admission (164). Defining hospital admissions due to COVID-19 using NPR data could arguably eliminate the need for NoPaR for routine COVID-19 surveillance purposes in this post-acute phase. However, an indicator based on a clinical assessment is still of value if the reporting burden can be minimised, especially in a future health crisis for a novel disease. Adding such an indicator for ICU admission could be considered.

Regardless of whether for routine surveillance or in future health crises, comparison of indicators for hospital admissions due to a specific disease with patient characteristics and other disease-specific data should be conducted regularly. This would enable better understanding of temporal changes in disease characteristics and reporting practices and best ensure measurably consistent outcome definitions over time. Patient-level data in NPR-MSIS and NIPaR were first able to be linked from November 2020 in Beredt C19. However, partially due to data minimisation (range of ICD-10 codes available), the first such comprehensive comparison during the COVID-19 pandemic was not conducted until paper II, when SARI surveillance had been established.

Furthermore, while other clinical data beyond main cause of admission were collected in NoPaR (e.g. patient's clinical condition, see chapter 3.2.4), these variables were not available in Beredt C19 as they were considered to fall outside the aim of the preparedness registry (see chapter 3.2.2). Papers V and VI demonstrate the power of linked EHR-data for the timely and accurate assessment of factors associated with severe disease in the response to a health crisis. On the other hand, papers III and IV provide examples of when more detailed clinical data could have helped provide important nuance in such an assessment. In papers III – VI, other clinical data also would have allowed additional sensitivity analyses, some validation of whether the clinical assessment of main cause of admission was consistent over time and more standardised international comparisons, for example by calculating standardised clinical severity scores (235). One must strike a balance between clinical research and what is necessary for surveillance. However, to better ensure a timely, appropriate and evidence-based public health response in a health crisis, the justification not to transfer more detailed clinical data to a future preparedness registry should be revisited, especially if such data are collected independent of their use for surveillance.

For bed occupancy indicators, our results suggest that EHR-data on hospitalised patients would have been precise and timely. However, the vulnerabilities we identified emphasise that, if using an EHR-based system for monitoring disease-specific bed occupancy, having supplementary systems for validation at hospitals (for example through a system like the daily collection by Hdir) would be of value, especially at the

start of a health crisis. Also, question marks remain over how accurate and timely an EHR-based system is for the surveillance of bed occupancy for greater severity indicators, particularly in NPR. Potential solutions, like developing protocols for temporarily adapting registration practices for specific codes/patients during a health crisis, could be explored.

Stemming from lessons learnt during the influenza A(H1N1)pdm09 pandemic, Beredt C19 was the first preparedness registry established in Norway. The linkage of data from a wide range of national registries ensured comprehensive, timely and accurate surveillance and research for public health action, including the studies in papers I – VI. Through Beredt C19, NPR and NIPaR also demonstrated the feasibility and benefit of integrating the strengths of both systems for the surveillance of persons admitted to hospital. However, preparedness registries in Norway are temporary and are to be deleted once the 'event' (in this case the COVID-19 pandemic) has ended and been evaluated. Also, the necessity for reporting of data on hospital bed occupancy to Hdir and need to establish NoPaR reflect a gap in pandemic preparedness and surveillance plans in Norway prior to COVID-19. Establishment of a more permanent version of a registry like Beredt C19 is essential to ensure continued routine EHR-based surveillance of persons admitted to hospital with COVID-19 and other respiratory viruses and to lay a platform for establishing reporting systems that incorporate the strengths of both NIPaR and NPR in preparedness for hospital-based surveillance during similar health crises.

At the time of writing, there is an ongoing process in Norway to develop better digital preparedness in advance of future health crises, for example through strengthening data flows and automating analyses (179). There is therefore an opportunity to adapt datasets and data flows to better integrate systems like NPR and NIPaR. While the future of NIPaR is under discussion, the infrastructure is in place and the aim of the registry is not limited to COVID-19 (188).

An example of a data flow adaptation for COVID-19 could be the automatic transfer of overlapping data items for patients registered with U07.1 in NPR (or better yet, also

those without U07.1 but a recent positive test in the MSIS-laboratory database) to the COVID-19-specific form in NoPaR. For patients admitted to ICU, the procedure code in NPR (B0050, (236)), with the same registration criteria as NIR, has recently been introduced. If high sensitivity, specificity and timeliness for this code can be achieved, disease-specific ICU admissions may also be distinguished in such an integrated data transfer. Plans for scale up of disease-specific components should cover several scenarios, such as changes in the epidemiology of a known threat (e.g. a new SARS-CoV-2 VOC) or emergence of a novel pathogen. Detailed reporting on a representative sample of patients may be considered to further limit reporting burden, if this can be done in a timely manner for public health action (237), although this may not be necessary in a country with a smaller population like Norway. System timeliness should be able to be assessed, as it was possible for NIPaR during COVID-19 through time stamps for form registration. Such data were not available from NPR in the data transferred to Beredt C19.

Also, as presented in chapter 3.4, the ethical considerations for papers I – VI varied, relating somewhat to a lack of clarity as to what was permitted under the framework of Beredt C19. This impacted the research in this thesis. For example, we could have conducted the supplementary analysis in Table 10 at the time the study was first conducted. However, at the time the ethics committee approved research protocol did not include data from NPR beyond the outcome MIS-C. The establishment of a more permanent integrated system for digital preparedness could allow research protocols to be developed and data use to be clarified in advance of future health crises. This would minimise delays and uncertainties at critical times.

Furthermore, throughout the pandemic, data from Beredt C19 were not able to be shared outside the NIPH. This led to discrepancies between the Norwegian surveillance data housed by international partners like the ECDC (hospital admission based on MSIS only) and the data that was informing the public health response in Norway (hospital admission based on NIPaR). While issues surrounding data protection need to be carefully considered, the potential benefit of more integrated European surveillance has been recognised. The revised European Commission regulation on

serious cross-border threats to health (177) and European Union Joint Action 'UNITED4Surveillance' (238) aim to promote the establishment of interoperable and reliable real-time digital surveillance systems. This could more easily facilitate intercountry collaborations (239) and allow closer examination of differences in effects between sites to more rapidly reach consensus. Regarding the studies in this thesis, this could particularly assist in studies when outcomes are rare (paper III) or individual datasets may be underpowered (paper IV).

Finally, the benefits of a more permanent version of a registry like Beredt C19 to the routine surveillance of infectious diseases in Norway, independent of preparedness aspects, should not be overlooked. An example of this is for hepatitis B and C, where data on linkage to care, treatment and severe disease among diagnosed cases are essential to monitor progress to global elimination goals (240). Current processes for conducting registry-based research in Norway do not permit the timely compilation of relevant data for surveillance purposes. The wide range of analyses done through Beredt C19 have clearly shown the benefit of this during the COVID-19 pandemic.

8. References

The literature reviewed in this thesis is up to date until 30 June 2023.

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9. Appendices

9.1 Papers I – VI

9.1.1 Paper I

Tidsskriftet
DEN NORSKE LEGEFORENING

Hospitalisations for COVID-19 – a comparison of different data sources

ORIGINAL ARTICLE

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BACKGROUND

Three different data sources exist for monitoring COVID-19-associated hospitalisations in Norway: The Directorate of Health, the Norwegian Intensive Care and Pandemic Registry (NIPaR), and the linking of the Norwegian Patient Registry (NPR) and the Norwegian Surveillance System for Communicable Diseases (MSIS). A comparison of results from different data sources is important to increase understanding of the data and to further optimise current and future surveillance. We compared results from the three data sources from March to June 2020.

MATERIAL AND METHOD

We analysed the number of new admissions, as well as the total number of hospitalised patients and those on ventilatory support, reported per day and by regional health authority. The analysis was descriptive.

RESULTS

The cumulative number of new admissions according to NPR-MSIS (n=1260) was higher than NIPaR (n=1153). The discrepancy was high early in the epidemic (93 as of 29 March). The trend in the number of hospitalised patients was similar for all three sources throughout the study period. NPR-MSIS overestimated the number of hospitalised patients on ventilatory support.

INTERPRETATION

The discrepancy in new admissions between NIPaR and NPR-MSIS is primarily due to missing registrations for some patients admitted before NIPaR became operational. Basic information retrieved daily by the Directorate of Health give comparable results to more comprehensive daily information retrieval undertaken in NIPaR and NPR-MSIS, adjusted retrospectively. Further analysis is necessary regarding whether NIPaR and NPR-MSIS provide timely data and function as required in an emergency preparedness situation.

MAIN FINDINGS

Three different data sources for measurement of hospitalisations for COVID-19 (daily reports to the Directorate of Health/reporting to NIPaR/registry linkage of NPR and MSIS) gave comparable results.

NPR-MSIS included more new admissions than NIPaR per day at the start of the epidemic in Norway.

Daily registrations by the Directorate of Health have provided a good picture of the number of hospitalised patients per day during the epidemic when compared to figures from NIPaR and NPR-MSIS that had been adjusted retrospectively.

Continuous monitoring of hospitalisations for COVID-19 is required to maintain an overview of the epidemiological situation and the burden on hospitals over time. During the pandemic, different countries have chosen different monitoring strategies at the national level. Some countries collect individual-level data from existing patient registries (1) or recently established systems (2). Others have comprehensive systems for admissions to intensive care units, but not for new hospitalisations (3,4). Not all countries have nationwide systems (5).

Most countries have implemented national monitoring of the burden on hospitals, either of all patients hospitalised for COVID-19 (1, 2, 6) and/or patients admitted to intensive care units (3). To collect daily information on COVID-19 patients who are hospitalised and/or in intensive care units in Norway, the Directorate of Health, the Norwegian Institute of Public Health and the Norwegian Intensive Care and Pandemic Registry (NIPaR) have established

three different data sources: reporting from the hospitals to the Directorate of Health; NIPaR; and linking of raw data in the Norwegian Patient Registry (NPR) and data in the Norwegian Surveillance System for Communicable Diseases (MSIS).

During the influenza pandemic in 2009, weekly aggregated reporting of admissions to hospitals and intensive care units was established at the national level in Norway, since a continuous collection of data for use in routine surveillance of influenza did not previously exist (7). It was considered that the anonymity of the reporting made for a significant reduction in quality and eliminated the opportunity for further epidemiological research. Nor was this system coordinated with the regional health authorities (7). Since we now have a number of different systems for monitoring of hospitalisations for COVID-19 in Norway, and because these data are important for the management of the epidemic, it is essential to continuously compare figures from different monitoring systems to see whether they provide an identical picture of the situation. This may help increase our understanding of the data and optimise current and future surveillance. No comparisons have yet been made of the figures from the three different data sources that are used for monitoring of hospitalisations for COVID-19 in Norway.

The objective of this study was to compare the daily number of new admissions, as well as the daily total number of hospitalised patients and the number of patients on ventilatory support reported from the three data sources in the period March – June 2020 to see whether they provided a comparable picture of the epidemic in the country.

Material and method

DATA SOURCES

The three data sources used for daily monitoring of hospitalisations for COVID-19 in Norway are summarised in Table 1. Although there is some overlap in the information that these three sources collect, the data sources differ in terms of their methods of data collection and definitions of hospitalisation. The Directorate of Health collects data on daily prevalence for a few key variables (8). The other two data sources are registry-based and collect personally identifiable data (9). A description of the patient group registered in NIPaR and NPR-MSIS is published weekly in reports from the Norwegian Institute of Public Health (10). All three data sources collect data from all Norwegian hospitals, and reporting to all three is mandatory.

Table 1

Summary of the data sources for the Directorate of Health, the Norwegian Intensive Care and Pandemic Registry (NIPaR) and the linkage between the Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases (MSIS) for daily monitoring of hospitalisations for COVID-19 in Norway.

Characteristic	Directorate of Health	Norwegian Intensive Care and Pandemic Registry	Linkage Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases

Characteristic	Directorate of Health	Norwegian Intensive Care and Pandemic Registry	Linkage Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases
Reporting method	Manual counting and reporting to the Directorate of Health	Data registered in the Norwegian Pandemic Registry (NoPaR) and the emergency preparedness form from the Norwegian Intensive Care Registry (NIR)	Data collected automatically with the aid of the NPR infrastructure. In addition, data from MSIS.
Data collected	Daily prevalence, including the number of patients hospitalised and on invasive ventilatory support	Personally identifiable information from NoPaR and NIR[1]	Personally identifiable information from NPR and MSIS[1]
Date of first data collection	12 March 2020	For NoPaR: 31 March 2020 For NIR: 10 March 2020	First half of April 2020
Data available from	8 March 2020	No limitation	1 January 2020
Time of data collection	Data are reported to the directorate before 12.00 and reflect the status as of 08.00 on the same day	Continuous data registration. The NIPH dataset is updated at 06.00 every day.	Continuous data registration. The linkage NPR-MSIS takes place at 09.00 every day.

Characteristic	Directorate of Health	Norwegian Intensive Care and Pandemic Registry	Linkage Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases
Definition of a hospitalisation for COVID-19	Patients with COVID-19 confirmed by a laboratory, including patients hospitalised with other diseases or injuries if these are considered contagious.	Patients with COVID-19 confirmed by a laboratory admitted to a hospital and/or intensive care unit, irrespective of reason for admission	Patients with COVID-19 confirmed by a laboratory, who were hospitalised in the period two days before until 14 days after sampling date, and/or inpatient admissions where the patient was diagnosed with U07.1

[1]For links to information on items registered in NPR, MSIS, NoPaR and NIR, see the Norwegian Institute of Public Health (9)

DATA PROCESSING

We retrieved data from the three sources on 29 June 2020. We included data from 1 March until 28 June 2020 from NIPaR and NPR-MSIS, and data from 8 March through 26 June from the Directorate of Health. The Directorate of Health does not have data prior to 8 March, and data were only reported on weekdays in June (8).

From NIPaR, all admission and discharge forms were linked to patient trajectories at the individual level. Ventilation periods were defined by the start and end times of the ventilatory support. New admissions with less than 24 hours between discharge and renewed admission were defined as a single hospitalisation episode. The same definition was applied to hospitalised patients on ventilatory support, but with a 12-hour time limit. The data set provided by NIPaR to the Norwegian Institute of Public Health does not distinguish between invasive and non-invasive ventilatory support.

From NPR, all admission and discharge dates were linked to patient trajectories at the individual level. New admissions with less than 24 hours between discharge and renewed admission were defined as a single hospitalisation episode. Ventilation periods were defined by the start time of the ventilatory support and the discharge date from the ward where ventilatory support was used, because of incomplete data on the time when the ventilatory support had ended. We used the code for invasive ventilatory support (GXAV01) from the Norwegian clinical procedure coding system to define an invasive ventilatory support episode. We defined non-invasive ventilatory support as episodes for which codes had been entered for non-invasive treatment with continuous positive and/or biphasic positive airway pressure (GAXV10 and GAXV20 respectively).

In NIPaR and NPR-MSIS we defined a new admission as the first admission date per patient with confirmed COVID-19. Readmissions were not included in the count of new admissions. We defined a patient as hospitalised starting from the date after the admission date up to and including the last discharge date for the episode. An equivalent definition was used for hospitalised patients on ventilatory support.

DATA ANALYSIS

The data analysis was descriptive. We compared the number of new admissions in NIPaR and NPR-MSIS, as well as the total number of hospitalised patients and patients on ventilatory support in the Directorate of Health, NIPaR and NPR-MSIS per day and per regional health authority. We compared the number of hospitalised patients on ventilatory support in NPR-MSIS for all ventilation episodes and for invasive ventilation episodes only. Data processing and analysis were performed in STATA 16.0 and Microsoft Excel.

ETHICS

No approval by the Regional Committee for Medical and Health Research Ethics (REK) was required for the data from the Directorate of Health, since we were using aggregated and anonymous data that are publicly available. NIPaR and NPR-MSIS are included in the emergency preparedness registry for COVID-19, called Beredt C19, established by the Norwegian Institute of Public Health (9). A thorough data protection impact assessment (DPIA) of this registry has been made, and in its submission assessment on 2 June 2020, the Regional Committee of Medical and Health Research Ethics concluded that analyses of health service use fall outside the scope of the Health Research Act (REK South-Eastern Norway B, 153204).

Results

NEW ADMISSIONS TO HOSPITAL

The cumulative number of new admissions reported by NPR-MSIS (n=1260) was higher than in NIPaR (n=1153) throughout the study period. The discrepancy was high at the early stage of the epidemic (93 as of 29 March) (Figure 1). A similar trend was observed for all the regional health authorities, except for late in the period, when nearly all new admissions were in South-Eastern Norway Regional Health Authority (data not shown).

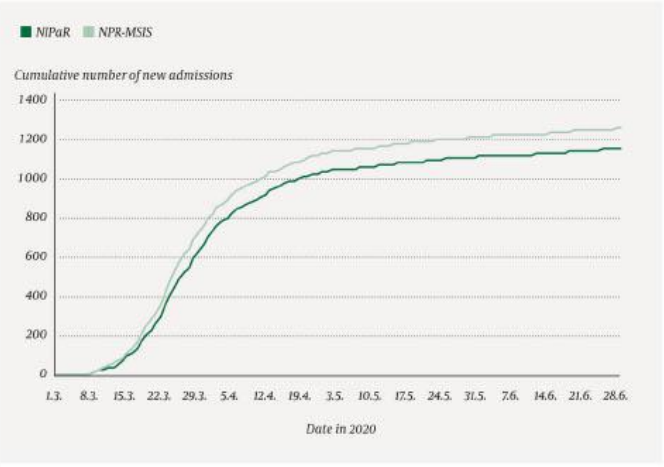

Figure 1 Cumulative number of new admissions for confirmed COVID-19 per day in Norway according to the Norwegian Intensive Care and Pandemic Registry (NIPaR) and linkage between the Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases (MSIS) in the period 1 March – 28 June 2020. A new admission is defined according to the first date of admission per patient. Readmissions are not included.

HOSPITALISED PATIENTS

The trend in the number of hospitalised patients per day was consistent in all three data sources throughout the study period, with some daily variations (Figure 2). In March, there were on average 16 more hospitalised patients per day in NPR-MSIS than in NIPaR, and 21 more than in the figures from the Directorate of Health. The peak number was 351 (30 March) according to NPR-MSIS, 327 (31 March) according to NIPaR and 325 (1 April) according to the Directorate of Health. From 5 April to 28 June, the figures from both NPR-MSIS and NIPaR showed nine more hospitalised patients on average than the figures from the Directorate of Health (Figure 2).

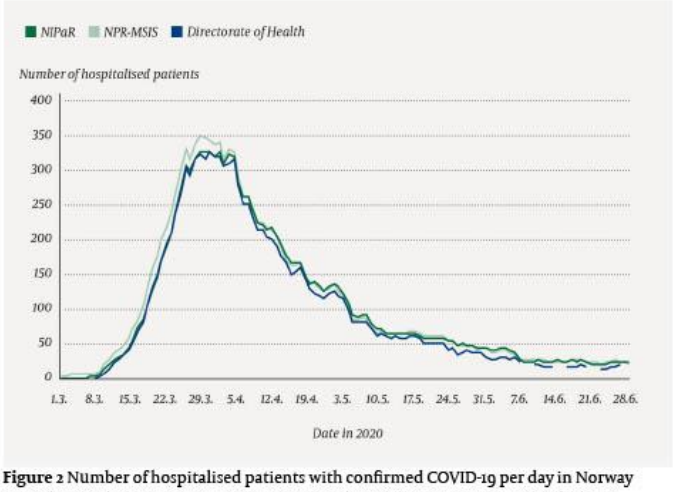

Figure 2 Number of hospitalised patients with confirmed COVID-19 per day in Norway according to the Norwegian Intensive Care and Pandemic Registry (NIPaR), linkage between the Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases (MSIS) and reporting to the Directorate of Health in the period 1 March – 28 June 2020.

VENTILATORY SUPPORT

The trend in the number of hospitalised patients on ventilatory support in NPR-MSIS was similar to the trend in NIPaR at the start and end of the study period. From 5 April until 31 May, there were on average 21 more patients on ventilatory support in NPR-MSIS than in NIPaR. The peak number of hospitalised patients on ventilatory support was 94 (3 April) according to NIPaR and 118 (6 April) according to NPR-MSIS (Figure 3).

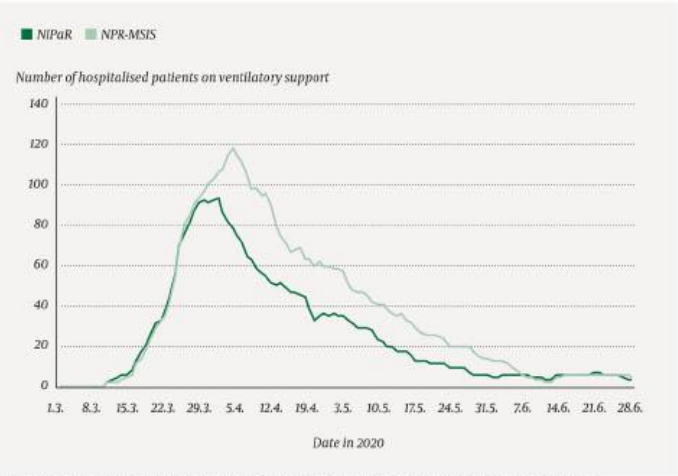

Figure 3 Number of hospitalised patients with confirmed COVID-19 and need for ventilatory support per day according to the Norwegian Intensive Care and Pandemic Registry (NIPaR) and linkage between the Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases (NPR-MSIS) in the period 1 March–28 June 2020.

INVASIVE VENTILATORY SUPPORT

The trend in the number of hospitalised patients on invasive ventilatory support in NPR-MSIS was similar to the trend for the Directorate of Health at the start and end of the study period. From 5 April until 31 May, there were on average 15 more patients on invasive ventilatory support in NPR-MSIS than are indicated by the figures from the Directorate of Health. The peak number was 99 (1 April) according to the Directorate of Health and 111 (6 April) according to NPR-MSIS (Figure 4).

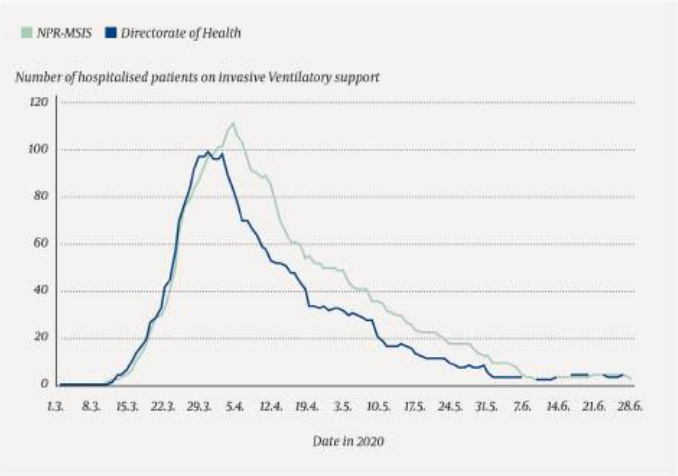

Figure 4 Number of hospitalised patients with confirmed COVID-19 and need for invasive ventilatory support per day according to linkage between the Norwegian Patient Registry

and the Norwegian Surveillance System for Communicable Diseases (NPR-MSIS) and data reported to the Directorate of Health in the period 1 March–28 June 2020.

Discussion

This analysis is the first comparison of different data sources that collect data on hospitalisations for COVID-19 in Norway, and as far as we are aware the first to compare results from three different data sources. Few similar analyses from other countries have been published. In an analysis of two different data sources on hospitalisations for COVID-19 in Belgium, 71 per cent of hospitalisations were registered in a system that was based on voluntary reporting of individual-level data, compared with a mandatory reporting system based on collection of aggregated data (2). In our study, there were nearly one hundred more new admissions for COVID-19 in NPR-MSIS than in NIPaR at the start of the study period, and more hospitalised patients per day in March. This could be due to some patients admitted to hospital before the pandemic registry came into operation not being registered retrospectively, or patients without a national identity number or a D-number (a temporary identity number for foreign residents) not being able to be registered. Since November 2020 it has been possible to link NIPaR to MSIS in the Beredt C19 registry, which enables further analysis of differences between these two data sources in terms of patients registered.

The trend in the number of hospitalised patients per day in the three sources confirms that the figures reported to the Directorate of Health have given a good picture of the situation in Norway during the COVID-19 pandemic. Day-to-day variation between the data sources in the number of hospitalised patients can be due to differences in data collection practices and in the ways in which patient trajectories are collated. The reporting to the Directorate of Health was crucial at the start of the COVID-19 pandemic when the other two data sources were unavailable, and it also reveals a gap in preparedness that also came to light in connection with the influenza pandemic in 2009, both in Norway (7, 11) and internationally (12, 13). The reporting to the Directorate of Health required a manual daily count, at a time when the health authorities were facing a substantial workload. The concurrent results give grounds for assessing whether NIPaR and NPR-MSIS can replace the hospitals' reporting to the Directorate of Health. It is desirable to have automated systems in place that use existing data instead of manual solutions, but both of these approaches are required for the time being.

The daily data retrievals from the hospitals' electronic systems (NPR) that have been established during the pandemic are a major step in the direction of updated registry information from the Norwegian specialist health service. A continuation of this practice also after the pandemic will be important to improve the national monitoring of future known and unknown serious health threats. NPR-MSIS provides a quick and complete registration of admissions and discharges of patients infected by SARS-CoV-2, because the linkage is largely based on established reporting procedures. On the other hand, it is difficult to determine whether the patient is being treated for COVID-19 or for some other disease or injury. Registration in NIPaR requires is done manually, and thereby has similar disadvantages to those of registration by the Directorate of Health. The advantage is that NIPaR collects far more clinical information, which makes this source well suited for analysing the condition of COVID-19 patients and the therapeutic procedures that are initiated.

As national registries, NIPaR and NPR-MSIS can be used for ongoing research and surveillance of COVID-19. If the information in NIPaR and NPR-MSIS is also to be used in the context of emergency preparedness, it is essential that these data sources provide updated, real-time information on the workload in hospitals that can quickly be fed back to decision-makers. In an emergency preparedness situation, information gathering needs to

be robust and feasible without burdening the health services, especially the clinicians. Information ought to be collected from persons without a national ID number or D-number as well as from any recently established hospitals and intensive care units.

This study is retrospective, and the information from NIPaR and NPR-MSIS has been adjusted retrospectively. This may explain why more hospitalised patients were generally registered in NIPaR and NPR-MSIS than in the figures from the Directorate of Health. The results are therefore not transferable to an emergency preparedness situation where daily updated information is required. An analysis based on a daily data retrieval from NIPaR and NPR-MSIS must be undertaken over a period to be able to assess whether these data sources are suitable as replacements for the hospitals' reporting to the Directorate of Health.

The number of patients on ventilatory support was higher in NPR-MSIS than in NIPaR, and the number of patients on invasive ventilatory support was higher in NPR-MSIS than in the figures from the Directorate of Health. In NPR-MSIS, the end time of ventilatory support was based on the time of discharge from the ward, due to incomplete or missing data for end time of ventilatory support. Most likely, this has led to an overestimation of the number of patients on ventilatory support at any given time. NIPaR is therefore better suited to measure the time on ventilatory support. Another possibility is to increase the quality of the coding of start and end times for implemented interventions and procedures in NPR.

CONCLUSION

In combination, the three different data sources provide good information on hospitalisations for COVID-19 for the various purposes that are relevant in an emergency preparedness situation, on an ongoing basis as well as in retrospect. The figures reported to the Directorate of Health have provided a good picture of the daily number of COVID-19 patients in Norway. Further analysis is required as to whether NIPaR and NPR-MSIS provide real-time data and function well in an emergency preparedness situation.

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9.1.2 Paper II

SURVEILLANCE

A comparison of two registry-based systems for the surveillance of persons hospitalised with COVID-19 in Norway, February 2020 to May 2022

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Background: The surveillance of persons hospitalised with COVID-19 has been essential to ensure timely and appropriate public health response. Ideally, surveillance systems should distinguish persons hospitalised with COVID-19 from those hospitalised due to COVID-19. **Aim:** We compared data in two national electronic health registries in Norway to critically appraise and inform the further development of the surveillance of persons hospitalised with COVID-19. **Method:** We included hospitalised COVID-19 patients registered in the Norwegian Patient Registry (NPR) or the Norwegian Pandemic Registry (NoPaR) with admission dates between 17 February 2020 and 1 May 2022. We linked patients, identified overlapping hospitalisation periods and described the overlap between the registries. We described the prevalence of International Classification of Diseases (ICD-10) diagnosis codes and their combinations by main cause of admission (clinically assessed as COVID-19 or other), age and time. **Results:** In the study period, 19,486 admissions with laboratory-confirmed COVID-19 were registered in NoPaR and 21,035 with the corresponding ICD-10 code U07.1 in NPR. Up to late 2021, there was a 90–100% overlap between the registries, which thereafter decreased to<75%. The prevalence of ICD-10 codes varied by reported main cause, age and time. **Conclusion:** Changes in patient cohorts, virus characteristics and the management of COVID-19 patients from late 2021 impacted the registration of patients and coding practices in the registries. Using ICD-10 codes for the surveillance of persons hospitalised due to COVID-19 requires age- and time-specific definitions and ongoing validation to consider temporal changes in patient cohorts and virus characteristics.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the spectrum of disease may range from asymptomatic infection to severe respiratory failure. Since the start of the COVID-19 pandemic in early 2020, the surveillance of persons hospitalised with COVID-19 has been essential to ensure timely and appropriate public health response. Data from this surveillance have informed understanding of the trend and severity of the pandemic and also been used to study factors associated with severe disease [1-7]. Different approaches to this surveillance have emerged around Europe. Examples include data collection integrated with infectious disease notifications [2,8], systems based on pre-existing national patient registries [9-11], systems for the surveillance of severe acute respiratory infection (SARI) [8,12] and implementation of a voluntary patient-level clinical survey [13].

During the first 2 years of the COVID-19 pandemic, concern about healthcare capacity led to strict infection prevention and control measures worldwide. However, with high vaccine effectiveness against severe disease found to be more sustained than against infection [3,4] and the global spread of the less virulent Omicron variant (Phylogenetic Assignment of Named Global Outbreak (Pango) lineage designation B.1.1.529) from late 2021 [5-7], many countries scaled back non-pharmaceutical interventions and testing for SARS-CoV-2. These developments increased community transmission and reduced the proportion of COVID-19 cases diagnosed, but also reduced the proportion of cases who developed severe disease. This increased the importance of the surveillance of hospitalisation, not only with, but due to COVID-19, as a positive test for SARS-CoV-2 could be incidental in a

KEY PUBLIC HEALTH MESSAGE

What did you want to address in this study?
During the COVID-19 pandemic, surveillance systems that collect data on people hospitalised with COVID-19 have been essential to ensure timely and appropriate public health response. To critically appraise and further develop the surveillance of people hospitalised with COVID-19, we compared data on hospitalised COVID-19 patients from two national health registries in Norway from February 2020 to May 2022.

What have we learnt from this study?
Both registries recorded a high proportion of COVID-19 patients. However, this proportion declined from late 2021, coinciding with high vaccination coverage, emergence of the milder Omicron virus variant and changes in the management of hospitalised COVID-19 patients. The overlap between hospital diagnosis codes and the clinician's assessment of whether a patient was hospitalised due to COVID-19 varied by age and time.

What are the implications of your findings for public health?
National health registry data provided an accurate picture of people hospitalised with COVID-19 in Norway. However, there are challenges with using health registries for this surveillance. This comparison has improved our understanding of the data in each registry through different phases of the pandemic and can inform the ongoing development of surveillance systems for COVID-19 and in preparation for future pandemics.

larger proportion of hospitalised persons. Some countries have developed indicators for this surveillance [9,14].

Norway (population 5.4 million) confirmed its first case of COVID-19 in February 2020 and has experienced several waves of SARS-CoV-2 infection, including those driven by the Alpha (Pango lineage designation B.1.1.7), Delta (Pango lineage B.1.617.2) and Omicron variants [15]. Throughout the pandemic, Norway has been in the unique position of having two national electronic health registries (EHR) for the surveillance of persons hospitalised with COVID-19, one of which also disaggregates admissions due to COVID-19 based on a clinical assessment. To critically appraise and inform the further development of the surveillance of persons hospitalised with COVID-19, we linked and compared data in the two EHR from the first 2 years of the pandemic.

Methods

Data sources

Norwegian Pandemic Registry (NoPaR)

The Norwegian Pandemic Registry (NoPaR) has been the primary data source in Norway for the surveillance of persons hospitalised with COVID-19. It is a national clinical registry established in March 2020 as an expansion of the Norwegian Intensive Care Registry [16]. Data on hospital stays for patients who test positive for SARS-CoV-2 by PCR are collected in NoPaR. Patients admitted with sequelae of COVID-19 are registered if they tested positive < 3 months before admission. Patients readmitted for non-COVID-19-related causes are not registered if they are not isolated. Outpatient visits are not registered [17]. All Norwegian hospitals report to NoPaR. Reporting is mandatory and reporting criteria in the study period were consistent. Data collected include demographic characteristics (age, sex, underlying comorbidities), time of admission and discharge, and clinical condition and treatment at admission and during the stay of the patient. The reported main cause of hospitalisation (COVID-19 or other) is the physician's clinical assessment. For patients with underlying comorbidities, COVID-19 is reported as the main cause if it contributed to a worsening of the underlying condition that necessitated hospitalisation. International Classification of Diseases (ICD) diagnosis codes [18] are not registered.

Norwegian Patient Registry (NPR)

The Norwegian Patient Registry (NPR) is a central health registry established in 1997 and contains data on all patients who are referred to or receive specialist healthcare at a hospital, outpatient clinic or contracted specialist in Norway [19]. All Norwegian hospitals report to NPR, and reporting is mandatory [20]. At discharge, at the latest, the ICD diagnosis codes are registered and related to the reimbursement claims of the hospitals. Throughout the pandemic, national guidelines have recommended the use of the ICD-10 code U07.1 (COVID-19, virus identified) when COVID-19 is laboratory-confirmed, regardless of the clinical illness of the patient, and that the code is registered in addition and secondary to relevant codes for the clinical illness (e.g.

TABLE 1

Defined time periods and public health measures taken during the COVID-19 pandemic, Norway, 17 February 2020–1 May 2022

Week/year	Dominant circulating virus variant [15]	COVID-19 vaccination programme [15]	Summary of major national public health measures implemented during periods of peak transmission[a] [38]
9/2020–6/2021	Wild type/'Wuhan'	Started week 52/2020	In mid-March 2020, public health measures were implemented, including the closure of preschools, schools and hospitality services and businesses with one-to-one customer contact, cancellation of cultural and sporting arrangements and closing of borders to non-residents. Cases, close contacts and travellers returning from areas with high transmission were obliged to quarantine. Hospitals were instructed to reduce normal operations and prepare for an influx of COVID-19 patients. The restrictions were gradually lifted from mid-April 2020, although some remained (e.g. quarantine for cases, close contacts and most travellers), as well as the general recommendations to stay home when sick, wash hands, limit social contact and maintain a 1 m distance.
7/2021–26/2021	Alpha	Second dose coverage reached 95% among persons ≥ 75 years and first dose coverage reached 66% among persons ≥ 18 years, few hospitalised COVID-19 patients vaccinated.	Mitigating measures in place. In addition to the general recommendations, quarantine for cases, close contacts and most travellers, obligatory testing on arrival for travellers, limitations on who may enter Norway, use of face masks in public spaces recommended or required, alcohol serving banned or restricted, many clubs and activities for adults closed, limits on number of guests allowed at private homes, limits on number of people allowed at indoor and outdoor events and in businesses with one-to-one contact. Preschools and schools remained open, but working or studying from home was recommended where possible for workplaces and tertiary educational institutions. Hospitals were under pressure but functioned within capacity with consistent criteria for admission of COVID-19 patients.
27/2021–51/2021	Delta	Second dose coverage reached 89% among persons ≥ 18 years, increasing proportion of hospitalised COVID-19 patients vaccinated with at least two doses.	Measures similar to the Alpha period aligned with disease burden and vaccination coverage, but with use of COVID-19 passes to relax restrictions for those with documented vaccination or previous infection, such as exemption from quarantine for close contacts and arriving travellers.
52/2021–17/2022	Omicron	Third dose coverage reached 90% among persons ≥ 75 years and 66% among persons ≥ 18 years, majority of hospitalised COVID-19 patients vaccinated with three doses.	Initially similar to the Alpha and Delta periods, but moving from a control strategy to a preparedness strategy with the gradual relaxation of measures and return to a 'normal every-day'. For example, all statutory measures, including requirements for face masks, a 1 m distance and the obligation of cases to quarantine were removed on 12 February 2022.

[a] The range and timing of the measures implemented were not always uniform across Norway, particularly during periods when the level of transmission differed notably between regions. A comprehensive timeline is presented in [38].

pneumonia) [21]. Throughout the pandemic and as of March 2023, national guidelines recommend PCR to confirm all patients who seek healthcare for COVID-19 and in all cases where confirmation is important for differential diagnosis and choice of treatment.

The Norwegian surveillance system for communicable diseases laboratory database (MSIS-labdatabase)

The Norwegian surveillance system for communicable diseases laboratory database (MSIS-labdatabase) [22] contains results for microbiological samples analysed for SARS-CoV-2 in all medical microbiological laboratories in Norway.

The national population registry

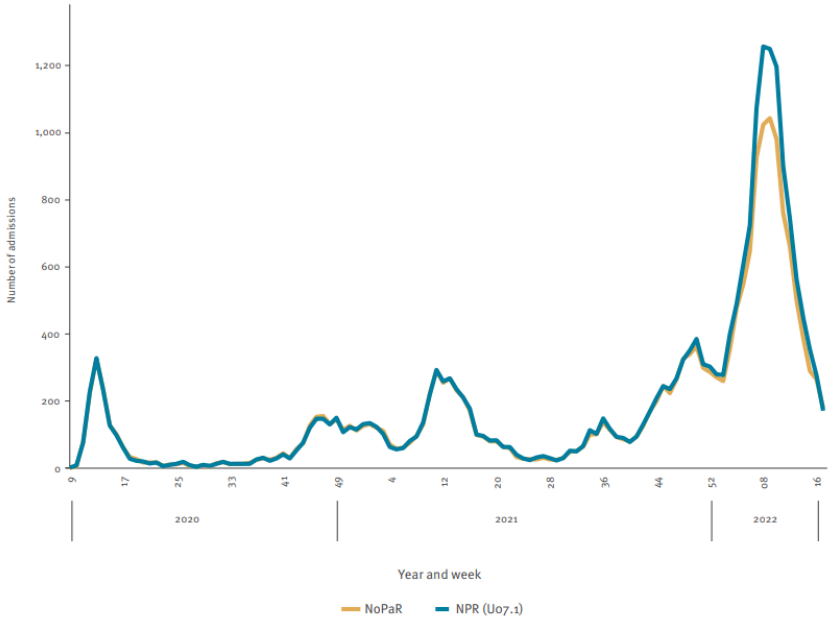
The national population registry includes demographic and administrative information on all individuals who reside or have resided in Norway [23]. This includes the national identification number, which was essential in our study for analyses that required linking registries.

Data access

We obtained data through the emergency preparedness registry for COVID-19 (Beredt C19), housed at the Norwegian Institute of Public Health. This registry contains individual-level, daily updated data from different central health registries, national clinical registries and other relevant national registries [24]. Owing to the principle of data minimisation, researchers in Beredt C19 are only given access to full ICD-10 codes from NPR that are necessary for performing the required analyses. The full ICD-10 codes we had access to are presented in Supplement 1. We extracted data on 12 May 2022.

FIGURE 1

Weekly number of hospital admissions of patients with confirmed COVID-19 in the Norwegian Pandemic Registry (n = 19,486) and the Norwegian Patient Registry (n = 21,035), Norway, 17 February 2020–1 May 2022



NoPaR: Norwegian Pandemic Registry; NPR: Norwegian Patient Registry; U07.1: COVID-19, virus identified.

The data behind the figure are available in Supplement 2.

Data analysis

Patient cohorts

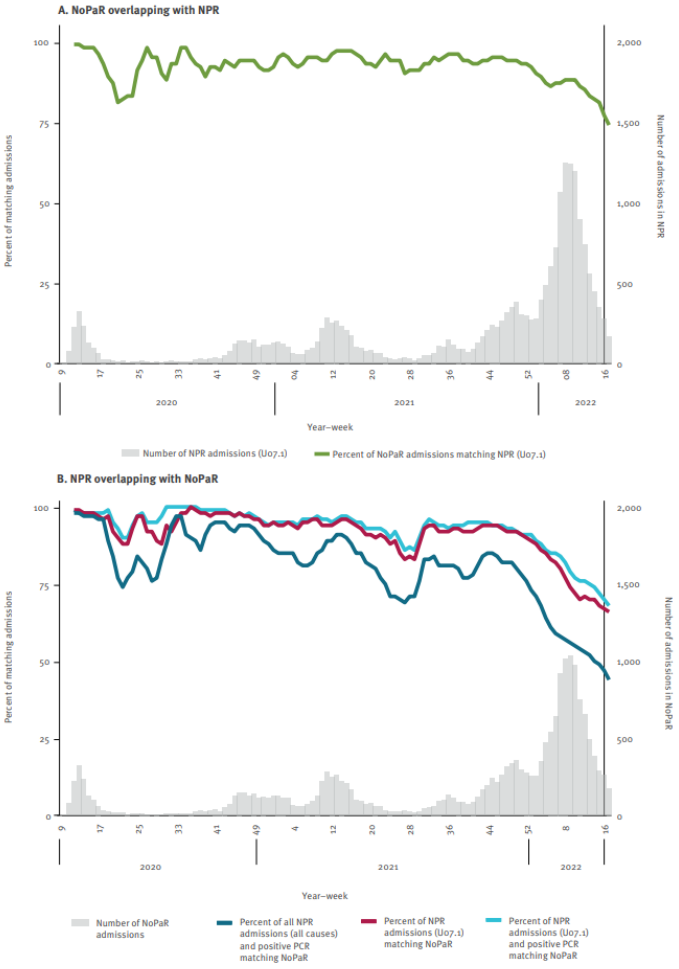
We included patients registered in NPR or NoPaR with hospital admission dates between 17 February 2020 and 1 May 2022. From NPR, we included overnight stays (both urgent and elective admissions). We considered individual stays for the same patient with < 2 days between discharge and subsequent admission to be part of the same hospitalisation period, regardless of the main cause (NoPaR) or diagnosis codes (NPR) registered for subsequent admissions. An individual could thus have several COVID-19 hospitalisation periods if there were ≥ 2 days between stays. We calculated the age of the patients at the start of the hospitalisation period from birth dates in the national population register and defined four age groups (0–17, 18–54, 55–74 and ≥ 75 years). We defined four time periods which are presented in Table 1.

System coverage

We identified overlapping hospitalisation periods in NPR and NoPaR. To explore what proportion of all patients with a recent positive SARS-CoV-2 test were registered in NoPaR or with the ICD-10 code U07.1 in NPR, we also linked NPR with positive SARS-CoV-2 PCR tests in MSIS-labdatabase taken ≤ 14 days before admission until discharge. We chose 14 days to ensure we identified all patients with recent positive tests that could reasonably be expected to be registered with U07.1 or in NoPaR, while 14 days was also the cut-off used in comparable registry-based surveillance systems in other countries [9,14] and studies on variant severity [6]. To identify admissions with COVID-19 in NPR, we used three definitions: (i) positive PCR test,

FIGURE 2

Number of COVID-19 admissions in Norwegian Pandemic Registry and Norwegian Patient Registry and a 4-week moving average of the proportion of overlapping admissions between the registries, Norway, 17 February 2020–1 May 2022



NoPaR: Norwegian Pandemic Registry; NPR: Norwegian Patient Registry; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; U07.1: COVID-19, virus identified.

Panel A: 4-week moving average of the proportion of weekly admissions with confirmed COVID-19 in NoPaR that overlapped with admissions with confirmed COVID-19 (U07.1) in NPR and weekly number of admissions in NPR.

Panel B: A 4-week moving average of the proportion of weekly admissions in NPR with U07.1 and/or positive PCR test for SARS-CoV-2 ≤14 days before admission until discharge in the Norwegian surveillance system for communicable diseases laboratory database that overlapped with admissions with confirmed COVID-19 in NoPaR and weekly number of admissions in NoPaR.

The data behind the figure are available in Supplement 2.

(ii) U07.1 and (iii) positive PCR test and U07.1. For NoPaR, we included all admissions. We calculated the proportion of admissions with COVID-19 in NPR that overlapped with admissions in NoPaR and the proportion of admissions in NoPaR that overlapped with U07.1 admissions in NPR. Proportions are presented as 4-week moving averages. Among U07.1 patients, we also described the proportion with a positive PCR test>14 days before admission or positive rapid antigen test≤14 days before admission until discharge.

Hospitalisation due to COVID-19

To study the association between ICD-10 diagnosis codes and the clinical assessment of main cause of admission, we retrieved ICD-10 codes from NPR for the first overlapping hospitalisation period for each patient in NoPaR. We only included the first overlapping period, as the similarity of multiple hospitalisations for a particular patient could distort the distribution. The ICD-10 codes available included full codes on acute upper and lower respiratory infections (ARI), while for other codes only the first letter was available (Supplement 1). For J codes (diseases of the respiratory system), we grouped codes for pneumonia (J12–J18), other acute lower respiratory infections (J20–J22 and J80) and acute upper respiratory infections (URI) (J00–J06). We grouped the respiratory syncytial virus-specific codes for pneumonia (J12.1) and acute lower respiratory infections (J20.5 and J21.0) separately, as respiratory syncytial virus should be distinguished in an integrated (meaning covering several diseases) surveillance system for viral respiratory infections [25]. Other respiratory diseases (J codes, excluding J00–J22 and J80) were grouped according to the first letter of the diagnosis code (J (non-ARI)). We calculated the prevalence of all different ICD-10 codes and their combinations by reported main cause of admission (COVID-19 or other), age group and period. For efficiency, we used an a priori algorithm (R package arules [26]). For each age group or period, we also calculated the sensitivity and specificity of selected diagnosis code combinations for representing U07.1 patients' main cause of admission. We also present the trend in new admissions for patients with COVID-19 as main cause in NoPaR and selected ICD-10 code combinations in NPR using data aggregated separately from each registry.

All analyses were conducted with R (version 4.0.2) [27].

Results

Patient cohorts

Between 17 February 2020 and 1 May 2022, 19,486 admissions were registered in NoPaR and 1,790,062 overnight admissions in NPR (21,035 with U07.1). The number of weekly admissions followed a similar trend in both registries. Since the beginning of 2022, NoPaR registered fewer admissions compared with U07.1 in NPR (Figure 1).

System coverage

Of the 19,486 admissions in NoPaR and 21,035 admissions with U07.1 in NPR, respectively, 19,250 (99%) and 20,815 (99%) had a national identification number and could be linked. Characteristics of these patients are appended in Supplement 1. Of the 19,250 admissions in NoPaR, 17,292 (90%) overlapped with a U07.1 admission in NPR, while 1,696 (8.8%) had ICD-10 codes other than U07.1 as detailed in Supplement 1. The remaining 262 (1.4%) did not overlap with an admission in NPR. The median length of stay for these 262 individuals was 3 days (interquartile range: 1–7), thus some may not have qualified as an overnight admission in NPR. Of the 20,815 U07.1 admissions in NPR, 17,307 (83%) overlapped with an admission in NoPaR. Generally, 90–100% of the hospitalisation periods overlapped between the two registries until late 2021, with exceptions predominantly in weeks with few admissions (Figure 2). From late 2021, the overlap gradually decreased to<75%.

Of the 20,815 U07.1 admissions in NPR, 18,918 (91%) linked to a recent positive PCR test. Of the 1,897 remaining patients (1,574 admitted from week 52/2021 (83%)), 248 (13%) had a positive PCR 15–28 days before admission, 29 (1.5%) a positive PCR 29–60 days before admission and 72 (3.8%) had a positive rapid antigen test≤14 days before admission until discharge.

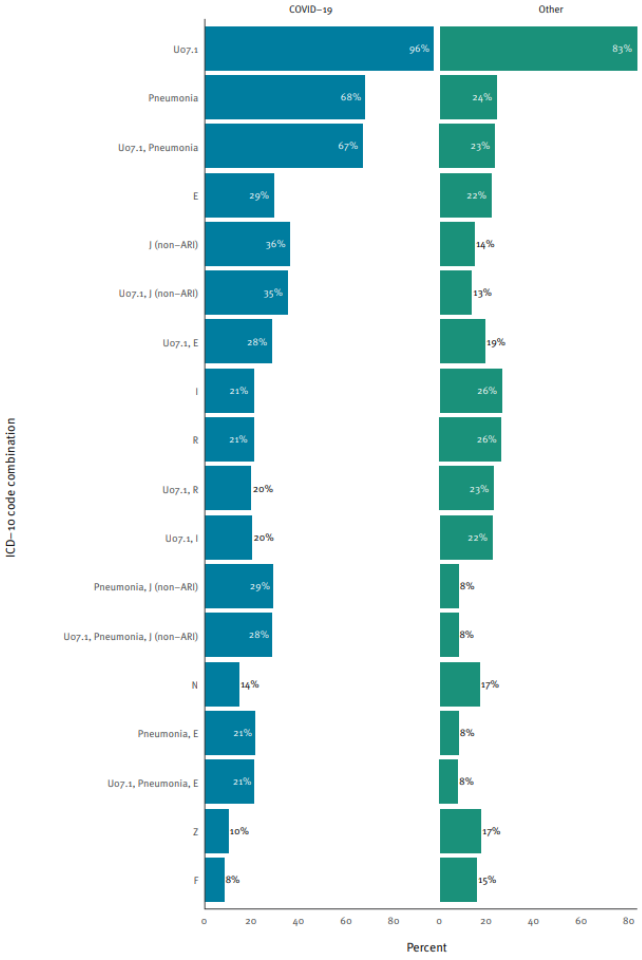
Of the 26,506 admissions in NPR with a positive PCR≤14 days before admission until discharge, 18,918 (71%) had U07.1 registered. The proportion with U07.1 decreased from late 2021 (9,276/10,722 (87%) up to 51/2021, 9,642/15,784 (61%) from 52/2021). The proportion registered in NoPaR followed a similar pattern (9,128/10,722 (85%) up to 51/2021, 8,631/15,784 (55%) from 52/2021) (Figure 2).

Hospitalisation due to COVID-19

We included 18,009 overlapping first admissions in NoPaR and NPR, excluding 163 for which the reported main cause was unknown. The prevalence of different ICD-10 code combinations by main cause are shown in Figure 3. For both admissions with main cause COVID-19 (n=11,803) and other (n=6,206), U07.1 was the most common code registered. For admissions with COVID-19 as main cause, 7,976 (68%) were registered with a pneumonia code and 4,244 (36%) with a J (non-ARI) code. There was more variation in the ICD-10 codes for admissions with another main cause than COVID-19. Detailed data by age group and period are available in Supplement 1. Regardless of period or main cause, there was generally a greater prominence of a wider range of codes among older than younger age groups. For patients≥75 years, pneumonia followed by J (non-ARI) codes were most common among those admitted with COVID-19 as main cause across all periods, although less prominent from week 52/2021. A similar pattern was observed among patients 18–54 and 55–74 years, with increased prominence of R (symptoms, signs and abnormal clinical and laboratory

FIGURE 3

Prevalence of international classification of diseases diagnosis codes and code combinations by clinically assessed main cause of admission, Norway, 17 February 2020–1 May 2022



ARI: acute respiratory infections; ICD-10: International Classification of Diseases 10th revision.

ICD-10 codes: E: endocrine, nutritional and metabolic diseases; F: mental, behavioural and neurodevelopmental disorders; I: diseases of the circulatory system; J: diseases of the respiratory system; N: diseases of the genitourinary system; R: symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified; U07.1: COVID-19, virus identified; Z: factors influencing health status and contact with health services.

Pneumonia: ICD-10 codes J12–J18, excluding J12.1. J (non-ARI): ICD-10 codes from group J excluding J00–J22 and J80.

Only codes and code combinations with at least 15% of patients for either main cause are presented. Data on ICD-10 diagnosis codes come from the Norwegian Patient Registry and data on the main cause of admission (COVID-19 or other) from the Norwegian Pandemic Registry. Code combinations may overlap, for example patients registered with U07.1 and a pneumonia code are included in U07.1, pneumonia, and U07.1+pneumonia. The data behind the figure are available in Supplement 2.

TABLE 2A

Sensitivity and specificity of selected international classification of diseases diagnosis code combinations for representing the main cause of admission of COVID-19 patients[a], Norway, 17 February 2020–1 May 2022

Norwegian Patient Registry	Norwegian Pandemic Registry			Sensitivity	Specificity
Diseases and ICD-10 disease code combinations of COVID-19 patients	Diagnosis	COVID-19 as main cause	Other main causes		
		n	n	%	%
Overall					
Pneumonia	Yes	7,857	1,436	69	72
	No	3,523	3,707		
Pneumonia or J (non-ARI)	Yes	8,665	1,785	76	65
	No	2,715	3,358		
URI or R	Yes	2,829	1,545	25	70
	No	8,551	3,598		
Pneumonia or J (non-ARI) or URI or R	Yes	10,149	2,910	89	43
	No	1,231	2,233		
By age group (years)					
Age group 0–17 years					
Pneumonia	Yes	38	17	8	94
	No	413	269		
Pneumonia or J (non-ARI)	Yes	63	27	14	91
	No	388	259		
URI or R	Yes	267	125	59	56
	No	184	161		
Pneumonia or J (non-ARI) or URI or R	Yes	320	145	71	49
	No	131	141		
18–54 years					
Pneumonia	Yes	2,687	329	71	82
	No	1,085	1,536		
Pneumonia or J (non-ARI)	Yes	2,861	398	76	79
	No	911	1,467		
URI or R	Yes	921	502	24	73
	No	2,851	1,363		
Pneumonia, J (non-ARI), URI or R	Yes	3,404	822	90	56
	No	368	1,043		
55–74 years					
Pneumonia	Yes	2,847	421	76	68
	No	880	908		
Pneumonia or J (non-ARI)	Yes	3,079	533	83	60
	No	648	796		
URI or R	Yes	821	418	22	69
	No	2,906	911		
Pneumonia or J (non-ARI) or URI or R	Yes	3,411	817	92	39
	No	316	512		
≥75 years					
Pneumonia	Yes	2,285	669	67	60
	No	1,145	994		
Pneumonia or J (non-ARI)	Yes	2,662	827	78	50
	No	768	836		
URI or R	Yes	820	500	24	70
	No	2,610	1,163		
Pneumonia or J (non-ARI) or URI or R	Yes	3,014	1,126	88	32
	No	416	537		

ARI: acute respiratory infections; ICD-10: International Classification of Diseases 10th revision. URI: upper respiratory infections.

ICD-10 codes: J: diseases of the respiratory system; R: symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified.

Pneumonia: ICD-10 codes J12–J18 excluding J12.1. J (non-ARI): ICD-10 codes from group J excluding J00–J22 and J80. URI: ICD-10 codes J00–J06. Data on ICD-10 diagnosis codes come from the Norwegian Patient Registry and data on the main cause of admission (COVID-19 or other) from the Norwegian Pandemic Registry.

[a] ICD-10 code U07.1 (COVID-19, virus identified).

TABLE 2B

Sensitivity and specificity of selected international classification of diseases diagnosis code combinations for representing the main cause of admission of COVID-19 patients[a], Norway, 17 February 2020–1 May 2022

Norwegian Patient Registry	Norwegian Pandemic Registry			Sensitivity	Specificity
Diseases and ICD-10 disease code combinations of COVID-19 patients	Diagnosis	COVID-19 as main cause	Other main causes		
		n	n	%	%
By time (week/year)					
9/2020–6/2021[b]					
Pneumonia	Yes	1,917	271	77	54
	No	564	316		
Pneumonia or J (non-ARI)	Yes	2,035	303	82	48
	No	446	284		
URI or R	Yes	506	179	20	70
	No	1,975	408		
Pneumonia or J (non-ARI) or URI or R	Yes	2,275	405	92	31
	No	206	182		
7/2021–26/2021[c]					
Pneumonia	Yes	1,710	144	88	58
	No	230	195		
Pneumonia or J (non-ARI)	Yes	1,746	163	90	52
	No	194	176		
Upper respiratory infections or R	Yes	342	87	18	74
	No	1,598	252		
Pneumonia or J (non-ARI) or URI or R	Yes	1,876	222	97	35
	No	64	117		
27/2021–51/2021[d]					
Pneumonia	Yes	1,881	364	80	58
	No	476	500		
Pneumonia or J (non-ARI)	Yes	1,979	416	84	52
	No	378	448		
URI or R	Yes	494	239	21	72
	No	1,863	625		
Pneumonia or J (non-ARI) or URI or R	Yes	2,176	553	92	36
	No	181	311		
52/2021–17/2022[e]					
Pneumonia	Yes	2,349	657	51	80
	No	2,253	2,696		
Pneumonia or J (non-ARI)	Yes	2,905	903	63	73
	No	1,697	2,450		
URI or R	Yes	1,487	1,040	32	69
	No	3,115	2,313		
Pneumonia or J (non-ARI) or URI or R	Yes	3,822	1,730	83	48
	No	780	1,623		

ARI: acute respiratory infections; ICD-10: International Classification of Diseases 10th revision. URI: upper respiratory infections.

ICD-10 codes: J: diseases of the respiratory system; R: symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified.

Pneumonia: ICD-10 codes J12–J18 excluding J12.1. J (non-ARI): ICD-10 codes from group J excluding J00–J22 and J80. URI: ICD-10 codes J00–J06. Data on ICD-10 diagnosis codes come from the Norwegian Patient Registry and data on the main cause of admission (COVID-19 or other) from the Norwegian Pandemic Registry.

[a] ICD-10 code U07.1 (COVID-19, virus identified).

[b] Week 9/2020–6/2021: wild-type or 'Wuhan' variant dominant, COVID-19 vaccination programme started week 52/2020.

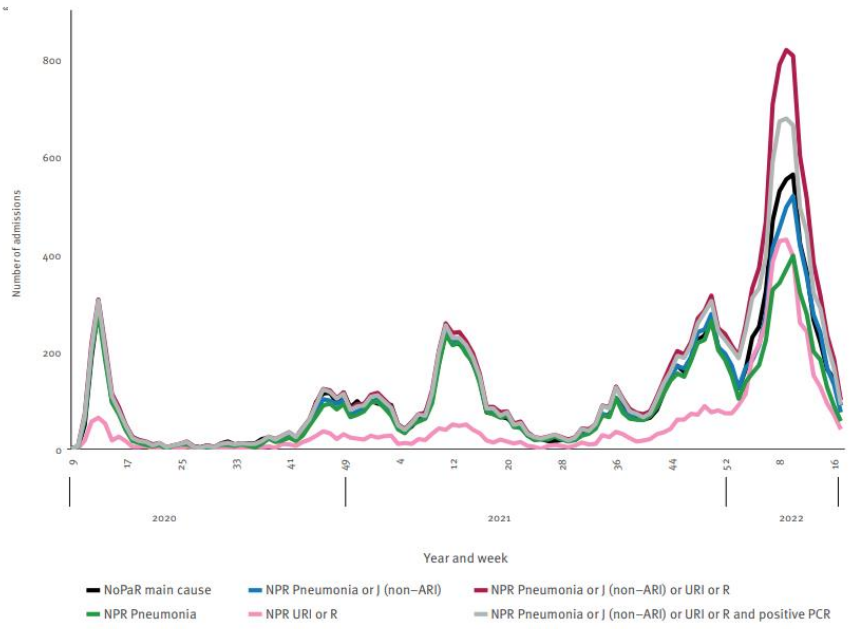
[c] Week 7/2021–26/2021: Alpha variant dominant, second dose vaccination coverage reached 95% among persons ≥ 75 years, first dose coverage reached 66% among persons ≥ 18 years, few hospitalised COVID-19 patients vaccinated.

[d] Week 27/2021–51/2021: Delta variant dominant, second dose vaccination coverage reached 89% among persons ≥ 18 years, increasing proportion of hospitalised COVID-19 patients vaccinated with at least two doses.

[e] Week 52/2021–17/2022: Omicron variant dominant, third dose vaccination coverage reached 90% among persons ≥ 75 years and 66% among persons ≥ 18 years, majority of hospitalised COVID-19 patients vaccinated with three doses.

FIGURE 4

Weekly number of hospital admissions with confirmed COVID-19 as main cause or different international classification of diseases diagnosis code combinations among COVID-19 patients[a], Norway, 17 February 2020–1 May 2022



ARI: acute respiratory infections; NoPaR: Norwegian Pandemic Registry; NPR: Norwegian Patient Registry; URI: upper respiratory infections.

International Classification of Diseases 10th revision (ICD-10) codes: J: diseases of the respiratory system; R: symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified.

Pneumonia: ICD-10 codes J12–J18 excluding J12.1. J (non-ARI): ICD-10 codes from group J excluding J00–J22 and J80. URI: ICD-10 codes J00–J06.

[a] ICD-10 code U07.1 (COVID-19, virus identified).

Positive PCR: positive test ≤ 14 days before admission until discharge. ICD-10 diagnosis codes come from NPR. Data on the main cause of admission (COVID-19 or other) come from NoPaR.

The data behind the figure are available in Supplement 2.

findings not elsewhere classified) and Z codes (factors influencing health status and contact with health services) in later periods. Among patients 0–17 years, R codes were prominent in all time periods regardless of main cause, while the proportion of URI codes increased over time, particularly among those admitted with COVID-19 as main cause.

The sensitivity and specificity of selected ICD-10 code combinations for representing patients' main cause of admission are presented in Table 2. For this analysis, among 18,009 first overlapping hospitalisation periods in NoPaR, we only included those with U07.1 registered (n = 16,523, 92%), to explore code combinations beyond U07.1. We explored combinations of pneumonia, J (non-ARI), URI and R codes based on those most prominent among patients admitted with COVID-19 as main cause in different age groups and periods. The prevalence of ICD-10 diagnosis codes and code combinations by main cause of admission, age group and period are provided in Supplement 1. The three code combinations including pneumonia had a higher sensitivity among patients ≥ 18 years than 0–17 years. Conversely, the combination URI or R had the lowest sensitivity among all age groups and periods, except patients 0–17 years. In the period from 52/2021 the

sensitivity of all code combinations including pneumonia was lower and the specificity higher, compared with earlier periods.

Using data aggregated separately from each registry, the code combination pneumonia or J (non-ARI) (n=12,221) most closely followed the trend in new admissions with COVID-19 as main cause in NoPaR (n=12,638), although the same general trend was observed in all code combinations, aside from URI or R before the end of the study period (Figure 4).

Discussion

Despite different registration criteria in each registry, 90–100% of hospitalisation periods overlapped between U07.1 patients in NPR and patients in NoPaR, until late 2021 when the proportion of overlapping patients gradually decreased. Our results support previous studies in different settings that found high uptake and accurate use of U07.1 to identify COVID-19 patients earlier in the pandemic [28-31]. However, from late 2021, an increasing proportion of patients in NPR with a recent positive PCR test was not registered with U07.1, nor registered in NoPaR. Furthermore, over 1,600 U07.1 patients in NPR, predominantly admitted from late 2021, did not have a registered positive PCR test≤60 days before admission until discharge. This suggests increasing registration of U07.1 for patients without a positive PCR test, contrary to national guidelines. Most U07.1 patients without a positive PCR test≤60 days before admission until discharge did not have a recent rapid antigen test registered, however, self-tests are not registered in MSIS-labdatabase [22], thus these data must be interpreted with caution.

The decreasing overlap between the registries from late 2021 coincided with the Delta variant being superseded by the milder Omicron variant [5], increasing vaccination coverage [15] and the gradual scaling back of non-pharmaceutical interventions and testing in Norway. This consequently impacted the flow to, and management of, COVID-19-positive persons in hospital. Patients gradually became more spread out across hospitals, instead of being treated in specific wards usually under the care of infectious disease physicians. Our results suggest that this could have impacted the registration of new patients in NoPaR and ICD-10 codes in NPR, such that the two registries were identifying increasingly different patient cohorts and a decreasing proportion of all patients with a recent positive PCR test.

Since the start of the pandemic, Norway has disaggregated data on patients with COVID-19 as main cause of hospitalisation through a clinical assessment. The benefit of this disaggregation was clearly illustrated in late 2021, when the proportion of all COVID-19 patients hospitalised with COVID-19 as main cause fell markedly [15]. A similar trend was observed in other countries where 'due to COVID-19' was defined by diagnosis codes [9,11,32]. In our study, while certain ICD-10 code combinations closely followed the trend in new admissions with COVID-19 as main cause, the distribution of ICD-10 codes varied by age and time. The greater prominence of a wider range of codes among older age groups likely reflect a higher rate of underlying comorbidities. From late 2021 the frequency of pneumonia codes decreased in the age groups≥18 years, potentially related to the increasing proportion of vaccinated patients [33-35]. In the same period, the proportion of patients 0–17 years admitted due to COVID-19 who were registered with a URI code increased, in line with findings from elsewhere during a period of increasing Omicron dominance [36] and the lifting of restrictions. After week 52/2021, the sensitivity of all code combinations including pneumonia was lower, compared with earlier periods. Clinical validation of the algorithm for admissions 'due to COVID-19' in Denmark also found that sensitivity decreased between Delta (95%) and early Omicron (87%) periods [9]. This highlights the challenge of using diagnosis codes for the surveillance of persons hospitalised due to COVID-19, not least the importance of age- and time-specific definitions. Other definitions of 'due to COVID-19' have also been proposed. For example, Public Health Scotland revised their definition to community-acquired hospital admissions with a positive PCR test from emergency admissions, as data on clinical discharge diagnoses were not timely enough for ongoing surveillance [14]. Surveillance of SARI, either EHR- or questionnaire-based, is an alternative standardised approach established in several European countries [25]. However, in the context of the surveillance of persons hospitalised due to COVID-19, one must consider how the definition of SARI may influence the sensitivity of the system. For example, in the EHR-based sentinel system in Germany, SARI is defined as patients admitted with ICD-10 codes J09–J22 [8]. This will miss patients admitted with an URI (J00–J06), which we observed in an increasing proportion of younger persons hospitalised due to COVID-19 since Omicron emerged.

Hospital admissions remain a central indicator for COVID-19 surveillance. Data collection should be sensitive and timely for public health action, representative, accurate, sustainable, collect relevant data on the patient cohort, integrated with, but able to distinguish between, different pathogens and not entail an unnecessary reporting burden. A diverse landscape of systems for this surveillance has emerged across Europe [2,8-13], with designs naturally tailored to the local setting, resource-availability and existing data collection infrastructure and practices. Looking forward, a European Union Joint Action 'UNITED4Surveillance' now aims to promote the integration, digitalisation and establishment of real-time surveillance systems in the European Union, including through EHR [37].

In light of this, our study provides clear examples of advantages and disadvantages with EHR-based systems for the surveillance of COVID-19 hospitalisations. Both NPR and NoPaR have national coverage, allow

year-round surveillance, can be linked to other national registries to achieve integration between surveillance systems (e.g. molecular surveillance) and healthcare levels and may monitor additional severity outcomes like intensive care admission (not available for comparison in this study). These systems have thus outdated the sentinel, manual and weekly reporting Norway had for hospitalisation with another respiratory infection (influenza) before the pandemic. The pandemic registry collects COVID-19-specific data and data reporting has been timely [15]. However, in its current form, data registration in NoPaR entails an additional burden for hospitals and has more limited capacity to be integrated with the surveillance of other respiratory infections, as desired [25]. Surveillance systems based on electronic patient registries, like NPR, have the advantage of being part of the established data flow in hospitals and allow the integration of surveillance for different pathogens as well as syndromic and disease-specific components. Through linkage to laboratory results, they may also provide more complete data on persons hospitalised with COVID-19, as well as data on total and disease-specific hospital bed occupancy, which remains a recommended COVID-19 surveillance indicator [25]. However, the accuracy and timeliness of coding practices and changes in coding practices over time, must be considered. Also, NPR provides limited disease-specific data, such as on clinical severity and treatment. Furthermore, endeavours to accurately identify persons hospitalised due to COVID-19 will require ongoing validation to consider temporal changes in patient cohorts and virus characteristics. A future surveillance system would ideally encompass the benefits of both NoPaR and NPR, something Norwegian registries have demonstrated the feasibility of during the pandemic. A coordinated system will probably improve coverage by reducing the need for reporting via several systems.

Our study has several limitations. Firstly, different ICD-10 code combinations were registered among patients in both main cause categories. This highlights that clinicians may assess the main cause of admission differently for patients with similar diagnostic codes, leading to non-differential misclassification. This could potentially be alleviated by including more main cause categories beyond COVID-19/other [9]. Secondly, we cannot rule out that the decreasing overlap between U07.1 patients in NPR and patients in NoPaR from late 2021 affected our analysis of hospitalisation due to COVID-19 and the precision of our sensitivity and specificity estimates. Also, we did not have access to full ICD-10 codes for all diagnostic categories, which limited the exploration of whether more detailed code combinations could more precisely represent persons hospitalised due to COVID-19. We also only considered the distribution of ICD-10 codes in this analysis. However, other parameters could additionally inform more precise proxies. For example, in Denmark, the proportion of admission time related to certain diagnosis codes is considered [9]. Finally, we cannot rule out errors in data registration that may have influenced which patients and hospitalisation periods were able to be correctly linked. However, given the high degree of overlap and that most individuals have only been hospitalised with COVID-19 once, we do not believe this has unduly affected our results.

Conclusion

In this study we compared data in two EHR in Norway on persons hospitalised with COVID-19 during the first 2 years of the pandemic. Our results show that the EHR provided an accurate picture of persons hospitalised with COVID-19, but also highlight challenges with using EHR data. This comparison has allowed more comprehensive understanding of the data in each EHR through different phases of the pandemic and can inform the ongoing development of surveillance systems for COVID-19 and in preparation for future pandemics.

Ethical statement

The national emergency preparedness register for COVID-19 (Beredt C19) was established under the Health Preparedness Act §2-4 in response to the COVID-19 pandemic. Under the Infectious Disease Control Act §7-9, the Norwegian Institute of Public Health is responsible for the surveillance of infectious diseases in Norway. Approval by an ethical review board was not considered necessary.

Funding statement

This research was undertaken as part of routine work at the Norwegian Institute of Public Health. No specific funding was received.

Data availability

The dataset analysed in the study contains individual-level linked data from national registries in Norway. The researchers had access to the data through Beredt C19, housed at the Norwegian Institute of Public Health. In Beredt C19, only fully anonymised data (i.e. data that are neither directly nor potentially indirectly identifiable) are permitted to be shared publicly. Legal restrictions therefore prevent the researchers from publicly sharing the dataset used in the study that would enable others to replicate the study findings. However, external researchers are freely able to request access to linked data from the same registries from outside the structure of Beredt C19, as per normal procedure for conducting health research on registry data in Norway. Further information on Beredt C19, including contact information for the Beredt C19 project manager, and information on access to data from each individual data source, is available at https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/.

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Conflict of interest

None declared.

Authors' contributions

RW, EB, HK, THP and ES conceived the study. RW and ES co-ordinated the study. EB contributed to the acquisition of data in the Norwegian Pandemic Registry. RW, ST, KD, TML and ES contributed to data cleaning, linkage and analysis. All authors contributed to the interpretation of the results. RW and ES drafted the manuscript. All co-authors contributed to the revision of the manuscript and approved the final version for submission.

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9.1.3 Paper III

COVID-19 Hospitalization Among Children <18 Years by Variant Wave in Norway

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abstract

OBJECTIVES: There is limited evidence on whether the relative severity of coronavirus disease 2019 (COVID-19) in children and adolescents differs for different severe acute respiratory syndrome coronavirus 2 variants. We compare the risk of hospitalization to acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C) among unvaccinated persons <18 years with COVID-19 (cases) between waves of the Alpha, Delta, and Omicron (sublineage BA.1) variants in Norway.

METHODS: We used linked individual-level data from national registries to calculate adjusted risk ratios (aRR) with 95% confidence interval (CI) using multivariable log-binomial regression. We adjusted for variant wave, demographic characteristics, and underlying comorbidities.

RESULTS: We included 10 538 Alpha (21 hospitalized with acute COVID-19, 7 MIS-C), 42 362 Delta (28 acute COVID-19, 14 MIS-C), and 82 907 Omicron wave cases (48 acute COVID-19, 7 MIS-C). The risk of hospitalization with acute COVID-19 was lower in the Delta (aRR: 0.53, 95% CI: 0.30–0.93) and Omicron wave (aRR: 0.40, 95% CI: 0.24–0.68), compared to the Alpha wave. We found no difference in this risk for Omicron compared to Delta. The risk of MIS-C was lower for Omicron, compared to Alpha (aRR: 0.09, 95% CI: 0.03–0.27) and Delta (aRR: 0.26, 95% CI: 0.10–0.63).

CONCLUSIONS: We do not find clear evidence that different variants have influenced the risk of hospitalization with acute COVID-19 among unvaccinated children and adolescents in Norway. The lower risk of this outcome with Omicron and Delta may reflect changes in other factors over time, such as the testing strategy, maternal vaccination and/or hospitalization criteria. The emergence of Omicron has reduced the risk of MIS-C.

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Mr Whittaker conceptualized and designed the study, contributed to data cleaning and linkage between the different registries, conducted the data analysis, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Greve-Isdahl and Suren conceptualized and designed the study, contributed to interpretation of the results, and critically reviewed the manuscript; Dr Bøås conceptualized and designed the study, contributed to data cleaning and interpretation of the results, and critically reviewed the manuscript; Dr Buanes conceptualized and designed the study, coordinated data collection to the Norwegian Intensive Care and Pandemic Registry, contributed to interpretation of the results, and critically reviewed the manuscript; Ms Veneti conceptualized and designed the study, contributed to data cleaning, assisted with the data analysis, contributed to interpretation of the results, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: There is limited evidence about the potential association between the risk of hospitalization with acute COVID-19 among children and adolescents and different SARS-CoV-2 variants. Preliminary data suggests a lower risk of multisystem inflammatory syndrome in children following infection with Omicron.

WHAT THIS STUDY ADDS: We do not find clear evidence that different SARS-CoV-2 variants have influenced the risk of hospitalization with acute COVID-19 among children and adolescents in Norway. The risk of multisystem inflammatory syndrome was lower in children and adolescents infected with Omicron.

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From late 2020, the emergence and global spread of variants of concern (VOC)[1] of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have shaped the epidemiology of, and ongoing response to, the coronavirus disease 2019 (COVID-19) pandemic. More transmissible VOC have successively superseded their predecessors influencing transmission dynamics, viral virulence, and vaccine effectiveness.[2–8] The emergence of the Omicron variant (Phylogenetic Assignment of Named Global Outbreak Lineages [Pangolin] designation B.1.1.529) in November 2021 instigated a new wave of infections globally.[9]

Most children and adolescents with COVID-19 experience an asymptomatic or mild disease course. However, a small proportion develop severe disease that requires hospitalization, mostly because of acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C), a postinfectious complication of SARS-CoV-2 infection. Death is rare.[10,11]

There is currently limited evidence on whether the relative severity of COVID-19 in children and adolescents differs when infected with different VOC. Studies from England[5] and Denmark[12] did not find clear evidence that the risk of hospitalization because of acute COVID-19 among children and adolescents infected with Omicron differed compared to the Delta variant (Pangolin designation B.1.617.2). One study from the United States reported a reduced risk of hospitalization among children <5 years diagnosed with a SARS-CoV-2 infection during a period of Omicron dominance, compared to the preceding Delta period.[13] Some studies comparing the risk of hospitalization for the Delta variant to earlier VOC have presented descriptive data for younger age groups, without providing age-specific risk estimates.[14,15] Others have been restricted to hospital cohorts, with the reported findings inconsistent between settings.[16–18] In Denmark, the risk of MIS-C did not change among unvaccinated children and adolescents during a wave of Delta infections compared to when the wild-type SARS-CoV-2 variant was circulating.[19] Preliminary data from Denmark[20] and Southeast England[21] have reported a lower risk of MIS-C with Omicron compared to Delta.

Since the beginning of 2021, Norway has experienced 3 COVID-19 waves when different VOC were dominant; Alpha (Pangolin designation B.1.1.7),[4] Delta,[22] and Omicron.[8] We used linked individual-level data from national registries to compare the risk of hospitalization among unvaccinated persons <18 years to COVID-19 between these 3 variant waves.

METHODS

Study Setting

Norway (population <18 years 1.1 million) has had a broad testing strategy for COVID-19 in children and adolescents since autumn 2020. Four pillars of the national pandemic response have been testing, isolation, contact tracing, and quarantine. Through this framework SARS-CoV-2 tests have been available free of charge for everyone, including those with mild or no symptoms, close contacts, and individuals in quarantine. Routine biweekly screening of school children with rapid antigen tests in areas with high transmission was recommended for secondary school students from late August 2021 and for primary school students from November 2021 to January 2022. Positive rapid antigen tests were confirmed with polymerase chain reaction. Further details on the testing strategy for COVID-19 in children and adolescents are described in Supplement A, Section 1. COVID-19 vaccine recommendations for children and adolescents in Norway and data on vaccination coverage are presented in Supplement A, Section 2. From August 2021, pregnant women have been recommended to get vaccinated in the second or third trimester if healthy, and first trimester for women with underlying risk factors.[23]

Data Sources and Study Design

We obtained data through the Norwegian national preparedness registry for COVID-19.[24] The preparedness registry contains individual-level data from different central health registries, national clinical registries, and other national administrative registries. It covers all residents in Norway and includes data on all persons with laboratory-confirmed COVID-19 (cases) in Norway and all hospitalizations, intensive care admissions, and deaths among cases. Further details on the individual registries and data included in this study are presented in Supplement A, Section 1.

We conducted a cohort study, including persons aged <18 years who tested positive for COVID-19 from March 15, 2021 to January 30, 2022, were unvaccinated at date of positive test and had not previously been diagnosed with COVID-19, and had a national identity number registered (the study cohort). We extracted data up to April 12, 2022, a minimum of 72 days of follow-up. This ensures MIS-C diagnoses are not missed.

Definition of Variant Waves

In Norway, SARS-CoV-2 variants are identified on the basis of whole genome sequencing, Sanger partial S-gene sequencing, or polymerase chain reaction screening targeting specific single nucleotide

polymorphisms, insertions, or deletions. The laboratory testing for variants of SARS-CoV-2 in Norway has been described in further detail elsewhere.[25] We identified different variant waves on the basis of the date of the positive test. Variant distribution over time among COVID-19 cases <18 years is presented in Figure 1, with the underlying data available in Supplement B. We defined the Alpha dominant wave as week 11 to 20 (March 15 to May 23) 2021, the Delta dominant wave as week 35 to 48 (August 30 to December 5) 2021, and the Omicron dominant wave as week 2 to 4 (10 to 30 January) 2022. The Omicron wave was not extended beyond week 4 2022 because of the end of the recommendation for routine biweekly screening of school children, gradual downscaling of the national testing strategy, and to ensure analysis when 1 Omicron sublineage (BA.1) was predominant.[26] In models including COVID-19 cases of all ages in Norway, results based on these waves were consistent with analyses based on cases with known variant in periods when 1 variant was superseding another (see Supplement A, Section 3).

Severity Outcomes

Our severity outcomes were: (1) admission to hospital with acute COVID-19 (regardless of main cause of admission) ≤14 days after positive test, (2) admission to hospital ≤14 days after positive test in which acute COVID-19 was the reported main cause of admission, and (3) admission to hospital with MIS-C, defined as patients registered with the International Classification of Diseases, 10th Revision diagnosis code U10.9. Clinical criteria for MIS-C diagnosis in Norway are based on the World Health Organization case definition, as per national pediatric guidelines.[27] Hospitals in Norway functioned within capacity during each variant wave.

Data Analysis

We described the study cohort by variant wave, severity outcome, demographic characteristics, and underlying comorbidities. We also described other outcomes among hospitalized patients including length of stay (LOS) in hospital and admission to an ICU and all deaths in the study cohort. For our 3 severity outcomes, we calculated adjusted risk ratios (aRR) with 95% confidence intervals (CI) using multivariable log-binomial regression. Explanatory variables to analyze differences in our outcomes included variant wave (Alpha, Delta, or Omicron), age (as continuous or categorical

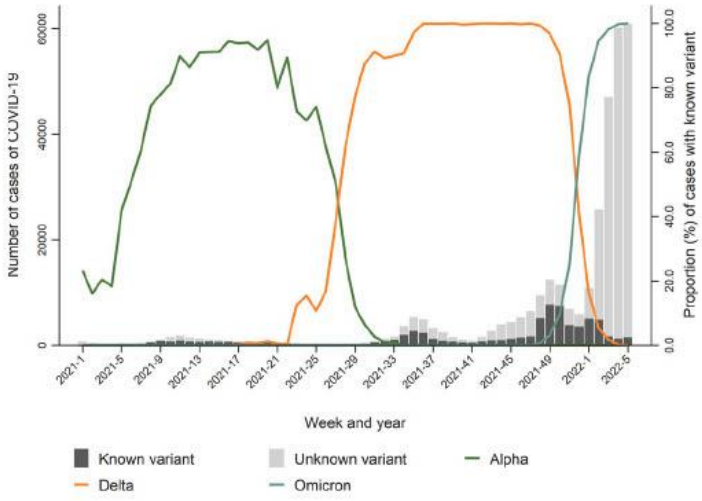

FIGURE 1

Persons aged <18 years diagnosed with COVID-19 in Norway with known and unknown SARS-CoV-2 variant (bars, left y-axis), and proportion with known variant that were the Alpha, Delta, or Omicron variant of concern (lines, right y-axis), by week, January 1, 2021 to February 6, 2022. The data behind the figure are available in Supplement B. During the Alpha wave (week 11 to 20, 2021), the proportion of persons diagnosed with COVID-19 that were known to be infected with the Alpha variant ranged from 86% to 95% of those with known variant. However, most other COVID-19 cases with known variant were reported as "probable variant of concern." In Norway, there was minimal circulation of other defined variants of concern (Beta, B.1.351 and Gamma, P.1); thus, it is reasonable to assume that most COVID-19 cases reported as 'probable variant of concern' were also infected with the Alpha variant. Taking these cases into account, the proportion infected with Alpha among those with known variant ranges from 94% to 100% in the Alpha wave.

variable), sex, country of birth, region of residence, and underlying comorbidities. The categorization of explanatory variables is presented in Table 1 and further detailed in Supplement A, Section 1. Explanatory variables were first checked in univariable models. Those with $P < .2$ were further explored in multivariable models. Explanatory variables were further categorized in some models to best fit the data, for example a dichotomous variable for underlying comorbidities (yes or no). We maintained the variant wave variable in each multivariable analysis, even if not significant. We used Akaike Information Criteria and the likelihood ratio test to check model fit. We ran models for each variant combination (Delta versus Alpha, Omicron versus Alpha, Omicron versus Delta) for the entire study cohort, and for the age subgroups <3 months, 3 to 11 months, 1 to 11 years, and 12 to 17 years. For infants <3 months we also described outcomes 1) and 2) among those whose mothers were unvaccinated. For cases 12 to 17 years, we conducted a sensitivity analysis to explore if results were robust when including vaccinated COVID-19 cases and reinfections in this age group (Supplement A, Section 4). Statistical analysis was performed in Stata version 16 (Stata Corporation, College Station, Texas, United States).

Ethics

Ethical approval was granted by Regional Committees for Medical Research Ethics South East Norway, reference number 249509.

RESULTS

Study Cohort

The number of persons aged <18 years diagnosed with COVID-19 was 10 620 during the Alpha wave, 53 724 during the Delta wave and 133 383 during the Omicron wave. Of these, 10 541 (99.3%) Alpha, 53 576 (99.7%) Delta, and 133 042 (99.7%) Omicron cases had a known national identity number. Of these 10 538 (99.9%) Alpha, 42 362 (79.1%) Delta and 83 884 (62.3%) Omicron cases were included in the study cohort as they were unvaccinated at date of positive test and had not been previously diagnosed with COVID-19. Characteristics of the study cohort by variant are presented in Table 1.

Risk of Hospitalization With Acute COVID-19

Overall, 174 (0.1%) cases were hospitalized ≤14 days after positive test, of which 97 with acute COVID-19 as main cause (0.07% of study cohort). Few additional admissions >14 days after positive test were observed (Table 1). Of the 97, 32 (33%) were aged <3 months, 44 (45%) were female, and 83 (86%) had no registered comorbidity.

In the Alpha, Delta, and Omicron waves, 21 (0.2%), 28 (0.07%), and 48 (0.06%) cases <18 years were hospitalized with acute COVID-19 as main cause ≤14 days after positive test, respectively (Table 1, Table 2). The risk of hospitalization with acute COVID-19 as main cause was lower in the Delta (aRR: 0.53, 95% CI: 0.30–0.93) and Omicron wave (aRR: 0.40, 95% CI: 0.24–0.68) compared to the Alpha wave. Among infants <3 months the proportion hospitalized with acute COVID-19 decreased from 14.6% (8 of 55) in the Alpha wave to 5.9% (7 of 118) in the Delta wave and 7.8% (17 of 218) in the Omicron wave. A similar difference between these outcome proportions in the Alpha and Delta waves was observed when restricting the analysis to infants whose mothers were unvaccinated up to 4 weeks after child's birth (Table 3). Results also suggested a decreased risk in children aged 1 to 11 years in the Omicron wave compared to the Alpha wave (aRR: 0.32, 95% CI: 0.13–0.83). We did not observe a difference in the adjusted risk in any age group in the Omicron wave compared to the Delta wave (Table 2). Results for the age group 12 to 17 years were consistent when we included vaccinated COVID-19 cases and adjusted for vaccination status (Supplement A, Section 4). Results for the outcome admission to hospital ≤14 days after positive test regardless of main cause were largely consistent with those for acute COVID-19 as the main cause, although we did observe a decreased risk for cases <18 years in the Omicron wave compared to the Delta wave (aRR: 0.67, 95% CI: 0.48–0.94) (Table 2).

Risk of MIS-C

Twenty-eight cases were diagnosed with MIS-C across the 3 waves (0.02% of study cohort) (Table 2). The median age was 6.5 years (interquartile range [IQR]: 4–9.5; range 1–17), 12 (43%) were female and 26 (93%) had no registered comorbidity. In the Alpha, Delta, and Omicron waves, 7 (0.07%), 14 (0.03%), and 7 (0.008%) cases were diagnosed with MIS-C, respectively (Table 1, Table 2). The risk of MIS-C was lower in the Omicron wave compared to the Alpha (aRR: 0.09, 95% CI: 0.03–0.27) and Delta wave (aRR: 0.26, 95% CI: 0.10–0.63) (Table 2). We did not observe a significant difference in the risk of MIS-C in the Delta wave compared to the Alpha wave.

Length of Hospital Stay, Admission to Intensive Care and Death

The median hospital LOS among cases hospitalized with acute COVID-19 as main cause was 0.8 days (IQR: 0.4–3.2) in the Alpha wave, 1.4 days (IQR: 0.7–3.1) in the

TABLE 1 Characteristics of Persons Aged <18 Years Diagnosed With COVID-19 Who Were Unvaccinated and Also Had Not Previously Been Diagnosed With COVID-19, by Variant Wave, Norway, March 15, 2021 to January 30, 2022

Characteristics	Variant Wave		
	Alpha Dominated Wave (n = 10 538) (%)	Delta Dominated Wave (n = 42 362) (%)	Omicron Dominated Wave (n = 82 907) (%)
Sex			
Male	5118 (48.6)	20 575 (48.6)	39 835 (48.0)
Female	5420 (51.4)	21 787 (51.4)	43 072 (52.0)
Age group			
<3 mo	55 (0.5)	118 (0.3)	218 (0.3)
3–11 mo	212 (2.0)	518 (1.2)	1395 (1.7)
1–11 y	5928 (56.3)	27 999 (66.0)	70 288 (84.8)
12–17 y	4343 (41.2)	13 727 (32.4)	11 006 (13.3)
Median age, y (IQR)	10 (6–1)	10 (7–13)	8 (5–10)
Born in Norway			
Yes, with at least 1 parent born in Norway	5510 (52.3)	29 143 (68.8)	63 225 (76.3)
Yes, 2 parents born outside of Norway	3425 (32.5)	8387 (19.8)	13 121 (15.8)
No	1598 (15.2)	4812 (11.4)	6555 (7.9)
Unknown	5 (<0.1)	20 (<0.1)	6 (<0.1)
Risk for severe COVID-19[a]			
No underlying comorbidities	9732 (92.4)	39 319 (92.8)	77 699 (92.6)
Medium-risk comorbidity	756 (7.2)	2886 (6.8)	5897 (7.0)
High-risk comorbidity	50 (0.5)	178 (0.4)	288 (0.3)
Region of residence[b]			
Southeast	8882 (84.3)	29 564 (69.8)	57 487 (69.3)
West	1265 (12.0)	5033 (11.9)	13 831 (16.7)
Mid	287 (2.7)	4669 (11.0)	8255 (10.0)
North	94 (0.9)	3057 (7.2)	3270 (3.9)
Unknown	10 (<0.1)	39 (<0.1)	64 (<0.1)
Admission to hospital			
No	10 507 (99.7)	42 303 (99.9)	82 819 (99.9)
Yes, ≤14 d after positive test	30 (0.3)	58 (0.1)	86 (0.1)
Yes, 15–28 d after positive test	1 (<0.1)	1 (<0.1)	2 (<0.1)
Admission to hospital with COVID-19 as main cause of admission			
No	10 517 (99.8)	42 334 (99.9)	82 858 (99.9)
Yes, ≤14 d after positive test	21 (0.2)	28 (<0.1)	48 (<0.1)
Yes, 15–28 d after positive test	0 (0.0)	0 (0.0)	1 (<0.1)
Diagnosed with MIS-C			
No	10 531 (99.9)	42 348 (100.0)	82 900 (100.0)
Yes	7 (<0.1)	14 (<0.1)	7 (<0.1)

[a] Risk for severe disease based on underlying comorbidities that are associated with a medium- or high-risk of serious illness regardless of age. Data on comorbidities were based on International Clinical Modification (ICD-10-CM) codes from the Norwegian patient registry, and International Classification of Primary Care, 2nd edition codes from the Norway Control and Payment of Health Reimbursement database. Medium-risk includes chronic liver disease or significant hepatic impairment, immunosuppressive therapy as in autoimmune diseases, diabetes, chronic lung disease including cystic fibrosis and severe asthma which have required the use of high dose inhaled or oral steroids within the past year, obesity with a BMI of ≥35 kg/m^2, dementia, chronic heart and vascular disease (with the exception of high blood pressure), and stroke. High-risk includes having received an organ transplant, immunodeficiency, hematologic cancer in the last 5 years, other active cancers, ongoing or recently discontinued treatment of cancer (especially immunosuppressive therapy, radiation therapy to the lungs or cytotoxic drugs), neurologic or neuromuscular diseases that cause impaired cough or lung function (eg, amyotrophic lateral sclerosis and cerebral palsy), Down syndrome and chronic kidney disease, or significant renal impairment. Further details on the definitions used are provided in Supplement A, Section 1.

[b] Southeast: counties Oslo, Viken, Innlandet, Agder, Vestfold and Telemark; West: counties Vestland and Rogaland; Mid: counties Trøndelag, and Møre and Romsdal; North: counties Nordland, and Troms and Finnmark.

Delta wave, and 1.1 days (IQR: 0.8–2.7) in the Omicron wave. Among the 28 MIS-C cases, the median LOS was 4 days (IQR: 2–6). Data on LOS is not presented by wave for MIS-C cases because of the small number of MIS-C cases in each wave. Across all 3 waves, 6 (6%) cases hospitalized with acute COVID-19 as main cause and 4 (14%) MIS-C cases were admitted to ICU. This equates to 0.007% of diagnosed COVID-19 cases being admitted to ICU for either acute COVID-19 or MIS-C in Norway. At the end of the follow-up, there were no reported deaths among those hospitalized (either for acute COVID-19 or MIS-C), nor within 30 days of positive test among those not hospitalized.

DISCUSSION

In this study we have analyzed national registry data from a setting with a broad COVID-19 testing strategy among children and

TABLE 2 Number of Cases Admitted to Hospital for Acute COVID-19 or MIS-C, and Crude and Adjusted Risk Ratios From Log-Binomial Regression, by Age Group and Variant Wave, Persons Aged <18 Years Diagnosed With COVID-19 Who Were Unvaccinated and Had Also Not Previously Been Diagnosed With COVID-19, Norway, March 15, 2021 to January 30, 2022

		Alpha Wave (wk 11–20 2021)		Delta Wave (wk 35–48 2021)				Omicron Wave (wk 2–4 2022)					
Outcome	Age Group	Number of Outcomes per Cases	%	Number of Outcomes per Cases	%	Crude Risk Ratio Compared to Alpha Wave (95% CI)	Adjusted Risk Ratio Compared to Alpha Wave (95% CI)	Number of Outcomes per Cases	%	Crude Risk Ratio Compared to Alpha Wave (95% CI)	Adjusted Risk Ratio Compared to Alpha Wave (95% CI)	Crude Risk Ratio Compared to Delta Wave (95% CI)	Adjusted Risk Ratio Compared to Delta Wave (95% CI)
Admission to hospital ≤14 d after positive test	<3 mo	10 of 55	18.2	11 of 118	9.3	0.51 (0.23–1.13)	0.43 (0.20–0.97)[d,f]	22 of 218	10.1	0.56 (0.28–1.10)	[a]	1.08 (0.54–2.15)	[a]
	3–11 mo	4 of 212	1.9	6 of 518	1.2	0.61 (0.18–2.15)	[a]	14 of 1395	1.0	0.53 (0.18–1.60)	[a]	0.86 (0.33–2.24)	[a]
	1–11 y	9 of 5928	0.2	25 of 27999	<0.1	0.59 (0.27–1.26)	1.12 (0.52–2.41)[b,c,d]	44 of 70288	<0.1	0.41 (0.20–0.84)[f]	0.49 (0.24–1.00)[b,c]	0.70 (0.43–1.14)	0.64 (0.39–1.05)[b,c,d]
	12–17 y	7 of 4343	0.2	16 of 13727	0.1	0.72 (0.30–1.75)	0.91 (0.37–2.24)[b,c]	6 of 11006	<0.1	0.34 (0.11–1.01)	[a]	0.47 (0.18–1.19)	[a]
	All <18 y	30 of 10541	0.3	58 of 42362	0.1	0.48 (0.31–0.75)[f]	0.70 (0.46–1.08)[b,c]	86 of 82907	0.1	0.36 (0.24–0.55)[f]	0.48 (0.31–0.72)[b,c,f]	0.76 (0.54–1.06)	0.67 (0.48–0.94)[b,c,f]
Admission to hospital with COVID-19 as main cause of admission ≤14 d after positive test	<3 mo	8 of 55	14.6	7 of 118	5.9	0.41 (0.16–1.07)	[a]	17 of 218	7.8	0.54 (0.24–1.18)	0.50 (0.23–1.09)[e]	1.31 (0.56–3.08)	[a]
	3–11 mo	3 of 212	1.4	3 of 518	0.6	0.41 (0.08–2.01)	[a]	10 of 1395	0.7	0.51 (0.14–1.82)	[a]	1.23 (0.34–4.47)	[a]
	1–11 y	6 of 5928	0.1	10 of 27999	<0.1	0.35 (0.13–0.97)[f]	0.72 (0.26–2.01)[b,c,d]	18 of 70288	<0.1	0.25 (0.10–0.64)[f]	0.32 (0.13–0.83)[b,c,f]	0.72 (0.33–1.55)	0.62 (0.28–1.35)[b,c,d,f]
	12–17 y	4 of 4343	<0.1	8 of 13727	<0.1	0.63 (0.19–2.10)	[a]	3 of 11006	<0.1	0.30 (0.07–1.32)	[a]	0.47 (0.12–1.76)	[a]
	All <18 y	21 of 10538	0.2	28 of 42362	<0.1	0.33 (0.19–0.58)[f]	0.53 (0.30–0.93)[b,c,f]	48 of 82907	<0.1	0.29 (0.17–0.48)[f]	0.40 (0.24–0.68)[b,c,f]	0.88 (0.55–1.40)	0.76 (0.47–1.23)[b,c,f]
MIS-C	<3 mo	0 of 55	0.0	0 of 118	0.0	—	—	0 of 218	0.0	—	—	—	—
	3–11 mo	0 of 212	0.0	0 of 518	0.0	—	—	0 of 1395	0.0	—	—	—	—
	1–11 y	6 of 5928	0.1	11 of 27999	<0.1	0.39 (0.14–1.05)	[a]	7 of 70288	<0.1	0.10 (0.03–0.29)[f]	[a]	0.25 (0.10–0.65)	[a]
	12–17 y	1 of 4343	<0.1	3 of 13727	<0.1	0.95 (0.10–9.12)	[a]	0 of 11006	0.0	—	—	—	—
	All <18 y	7 of 10538	<0.1	14 of 42362	<0.1	0.50 (0.20–1.23)	[a]	7 of 82907	<0.1	0.13 (0.04–0.36)[f]	0.09 (0.03–0.27)[b,e]	0.26 (0.10–0.63)	[a]

[a] The crude model was the best model.
[b] Adjusted for age.
[c] Adjusted for underlying comorbidities.
[d] Adjusted for country of birth.
[e] Adjusted for region of residence.
[f] Statistically significant result.
—, Risk ratio not calculated due to zero outcomes in one or both variant waves.

TABLE 3 Admission to Hospital Among Infants Aged <3 Months With COVID-19, by Variant Wave, Age Group and Whether the Mother of the Infant Had Been Vaccinated at Any Time up to 4 Weeks After Birth, Norway, March 15, 2021 to January 30, 2022

Variant Wave	Alpha (%)	Delta (%)	Omicron (%)
All infants aged <3 mo with COVID-19			
Total	55	118	218
Admission to hospital ≤14 d after positive test (% of total)	10 (18.2)	11 (9.3)	22 (10.1)
Admission to hospital with COVID-19 as main cause of admission ≤14 d after positive test (% of total)	8 (14.6)	7 (5.9)	17 (7.8)
Infants aged <3 mo with COVID-19 whose mother was unvaccinated with a COVID-19 vaccine up to 4 wk after child's birth[a]			
Total	54	91	73
Admission to hospital ≤14 d after positive test (% of total)	10 (18.5)	8 (8.9)	11 (15.1)
Admission to hospital with COVID-19 as main cause of admission ≤14 d after positive test (% of total)	8 (14.8)	4 (4.4)	8 (11.0)

[a] Mothers' vaccination status was known for 54 Alpha, 115 Delta, and 215 Omicron cases. For 3 infants diagnosed with COVID-19 in the Delta wave and 6 diagnosed with COVID-19 in the Omicron wave, the mother was unvaccinated but diagnosed with COVID-19 at least 2 weeks before the child's birth.

adolescents. Hospitalization because of acute COVID-19 or MIS-C was infrequent in all 3 waves.

We find no difference in the risk of hospitalization because of acute COVID-19 among persons <18 years in the Omicron wave, compared to the Delta wave. We did find a lower risk of hospitalization regardless of main cause in the Omicron wave compared to the Delta wave. However, results for this indicator should be interpreted with caution because it will include patients admitted for non-COVID-19 related causes. Our results are in line with similar national studies from both England[5] and Denmark.[12] Conversely, Omicron has been associated with a reduced risk of hospitalization and intensive care admission compared to Delta, among children <5 years of age with COVID-19 in the United States.[13] In comparing estimates, the study settings need to be considered, with each conducted in a different population and health care system. In studies including persons of all ages diagnosed with COVID-19, variation in variant-severity estimates from different settings has been reported.[14,15,22] A study from the United States has also suggested an increase in upper respiratory complications among young children since Omicron became dominant.[28] Such changes in the clinical presentation of hospitalized pediatric COVID-19 patients also need to be considered in future hospital capacity planning and management of pediatric patients as Omicron circulates.

Previous studies from the United States and Denmark estimated the incidence of MIS-C (defined based on the case definition from the Centers for Disease Control and Prevention) to be between 1 in 3000 to 1 in 4000 children infected with the wild-type SARS-CoV-2 variant.[29,30] A subsequent study from Denmark found that this risk did not change among unvaccinated children and adolescents during a wave of Delta infections.[19] We find that the incidence of MIS-C (based on the case definition from the World Health Organization) in Norway during the Delta wave was approximately 1 in 3000 children with COVID-19 who were unvaccinated and had not been previously diagnosed with COVID-19. This decreased to 1 in 12 000 in the Omicron wave, an estimated 75% decrease (95% CI: 37% to 90%) in risk. This may suggest a lower intrinsic risk of MIS-C for Omicron compared to Delta, which is supported by preliminary data from both Denmark[20] and Southeast England.[21] This is an encouraging finding, especially given evidence that this risk may be further reduced through vaccination. Studies from Denmark and the United States have estimated the effectiveness of 2 doses of the Pfizer-BioNTech BNT162b2 vaccine against MIS-C to be 91% to 94% during periods of Delta dominance.[19,31] It remains to be seen if the same level of vaccine effect against MIS-C is maintained during a period of Omicron dominance. Omicron has been linked to an increase in breakthrough infections[7,32] and lower vaccine effectiveness against some severity outcomes among children and adolescents 5 to 17 years.[33] The lower risk of MIS-C with Omicron must also be taken into account when considering vaccination for children and adolescents.

The proportion of MIS-C cases admitted to ICU in our study is notably lower than reported by others.[11,19,34] Here, differences in the settings, case definition of MIS-C, and the definition of ICU admission need to be considered. For example, our definition of ICU admission will exclude stays in intermediate observation posts in a pediatrics unit.

We find a lower risk of hospitalization because of acute COVID-19 among persons <18 years in the Delta and Omicron waves, compared to the Alpha wave. Although this could reflect a real

decrease in the risk because of the variant, other factors may have influenced these results. An important limitation with severity studies based on persons diagnosed with COVID-19 is that undiagnosed cases will affect reported outcome proportions, whereas systematic differences in undiagnosed cases between groups may affect comparisons. In our study, the testing strategy was further enhanced after the Alpha wave. Thus, a higher proportion of school-age children and adolescents with asymptomatic and mild COVID-19 may have been diagnosed in the Delta and Omicron waves, even if experiences from previous waves suggest that the proportion of children with COVID-19 who were diagnosed was high before routine biweekly screening of school children was recommended (Supplement A, Section 1). Also, maternal vaccination, which has been reported to protect infants from severe COVID-19,[35,36] was first recommended in Norway before the start of the Delta wave. However, the decrease in the proportion of hospitalized infants <3 months between the Alpha and Delta waves was also observed in infants born to unvaccinated mothers. Thus, other factors such as differences in physicians' decisions on whether to hospitalize an infant, may also have influenced our outcomes. The small cohort of infants <3 months, the small number of vaccinated mothers in the Delta wave, and lack of data on important confounders, such as breastfeeding and preterm birth, limited more in-depth analyses of this cohort.

A general limitation with our study is that the small number of outcomes restricted further exploration of our results. Given the low incidence of severe outcomes among children and adolescents with COVID-19, which may be further reduced through vaccination,[19,31,36,37] analyses of pooled data from several countries or meta-analyses may better elucidate differences in the risk of these outcomes between VOC in younger age groups. Also, we analyzed an Omicron wave when the sublineage BA.1 was the dominant circulating variant. Further studies are needed to establish differences in disease severity between different Omicron sublineages.

CONCLUSIONS

We do not find clear evidence that different SARS-CoV-2 variants have influenced the risk of hospitalization with acute COVID-19 among unvaccinated children and adolescents in Norway. Results suggest a decrease in the risk of MIS-C among those infected with the Omicron variant, compared to the Delta and Alpha variant.

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ABBREVIATIONS

aRR: adjusted risk ratio
CI: confidence interval
COVID-19: coronavirus disease 2019
IQR: interquartile range
LOS: length of stay
MIS-C: multisystem inflammatory syndrome in children
MSIS: Norwegian Surveillance System for Communicable Diseases
NIPaR: Norwegian Intensive Care and Pandemic Registry
NPR: Norwegian Patient Register
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
VOC: variant of concern

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9.1.4 Paper IV

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Letter to the Editor

Trajectories of hospitalisation for patients infected with SARS-CoV-2 variant B.1.1.7 in Norway, December 2020 – April 2021

Dear Editor,

The COVID-19 pandemic has put unprecedented strain on health systems around the world, and the emergence of variants of concern (VOC) remains an area of substantial concern as we continue to battle the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This includes lineage B.1.1.7 (alpha variant), first detected in south-east England in September 2020.[1] In Norway (population 5.4 million), the first infection with B.1.1.7 was sampled in week 48 2020, and B.1.1.7 became the predominant circulating variant nationally in week 5 2021. In addition to increased transmissibility,[1] B.1.1.7 infection has been associated with increased risk of hospitalisation compared to non-VOC in Norway,[2] as well as other European countries.[3,4] Evidence on differences in patient trajectories and outcomes among hospitalised patients infected with B.1.1.7 compared to other lineages is thus essential to support ongoing capacity planning in the health system.

In this journal, a study from Garvey and colleagues analysed a cohort of 152 patients from the UK's largest hospital trust infected with the VOC B.1.1.7 (and one B.1.351) compared to other variants.[5] They reported no statistically significant difference in the mean length of stay (LoS) in hospital or ICU, proportion of patients admitted to ICU, nor proportion of patients who died.[5] In Norway we have conducted a similar study on a representative cohort of 1103 SARS-CoV-2 positive patients using linked, patient-level data from national registries.

A full description of the data sources and methods is available here.[6] Briefly, the data come from the national emergency preparedness registry, which comprises data from a variety of central health registries, national clinical registries and other national administrative registries. We included notified cases of COVID-19 who were hospitalised not more than two days before and less than 28 days after a positive SARS-CoV-2 test in Norway between 21 December 2020 and 25 April 2021, who had available variant data after whole genome sequencing (WGS) or PCR screening, and who had not been vaccinated with a COVID-19 vaccine before sampling or hospitalisation. We extracted and linked data on 2 June 2021, ensuring a minimum of 36 days follow-up since last date of hospitalisation. Although elective surgeries in some regions were postponed during a surge in hospitalisations among COVID-19 cases in mid-March, hospitals in Norway functioned within capacity during the study period, while there were no major changes in treatment guidelines for SARS-CoV-2 patients in hospital or ICU. Variants were identified based on WGS using Illumina or Nanopore technology, partial sequencing by Sanger sequencing or PCR screening for selected targets. Of 2354 unvaccinated patients in the study period, 1186 (50%) had known virus variant, and few differences were observed between patients who had known virus variant and those who did not.[6] We used survival analysis (Kaplan Meier curves, adjusting for right censuring) to examine the association between B.1.1.7 and time from symptom onset to hospitalisation, and LoS in hospital and in ICU, compared to non-VOC. We used logistic regression to examine the association between B.1.1.7 and mortality up to 30 days post discharge compared to non-VOC. For the analysis of mortality, we analysed a subset of the dataset, including patients who had been discharged by 30 April 2021, in order to ensure at least 30 days of follow-up post discharge for all patients. We built multivariable models by forward model selection and AIC comparison. Explanatory variables included in the multivariable models are detailed in Table 2. Statistical modelling was performed using R version 3.6.

Of the 1186 patients, 946 (81%) were B.1.1.7 and 157 (13%) were non-VOC, while 27 (2%) were another VOC (B.1.351, P.1 or B.1.617.2) and 53 (4%) could not clearly be distinguished as VOC or non-VOC. Characteristics of the 1103 patients infected with B.1.1.7 or a non-VOC are presented in Table 1. The proportion of B.1.1.7 increased throughout the study period from 0% in week 52, 2020 to 41% in week 5, 2021 and 88% in week 7, 2021. From week 11, 2021 onwards, 99% of patients were B.1.1.7. In both the univariable and multivariable models, we did not observe a statistically significant difference in the time from symptom onset to hospitalisation, LoS in hospital nor LoS in ICU for B.1.1.7 patients compared to non-VOC patients (Table 2). Of the 1103 patients, 1037 (94%) were discharged by 30 April 2021; 880 B.1.1.7 and 157 non-VOC. For B.1.1.7, 50 patients died in hospital (6%), one died less than seven days post discharge (0.1%), and three died 7–30 days post discharge (0.3%). For non-VOC, 10 patients died in hospital (6%), two died less than seven days post discharge (1.3%), and two died 7–30 days post discharge (1.3%). In both the univariable and multivariable models, we did not observe a statistically significant difference in the odds of death for B.1.1.7 patients compared to non-VOC patients (Table 2).

Our findings indicate no difference in the time from symptom onset to hospitalisation, LoS in hospital and ICU, nor odds of mortality up to 30 days post discharge for persons infected with B.1.1.7 compared to non-VOC in Norway. These findings are in line with Garvey et al.[5], and other published studies from the UK.[7–9] This suggests that, while B.1.1.7 seems to increase the risk of hospitalisation,[2–4] other patient characteristics determine patient trajectories and healthcare required among those hospitalised with COVID-19. These findings, along with the success of vaccination programmes, are encouraging for ongoing capacity planning in the

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Table 1
Characteristics of hospitalised SARS-CoV-2 positive patients infected with B.1.1.7 or a non-VOC, Norway, 21 December 2020 – 25 April 2021.

Characteristics		Variant type Non-VOC (n = 157)	B.1.1.7 (n = 946)
Method used to determine variant	WGS	120 (76%)	451 (48%)
	PCR-screening	37 (34%)	495 (52%)
Sex	Female	69 (44%)	392 (42%)
	Male	88 (56%)	554 (59%)
Age group	0–24 years	9 (6%)	52 (6%)
	25–44 years	20 (13%)	236 (25%)
	45–64 years	65 (41%)	431 (46%)
	≥ 65 years	63 (40%)	227 (24%)
Born in Norway	Yes	97 (62%)	440 (47%)
	No	53 (34%)	475 (50%)
	Unknown	7 (4%)	31 (3%)
Risk factors	Asthma	18 (11%)	105 (11%)
	Diabetes	34 (22%)	169 (18%)
	Cancer	5 (3%)	42 (4%)
	Chronic lung disease, except asthma	19 (12%)	60 (6%)
	Chronic neurological or neuromuscular disease	5 (6%)	40 (4%)
	Heart disease including hypertension	70 (45%)	302 (32%)
	Immunocompromised, including HIV	9 (6%)	31 (3%)
	Kidney disease	16 (10%)	28 (3%)
	Liver disease	2 (1%)	6 (1%)
	Obesity (BMI≥ 30)*	22 (31%)	225 (43%)
	Pregnant	3 (2%)	25 (3%)
	Current smoker	9 (6%)	43 (5%)
At least one stay where COVID-19 was the reported main cause of admission	Yes	127 (81%)	815 (86%)
	No	28 (18%)	126 (13%)
	Unknown	2 (1%)	5 (1%)
Admission to ICU	Yes	25 (16%)	175 (18%)
	No	132 (84%)	771 (82%)
Mortality	Died in hospital	10 (6%)	52 (6%)
	< 7 days post discharge	2 (1%)	1 (0%)
	7–30 days post discharge	2 (1%)	4 (0%)
	Alive > 30 days after hospital discharge	143 (91%)	889 (94%)
Number of patients still in hospital at end of study period	In ICU	0 (0%)	8 (1%)
	In hospital, not in ICU	0 (0%)	8 (1%)
	Discharged from hospital	157 (100%)	930 (98%)

VOC: Variant of concern; WGS: Whole genome sequencing; ICU: Intensive care unit; BMI: Body mass index.
* In our dataset, 85 (54%) non-VOC and 424 (45%) B.1.1.7 patients had unknown information on height and weight, and thus unknown data on BMI.

hospital sector, particularly as societies ease lockdowns. Timely analysis on the association between current and future VOC, such as B.1.617.2 (which overlook B.1.1.7 as the predominant circulating variant in Norway in week 27, 2021), and the risk of severe disease and impact on patient trajectories remains essential to ensure health systems are best prepared and able to appropriately respond to this evolving public health threat. These analyses need to come from a variety of settings, considering local epidemiological characteristics.

CRediT authorship contribution statement

Robert Whittaker: Conceptualization, Writing – original draft, Data curation, Validation, Investigation, Formal analysis, Writing – review & editing. **Anja Bråthen Kristofferson:** Data curation, Validation, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Elina Seppälä:** Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Beatriz Valcarcel Salamanca:** Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Lamprini Veneti:** Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Margrethe Larsdatter Storm:** Funding acquisition, Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Håkon Bøås:** Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Umaer Naseer:** Funding acquisition, Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Karoline Bragstad:** Funding acquisition, Data curation, Validation, Investigation, Writing – original draft, Writing – review & editing. **Reidar Kvåle:** Funding acquisition, Data curation, Writing – original draft, Writing – review & editing. **Karan Golestani:** Writing – original draft, Writing – review & editing. **Siri Feruglio:** Writing – original draft, Writing – review & editing. **Line Vold:** Writing – original draft, Writing – review & editing. **Karin Nygård:** Writing – original draft, Writing – review & editing. **Eirik Alnes Buanes:** Conceptualization, Funding acquisition, Data curation, Writing – original draft, Writing – review & editing.

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Table 2
Crude and adjusted hazard ratios from survival analysis for time from symptom onset to hospitalisation, and length of stay in hospital and intensive care, and crude and adjusted odds ratios from logistic regression for death in-hospital or up to 30 days post discharge, among hospitalised SARS-CoV-2 positive patients infected with B.1.1.7 compared to a non-VOC, Norway, 21 December 2020 – 25 April 2021.

Outcome	Variant type Non-VOC Number of patients	Median (IQR)	B.1.1.7 Number of patients	Median (IQR)	Crude hazard ratio for B.1.1.7 compared to non-VOC (95%CI)	Adjusted^ hazard ratio for B.1.1.7 compared to non-VOC (95%CI)
Days from symptom onset to hospitalisation*	93	8(4–11)	445	8(5– 10)	1.22 (0.97 – 1.52)	1.21 (0.94 – 1.55)
Days in hospital for patients not admitted to ICU	132	4.1 (2.1 – 7.5)	771	4.0 (2.1 – 6.8)	1.08 (0.90 – 1.31)	0.96 (0.79 – 1.17)
Days in hospital before admission to ICU	25	2.1 (0.1 – 4.7)	175	1.2 (0.2 – 3.7)	1.28 (0.83 – 1.96)	1.03 (0.67 – 1.59)
Days in ICU	25	11.0 (7.2 – 16.4)	175	10.6 (5.4 – 19.6)	0.97 (0.61 – 1.56)	0.83 (0.51 – 1.34)
Days in hospital after discharge from ICU**	20	7.2 (3.5 – 11.3)	141	5.9 (3.2 – 9.8)	1.06 (0.65 – 1.71)	1.00 (0.61 – 1.63)
	Non-VOC No (%)	Yes (%)	B.1.1.7 No (%)	Yes (%)	Crude odds ratio for B.1.1.7 compared to non-VOC (95%CI)	Adjusted^^ odds ratio for B.1.1.7 compared to non-VOC (95%CI)
Death in-hospital or up to 30 days post discharge***	143 (91%)	14 (9%)	826 (94%)	54 (6%)	0.67 (0.36 – 1.23)	1.39 (0.68 – 3.01)

VOC: Variant of concern; ICU: Intensive care unit; IQR: Interquartile range; 95%CI: 95% confidence interval.
^ Adjusted for age (continuous variable either linearly or with a spline), sex, county of residence, regional health authority, week of admission, country of birth (Norway, overseas and unknown), main cause of hospitalisation (COVID-19, other, unknown) and underlying risk factors. The variables included in the final multivariable model were obtained by forward model selection and AIC comparison.[6]
^^ age (continuous variable either linearly or with a spline), sex, county of residence, regional health authority, week of admission, country of birth (Norway, overseas and unknown), main cause of hospitalisation (COVID-19, other, unknown), underlying risk factors and admission to ICU. The variables included in the final multivariable model were obtained by forward model selection and AIC comparison.[6]
* Number of patients with known date of symptom onset: non-VOC 93/157 (60%); B.1.1.7 445/946 (47%).
** Excludes eight B.1.1.7 patients who were still admitted to ICU at the end of the study period, and five non-VOC and 26 B1.1.7 who passed away in ICU.
*** Death in-hospital or up to 30 days post discharge is limited to patients who had been discharged by 30 April 2021 (157 non-VOC, 880 B1.1.7), in order to ensure at least 30 days of follow-up post discharge for all patients.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Role of funding sources

The authors received no specific funding for this work.

Ethics

Ethical approval for this study was granted by Regional Committees for Medical Research Ethics - South East Norway, reference number 249509.

Data availability statement

The datasets analysed during the current study come from the national emergency preparedness registry for COVID-19, housed at the Norwegian Institute of Public Health. The preparedness registry is temporary and comprises data from a variety of central health registries, national clinical registries and other national administrative registries. Further information on the preparedness registry, including access to data from each individual data source, is available at https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/.

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9.1.5 Paper V

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Original article

Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a register-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients

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ABSTRACT

Objectives: We estimated the length of stay (LoS) in hospital and the intensive care unit (ICU) and risk of admission to ICU and in-hospital death among COVID-19 patients ≥18 years in Norway who had been fully vaccinated with an mRNA vaccine (at least two doses or one dose and previous SARS-CoV-2 infection), compared to unvaccinated patients.

Methods: Using national registry data, we analyzed SARS-CoV-2–positive patients hospitalized in Norway between 1 February and 30 November 2021, with COVID-19 as the main cause of hospitalization. We ran Cox proportional hazards models adjusting for vaccination status, age, sex, county of residence, regional health authority, date of admission, country of birth, virus variant, and underlying risk factors.

Results: We included 716 fully vaccinated patients (crude overall median LoS: 5.2 days; admitted to ICU: 103 (14%); in-hospital death: 86 (13%)) and 2487 unvaccinated patients (crude overall median LoS: 5.0 days; admitted to ICU: 480 (19%); in-hospital death: 102 (4%)). In adjusted models, fully vaccinated patients had a shorter overall LoS in hospital (adjusted log hazard ratios (aHR) for discharge: 1.61, 95% CI: 1.24–2.08), shorter LoS without ICU (aHR: 1.27, 95% CI: 1.07–1.52), and lower risk of ICU admission (aHR: 0.50, 95% CI: 0.37–0.69) compared to unvaccinated patients. We observed no difference in the LoS in ICU or in risk of in-hospital death between fully vaccinated and unvaccinated patients.

Discussion: Fully vaccinated patients hospitalized with COVID-19 in Norway have a shorter LoS and lower risk of ICU admission than unvaccinated patients. These findings can support patient management and ongoing capacity planning in hospitals. **Robert Whittaker, Clin Microbiol Infect 2022;28:871**

Introduction

COVID-19 vaccination programmes have drastically reduced the burden of COVID-19–related hospitalizations and deaths [1–5]. However, the risk of breakthrough cases of severe COVID-19 after vaccination remains, particularly among groups at higher risk of severe disease [6,7].

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Norway (population 5.4 million) started COVID-19 vaccination in December 2020, initially focusing on individuals ≥65 years of age, health care workers, and individuals at increased risk of severe COVID-19 [8]. The mRNA vaccines Comirnaty (BioNTech-Pfizer, Mainz, Germany/New York, NY) and Spikevax (mRNA-1273, Moderna, Cambridge, MA) are the two predominant vaccines administered [9]. National second dose coverage among those ≥18 years of age reached 87% by 30 November 2021. Persons with specific immunosuppressive conditions were offered a third dose as part of the primary series from September 2021 [10]. Booster doses have been offered to persons ≥65 years of age and care home residents since October and health care workers since November 2021 [11].

With high national vaccination coverage, an increasing number and proportion of COVID-19–related hospitalizations are occurring among vaccinated patients, characterized by advanced age and underlying comorbidities that increase the risk of severe COVID-19 [8,12]. It is therefore essential to understand how vaccination may affect clinical endpoints among hospitalized COVID-19 patients to support patient management and capacity planning in hospitals. Published data on this are currently limited [13,14].

We linked individual-level data from national registries to estimate the length of stay (LoS) in hospital (with and without intensive care unit (ICU) stay) and ICU and the risk of ICU admission and in-hospital death among COVID-19 patients aged ≥18 years in Norway who had been fully vaccinated with an mRNA vaccine, compared to unvaccinated patients.

Methods

Patient cohort

We conducted a cohort study on patients aged ≥18 years hospitalized between 1 February and 30 November 2021 who had a national identity number registered. We included patients hospitalized ≤2 days before and ≤28 days after a positive SARS-CoV-2 test, where COVID-19 was the reported main cause of hospitalization. Patients hospitalized with other or unknown main cause were excluded. We did not restrict admissions by LoS. Initially, the Alpha variant was the predominant circulating variant, before being superseded by Delta in early July [15].

Data sources

We obtained data from the Norwegian national emergency preparedness registry for COVID-19 [16]. This registry contains individual-level data on all laboratory-confirmed COVID-19 cases, COVID-19 related hospitalizations and ICU admissions, and COVID-19 vaccinations among Norwegian residents. Further details are presented in supplementary materials A, part 1. We extracted data from the preparedness registry on 14 December 2021, ensuring a minimum 13 days follow-up since last date of hospitalization.

Definition of COVID-19 vaccination status

Vaccination status was defined on the date of positive SARS-CoV-2 test:

1. Unvaccinated: Not vaccinated with a COVID-19 vaccine.
2. Fully vaccinated: Positive test ≥7 days after second dose with at least the absolute minimum interval between doses depending on vaccine type [17], or ≥7 days after first dose if previously diagnosed with a SARS-CoV-2 infection ≥21 days before vaccination.

We excluded patients vaccinated with only one dose, those who had received a second dose <7 days before positive test, and patients vaccinated with a non-mRNA vaccine only. We also excluded unvaccinated patients with reported SARS-CoV-2 reinfections.

Outcome measures

Our outcomes were discharge from hospital (with and without ICU admission), admission to ICU, discharge from ICU, and in-hospital death. We calculated LoS as the time between first admission and last discharge. For patients with >1 registered hospital stay, we included the time between consecutive stays if < 24 hours. For LoS in ICU, we included the time between consecutive stays if < 12 hours. Separate stays were registered if a patient was discharged and readmitted, or transferred between wards or hospitals. Patients with unknown date of discharge from their last stay were considered to still be hospitalized. In-hospital death was registered at discharge.

Data analysis

Explanatory variables to analyze differences in our outcomes were vaccination status, age, sex, county of residence, regional health authority, date of admission, country of birth, virus variant, and underlying risk factors (Table 1).

Outcomes were explored univariably in a Cox proportional hazards model and by calculating Kaplan-Meier curves, with right censoring of patients still admitted to hospital. Crude log hazard ratios with medians and interquartile ranges (IQR) for LoS were obtained. Explanatory variables with $p < 0.2$ were further explored in multivariable models. Forward model selection was performed based on the Akaike information criterion. Only variables with a correlation of <0.5 were used in the same model. Vaccination status was maintained in all models regardless of significance. Continuous variables (date of admission and age) were tested as linear, spline, or categorical. The multivariable model was checked for the assumption of proportional hazards by checking Schoenfeld residuals, and some explanatory variables were stratified to satisfy the assumption. We also checked for interactions between variables included in multivariable models. Adjusted log hazard ratios (aHRs) obtained in the multivariable models were reported. For LoS outcomes, because hazard rates are not explicitly estimated in Cox regression, we also estimated a proxy for the expected difference in LoS as $1-(1/\text{aHR})$ by assuming an exponential survival distribution [18]. The fit of LoS outcomes to an exponential distribution is presented in supplementary materials A, part 2.

We ran models on all patients and the following age subgroups: 18–64, 65–79, and ≥80 years. Patients vaccinated with three doses were not analysed separately due to small numbers. LoS in ICU was not analyzed by age subgroup due to the small number of vaccinated ICU patients in each subgroup (≤50).

We also conducted sensitivity analyses by changing the definition of our study population, study period, or outcome definitions (supplementary materials A, part 3). The statistical analysis was performed in R version 3.6.2.

Ethics

Ethical approval for this study was granted by Regional Committees for Medical Research Ethics, South East Norway, reference number 249509. The need for informed consent was waived.

Table 1
Characteristics of SARS-CoV-2–positive patients aged ≥18 years hospitalized with COVID-19 as the main cause of hospitalization, by vaccination status (Norway, 1 February–30 November 2021)

Characteristics	Vaccination status		p value
	Unvaccinated ($n = 2487$)	Fully vaccinated ($n = 716$)	
Sex, *n* (%)			
Male	1472 (59.2%)	414 (57.8%)	0.531
Female	1015 (40.8%)	302 (42.2%)	
Age group, *n* (%)			
18–29 y	157 (6.3%)	6 (0.8%)	<0.001
30–44 y	640 (25.7%)	32 (4.5%)	
45–54 y	645 (25.9%)	49 (6.8%)	
55–64 y	510 (20.5%)	93 (13.0%)	
65–79 y	453 (18.2%)	260 (36.3%)	
≥80 y	82 (3.3%)	276 (38.5%)	
Age (y), median (IQR)	51 (41–62)	76 (64–83)	<0.001
Born in Norway, *n* (%)			
Yes, with at least one parent born in Norway	1037 (41.7%)	546 (76.3%)	<0.001
Yes, two parents born outside of Norway	62 (2.5%)	4 (0.6%)	
No	1311 (52.7%)	113 (15.8%)	
Unknown	77 (3.1%)	53 (7.4%)	
Underlying risk factors, *n* (%)			
Asthma	272 (10.9%)	74 (10.3%)	<0.001
Cancer[a]	63 (2.5%)	93 (13.0%)	
Chronic lung disease, excluding asthma	134 (5.4%)	143 (20.0%)	
Chronic neurological or neuromuscular disease	88 (3.5%)	60 (8.4%)	
Diabetes (type 1 and 2)	352 (14.2%)	166 (23.2%)	
Heart disease, including hypertension	659 (26.5%)	433 (60.5%)	
Immunosuppression, including HIV and immunosuppressive treatment[b]	63 (2.5%)	96 (13.4%)	
Kidney disease, including kidney failure	73 (2.9%)	126 (17.6%)	
Liver disease, including liver failure	24 (1.0%)	13 (1.8%)	
BMI ≥30 kg/m^2[c]	585 (23.5%)	104 (14.5%)	
Pregnant	66 (2.7%)	1 (0.1%)	
Current smoker	104 (4.2%)	25 (3.5%)	
Virus variant, *n* (%)			
Alpha	1038 (41.7%)	12 (1.7%)	<0.001
Beta	22 (0.9%)	1 (0.1%)	
Delta	375 (15.1%)	341 (47.6%)	
Non-VOC	70 (2.8%)	3 (0.4%)	
Uncategorized[d]	58 (2.3%)	2 (0.3%)	
Unknown	924 (37.2%)	357 (49.9%)	
Month of admission, *n* (%)			
February	197 (7.9%)	0 (0.0%)	<0.001
March	733 (29.5%)	6 (0.8%)	
April	560 (22.5%)	9 (1.3%)	
May	201 (8.1%)	3 (0.4%)	
June	97 (3.9%)	4 (0.6%)	
July	48 (1.9%)	11 (1.5%)	
August	113 (4.5%)	44 (6.1%)	
September	161 (6.5%)	105 (14.6%)	
October	121 (4.9%)	167 (23.3%)	
November	256 (10.3%)	367 (51.3%)	
Regional health authority, *n* (%)			
South-East	146 (5.9%)	86 (12.0%)	<0.001
West	142 (5.7%)	90 (12.6%)	
Mid	1919 (77.2%)	457 (63.8%)	
North	280 (11.3%)	83 (11.6%)	
Admission to ICU, *n* (%)			
No	2007 (80.7%)	613 (85.6%)	0.003

(continued on next page)

Table 1 (*continued*)

Characteristics	Vaccination status		p value
	Unvaccinated ($n = 2487$)	Fully vaccinated ($n = 716$)	
Yes	480 (19.3%)	103 (14.4%)	
Death, *n* (%)[e]			
Died in ICU	67 (2.7%)	30 (4.4%)	<0.001
Died in hospital, not in ICU	35 (1.4%)	56 (8.2%)	
Alive at discharge	2346 (95.8%)	594 (87.4%)	
In ICU	18 (0.7%)	15 (2.1%)	<0.001
Patients still in hospital at end of follow-up (13 December 2021), *n* (%)			
In hospital, not in ICU	21 (0.8%)	21 (2.9%)	
Discharged from hospital	2448 (98.4%)	680 (95.0%)	

P values compared to unvaccinated calculated using χ^2 tests or Wilcoxon rank sum tests as appropriate. P values for underlying risk factors based on proportion having any one of the listed risk factors. Equivalent descriptive data per age subgroup are available in supplementary materials B. BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; VOC, variant of concern.

[a] Refers to patients with cancer undergoing treatment or with regular controls (>1 per year).

[b] Includes ongoing use of steroids in doses equivalent to at least 5 mg prednisolone daily.

[c] In our dataset, 1 270 patients (40%) had unknown information on height and weight and thus unknown data on BMI. Of these 1 270, 962 were unvaccinated (39% of all unvaccinated) and 308 fully vaccinated (43%). In our models, BMI was therefore included as a three-level categorical variable: yes, no, and unknown.

[d] Cases for which VOC and non-VOC could not clearly be distinguished based on the available information. This does not potentially include cases of the Omicron VOC, which was not detected in any patients in our study cohort.

[e] Excludes patients still in hospital at end of follow-up.

Results

Description of cohort

During the study period, 3541 reported cases of COVID-19 were hospitalized with COVID-19 as the main cause of hospitalization ≤2 days before and ≤28 days after a positive SARS-CoV-2 test. Of these, 3476 (98%) had a national identity number registered. We excluded 262 patients vaccinated with only one dose or a second dose <7 days before positive test, four patients vaccinated with non-mRNA vaccines, one patient with unknown vaccine type, and two unvaccinated patients who had a reported SARS-CoV-2 reinfection. We also dropped four patients with a reported stay in ICU outside of their hospital stay, assuming incomplete reporting on hospital stays. Our study cohort included the remaining 3203 patients.

The median time from positive test to hospitalization was 5 days (IQR 1–8), and 3157 (99%) patients were admitted within 14 days of a positive test. In total, 583 (18%) patients were admitted to the ICU. At the end of follow-up, 75 (2.3%) patients were still hospitalized. Of the 3128 discharged patients, 188 (6.0%) died in hospital. In total, 716 (22%) patients were fully vaccinated, of whom 666 (93%) had received two doses, 47 (6.6%) three doses, and three (0.4%) one dose with a previous SARS-CoV-2 infection. Most patients (658, 92%) received a homologous Comirnaty regimen. A breakdown of vaccine types and time between doses is presented in supplementary materials A, part 4. The median time from last dose to diagnosis was 174 days (IQR: 126–217). Age and the frequency of certain underlying risk factors such as cancer, chronic lung disease, heart disease, immunosuppression (due to illness or treatment), and kidney disease were higher among fully vaccinated patients. Detailed characteristics of the study cohort by vaccination status are presented in Table 1. Equivalent descriptive data per age subgroup are available in supplementary materials B.

Length of stay in hospital and intensive care and risk of admission to intensive care and in-hospital death by vaccination status

Descriptive data and crude and adjusted hazard ratios for each outcome by age subgroup and vaccination status are presented in Tables 2 and 3 and Fig. 1. Estimates from all univariable and multivariable models in the main analysis are presented in supplementary materials Band C.

Our multivariable models suggested that fully vaccinated patients ≥18 years had a shorter overall LoS in hospital (aHR for discharge: 1.61, 95% CI: 1.24–2.08) and shorter LoS without ICU admission (aHR: 1.28, 95% CI: 1.07–1.52) compared to unvaccinated patients. Assuming exponential distribution, an aHR of 1.61 translates into an expected 38% (95% CI: 19%–52%) shorter LoS. Fully vaccinated patients also had a 50% lower risk of ICU admission (aHR: 0.50, 95% CI: 0.37–0.69) compared to unvaccinated patients. We did not observe a difference in the LoS in ICU (aHR: 1.03, 95% CI: 0.80–1.31) or risk of in-hospital death (aHR: 1.00, 95% CI: 0.54–1.85) between vaccinated and unvaccinated patients (Fig. 1, Table 3).

By age subgroup, fully vaccinated patients aged 18–64 years had an expected 48% (95% CI: 27%–62%) shorter overall LoS (aHR: 1.91, 95% CI: 1.37–2.66), 32% (95% CI: 10%–48%) shorter LoS without ICU admission (aHR: 1.46, 95% CI: 1.11–1.91), and 47% lower risk of ICU admission (aHR: 0.53, 95% CI: 0.32–0.88), compared to unvaccinated individuals. Fully vaccinated patients aged 65–79 years had an expected 22% (95% CI: 9%–34%) shorter overall LoS (aHR: 1.29, 95% CI: 1.10–1.52) and 36% lower risk of ICU admission (aHR: 0.64, 95% CI: 0.46–0.89) compared to unvaccinated patients. There was no difference in the adjusted risk of in-hospital death between vaccinated and unvaccinated patients in any age subgroup. We did

Table 2
Number of patients, median number of days from admission to discharge from hospital or ICU, admissions to ICU and deaths in hospital, and SARS-CoV-2–positive patients aged ≥18 years hospitalized with COVID-19 as the main cause of hospitalization (by vaccination status and age group, Norway, 1 February–30 November 2021)

Age group	Patients, *n*	Time from admission to discharge from hospital (d), median (IQR)[a]	Time from admission to discharge for patients not admitted to ICU (d), median (IQR)[a]	Patients admitted to ICU, *n* (%)	Time from admission to discharge from ICU (d), median (IQR)[a,b]	Deaths in hospital, *n* (%)[c]
Unvaccinated						
18–64 y	1952	4.8 (2.5–8.7)	3.9 (2.0–6.5)	343 (18%)	—	38 (2.0%)
65–79 y	453	7.1 (3.8–14.2)	5.0 (3.0–8.7)	131 (29%)	—	47 (11%)
≥80 y	82	5.6 (2.9–8.0)	5.4 (2.9–7.1)	6 (7.3%)	—	17 (21%)
≥18 y	2487	5.0 (2.7–9.6)	4.0 (2.1–6.8)	480 (19%)	9.9 (5.3–18.0)	102 (4.2%)
Fully vaccinated						
18–64 y	180	4.1 (2.0–10.6)	3.4 (1.6–6.5)	35 (19%)	—	9 (5.4%)
65–79 y	260	7.0 (3.3–12.4)	5.9 (2.8–9.2)	50 (19%)	—	33 (14%)
≥80 y	276	4.7 (2.2–9.1)	4.1 (2.1–8.1)	18 (6.5%)	—	61 (16%)
≥18 y	716	5.2 (2.6–10.5)	4.2 (2.1–8.1)	103 (14%)	9.9 (4.1–17.7)	86 (13%)

ICU, intensive care unit; IQR, interquartile range.
[a] Estimates from univariable Cox regression; see supplementary materials B.
[b] Median number of days from admission to discharge from ICU not presented for age subgroups due to the small number of fully vaccinated patients admitted to ICU in each age subgroup (≤50).
[c] Proportions calculated excluding those still admitted at the end of the study period. For 18–64 years: 25 unvaccinated, 12 fully vaccinated; 65–79 years: 13 unvaccinated, 17 fully vaccinated; ≥80 years: 1 unvaccinated, 7 fully vaccinated.

Table 3
Crude and adjusted hazard ratios for discharge from hospital with and without stay in ICU, ICU admission, discharge from ICU, and in-hospital death from a Cox proportional hazards model (SARS-CoV-2–positive patients aged ≥18 years hospitalized with COVID-19 as the main cause of hospitalization, by age group, Norway, 1 February–30 November 2021)

	Discharge from hospital		Discharge from hospital, patients not admitted to ICU		ICU admission		Discharge from ICU		Death in hospital	
Age group	Crude hazard ratio compared to unvaccinated (95% CI)	Adjusted[a] hazard ratio compared to unvaccinated (95% CI)	Crude hazard ratio compared to unvaccinated (95% CI)	Adjusted[a] hazard ratio compared to unvaccinated (95% CI)	Crude hazard ratio compared to unvaccinated (95% CI)	Adjusted[a] hazard ratio compared to unvaccinated (95% CI)	Crude hazard ratio compared to unvaccinated (95% CI)[b]	Adjusted[a,b] hazard ratio compared to unvaccinated (95% CI)	Crude hazard ratio compared to unvaccinated (95% CI)	Adjusted[a] hazard ratio compared to unvaccinated (95% CI)
18–64 y	0.913 (0.779–1.069)	**1.909 (1.372–2.658)**[c]	0.962 (0.811–1.142)	**1.455 (1.106–1.914)**[c]	1.137 (0.803–1.610)	**0.530 (0.319–0.882)**[c]	-	—	**2.177 (1.050–4.516)**[c]	1.351 (0.636–2.871)
65–79 y	**1.173 (1.001–1.375)**[c]	**1.287 (1.092–1.517)**[c]	0.866 (0.725–1.034)	1.218 (0.939–1.580)	**0.627 (0.453–0.869)**[c]	**0.639 (0.461–0.886)**[c]	-	—	**1.687 (1.074–2.651)**[c]	1.427 (0.892–2.284)
≥80 y	1.117 (0.869–1.434)	1.080 (0.839–1.389)	1.043 (0.806–1.349)	0.996 (0.769–1.290)	0.953 (0.378–2.403)	0.910 (0.361–2.295)	—	—	0.829 (0.473–1.453)	0.765 (0.436–1.340)
≥18 y	0.981 (0.901–1.068)	**1.607 (1.243–2.077)**[c]	**0.785 (0.716–0.861)**[c]	**1.272 (1.068–1.516)**[c]	**0.689 (0.556–0.852)**[c]	**0.503 (0.368–0.689)**[c]	1.027 (0.817–1.292)	1.025 (0.803–1.308)	**3.229 (2.417–4.315)**[c]	0.995 (0.536–1.847)

ICU, intensive care unit.
[a] Adjusted for age, sex, county of residence, regional health authority, date of admission, country of birth, virus variant, and underlying risk factors (Table 1). The variables included in the final multivariable models were obtained by forward model selection based on the Akaike information criterion (see supplementary materials C).
[b] Not analyzed for age subgroups due to the small number of fully vaccinated patients admitted to ICU in each age subgroup (≤50).
[c] Statistically significant results.

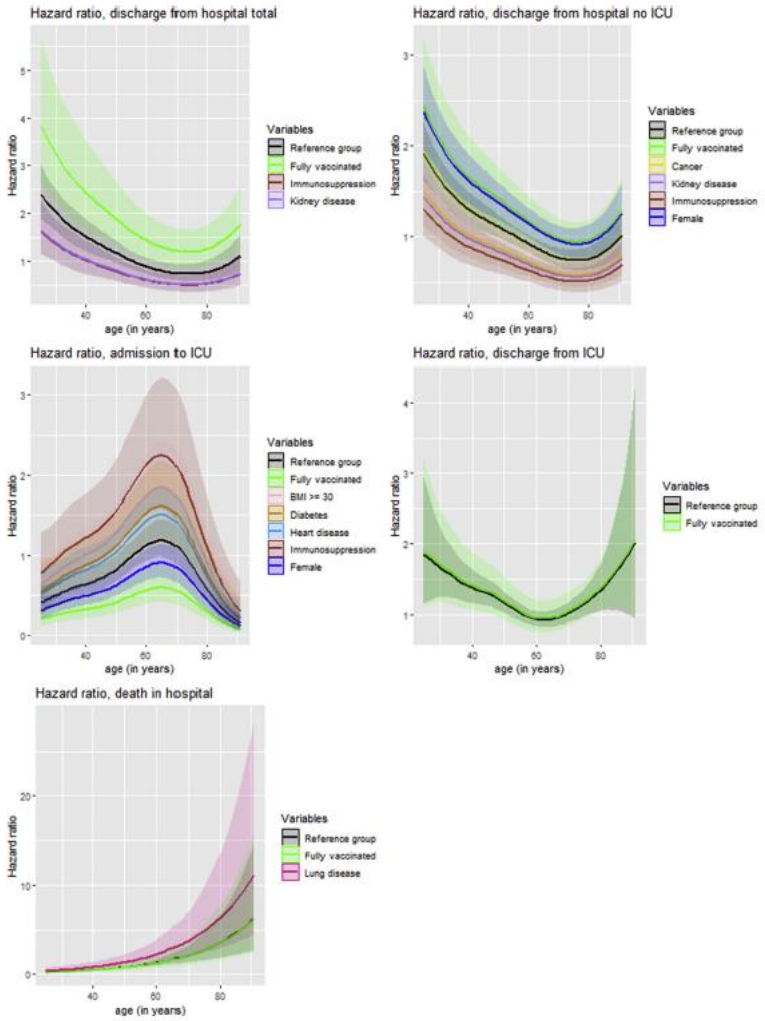

Fig. 1. Adjusted hazard ratios for discharge from hospital with and without stay in ICU, ICU admission, discharge from ICU, and in-hospital death from a Cox proportional hazards model for SARS-CoV-2 positive patients aged ≥18 years hospitalized with COVID-19 as the main cause of hospitalization, by age (Norway, 1 February–30 November 2021). The reference group with a hazard ratio = 1 is patients who are male, aged 56 years (median age in dataset), AND without underlying risk factors and unvaccinated. Hazard ratios were calculated using a Cox proportional hazards model. The variables shown in each panel are those significantly associated with each outcome in multivariable models, which were not stratified on (see supplementary materials C). The Akaike information criterion was used to determine whether age was included linearly or with a spline. ICU, intensive care unit.

not observe a difference between vaccinated and unvaccinated patients aged ≥80 years in adjusted estimates for any outcome.

Results were generally robust in our sensitivity analyses, including when analyzing a period after which all persons in different age subgroups had been offered two vaccine doses (supplementary materials A, part 3).

Discussion

In this study, we find that fully vaccinated patients with COVID-19 in Norway had a shorter LoS in hospital (both with and without ICU admission) and lower risk of ICU admission compared to unvaccinated patients. There was no difference in the LoS in ICU or

risk of in-hospital death. In line with other reports [7,13,14,19], vaccinated patients were generally older and had a higher prevalence of underlying risk factors than unvaccinated patients.

Our results suggest that, once hospitalized, the risk of death among fully vaccinated and unvaccinated patients in Norway is similar. However, for survivors the disease trajectory is milder in fully vaccinated patients, with reduced need for hospital care and organ support. For patients not admitted to ICU, the observed reduction in LoS may have been attenuated by vaccinated patients, who may have ended up in ICU if unvaccinated but now instead spend more time in regular wards.

In our subgroup analyses, patients aged 18–64 years appeared to have larger relative reductions in LoS and risk of ICU admission, although CIs overlapped with estimates for patients aged 65–79 years, and we did not observe an interaction between age and vaccination status in our model for patients aged ≥18 years. Analyses of larger cohorts may better discern if there are differences in the effect of vaccination status on these outcomes by age. For all outcomes, we observed no difference between vaccinated and unvaccinated patients aged ≥80 years. Vaccine effectiveness against hospitalization has been reported to be lower among older age groups in Norway [20]. This age group is also less frequently admitted to ICU, and treatment limitations could confound vaccine effects in the elderly. The small number of unvaccinated patients aged ≥80 years should also be considered. Our results also highlight that factors other than vaccination continue to influence patient outcomes. A longer LoS and/or increased risk of ICU admission or death were associated with advanced age, male sex, and certain risk factors such as immunosuppression, kidney disease, obesity and diabetes, as reported by others [21–24].

These findings build on previous evidence of high vaccine effectiveness against severe disease [1–5,20] and have important implications for patient management and ongoing capacity planning in hospitals. A study including 142 patients fully vaccinated with an mRNA vaccine from 21 sites across the United States also reported a shorter LoS, lower risk of death or invasive mechanical ventilation, and a lower level of clinical disease severity among vaccinated patients [13]. In contrast, a study from Michigan did not find a lower risk of ICU admission, mechanical ventilation, or death when comparing 129 fully vaccinated patients (vaccinated with Comirnaty, Spikevax, or Janssen) to unvaccinated patients [14]. Differences in the study cohorts, setting, and design need to be considered. In this study we compare fully vaccinated and unvaccinated patients; however, vaccination programmes are continuing to evolve, and future analyses are necessary to explore how parameters such as vaccine type, number of doses, time since vaccination, and dose intervals affect patient outcomes between groups of vaccinated patients. Although studies have suggested sustained high effectiveness of mRNA vaccines against hospitalization at least 6 months after vaccination [25,26], the duration of protection after the original two-dose schedules for mRNA vaccines and the effects of booster doses [27,28] require ongoing research.

A strength of our study is that all data sources had national coverage. We also had a notably larger cohort of fully vaccinated patients than previous studies [13,14]. Furthermore, hospitals in Norway functioned within capacity during the study period, and criteria for hospitalization and isolation for COVID-19 patients were consistent and not related to vaccination status. Although we did not have access to treatment data, there were no major changes in treatment guidelines for COVID-19 patients in hospital or ICU in Norway during the study period. We also had minimal censoring, with 2.3% of patients still hospitalized at the end of follow-up.

Our study also has limitations. Although we have controlled for several important confounders, the observational nature has the potential for residual confounding. In addition, our estimated proportional decrease in LoS among fully vaccinated patients is likely slightly underestimated for some age groups and LoS outcomes, as ≤5% of patients did not follow an exponential distribution (see supplementary materials A, part 2). Our fully vaccinated cohort is also predominantly representative of patients who received a homologous two-dose Comirnaty regimen. Moreover, some of our reported underlying risk factors do not distinguish potential differences within groups (e.g. whether risk factors are well regulated or treated). Also, 40% of patients had unknown body mass index. Our model may therefore not fully adjust for certain underlying risk factors. Furthermore, our study cohort does not include care home residents who, in Norway, are recommended to receive treatment for severe COVID-19 in their care home, not in hospital. Finally, previous natural infection has been associated with a high level of protection against SARS-CoV-2 reinfection [29,30]. Although we dropped two reported reinfections, there may have been other previously undiagnosed SARS-CoV-2 infections in our unvaccinated cohort. If present, this may underestimate the effect of vaccination.

Our study suggests that mRNA-vaccinated patients hospitalized with COVID-19 in Norway have a shorter LoS and lower risk of ICU admission than unvaccinated patients. These findings can support patient management and ongoing capacity planning in hospitals and underline the importance of vaccination programmes against COVID-19.

Transparency declaration

The authors declare that they have no competing interests. The authors received no specific funding for this work.

Author contributions

RW, ABK, BVS, ES, RK, and EAB conceived the idea for the study. RW drafted the study protocol and coordinated the study. RK and EAB contributed directly to the acquisition of data. RW and ABK contributed to data cleaning, validation, and preparation. RW and ABK led the data analysis. All co-authors contributed to the interpretation of the results. RW and ABK drafted the manuscript. All co-authors contributed to the revision of the manuscript and approved the final version for submission.

Access to data

The dataset analyzed in the study contains individual-level linked data from various central health registries, national clinical registries, and other national administrative registries in Norway. The researchers had access to the data through the national emergency preparedness registry for COVID-19 (Beredt C19), housed at the Norwegian Institute of Public Health (NIPH). In Beredt C19, only fully anonymized data (i.e. data that are neither directly nor potentially indirectly identifiable) are permitted to be shared publicly. Legal restrictions therefore prevent the researchers from publicly sharing the dataset used in the study that would enable others to replicate the study findings. However, external researchers are freely able to request access to linked data from the same registries from outside the structure of Beredt C19, as per normal procedure for conducting health research on registry data in Norway. Further information on Beredt C19, including contact information for the Beredt C19 project manager and information on access to data from each individual data source, is available at https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.01.033.

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9.1.6 Paper VI

Title: Milder disease trajectory among COVID-19 patients hospitalised with the SARS-CoV-2 Omicron variant compared with the Delta variant in Norway

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Abstract

Using individual-level national registry data, we conducted a cohort study to estimate differences in the length of hospital stay, and risk of admission to an intensive care unit and in-hospital death among patients infected with the SARS-CoV-2 Omicron variant, compared to patients infected with Delta variant in Norway. We included 409 (38%) patients infected with Omicron and 666 (62%) infected with Delta who were hospitalised with COVID-19 as the main cause of hospitalisation between 6 December 2021 and 6 February 2022. Omicron patients had a 48% lower risk of intensive care admission (aHR: 0.52, 95%CI: 0.34–0.80) and a 56% lower risk of in-hospital death (aHR: 0.44, 95%CI: 0.24–0.79) compared to Delta patients. Omicron patients had a shorter length of stay (with or without ICU stay) compared to Delta patients in the age groups from 18–79 years and those who had at least completed their primary vaccination. This supports growing evidence of reduced disease severity among hospitalised Omicron patients compared with Delta patients.

Key words: COVID-19, Omicron, hospitalisation, length of stay, intensive care, severe disease, Norway.

Word count: 1192 words

Introduction

The first coronavirus disease (COVID-19) cases infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant (Phylogenetic Assignment of Named Global Outbreak Lineages (Pangolin) designation B.1.1.529) were detected in Norway on 26 November 2021 (1). By late December, Omicron had superseded the Delta variant (Pangolin designation B.1.617.2) as the dominant circulating variant (2).

In order to provide timely and ongoing support for patient management and capacity planning in hospitals in Norway, we estimated the length of hospital stay (LoS) and risk of admission to an

intensive care unit (ICU) and in-hospital death among hospitalised patients infected with Omicron, compared to patients infected with Delta.

Methods

Study population

We conducted a cohort study on patients hospitalised with a positive SARS-CoV-2 test between 6 December 2021 and 6 February 2022. We included patients for whom COVID-19 was reported as the main cause of hospitalisation, who were known to be infected with the Omicron or Delta variant and who had a national identity number registered.

Data sources

We extracted data from the Norwegian national emergency preparedness registry – Beredt C19 (3). This registry contains individual-level national data on all COVID-19 related hospitalisations, ICU admissions and deaths. Further details on the data sources and definitions, including the categorisation of variants, can be found in supplement A, section 1. Data were extracted on 15 February 2022, allowing a minimum 8 days of follow-up since last date of hospitalisation.

Data analysis

Full details on the data analysis are presented in supplementary material A, section 2. Briefly, our outcomes were discharge from hospital (with and without ICU stay), admission to ICU, in-hospital death and a composite measure of ICU admission or in-hospital death. LoS was calculated as the time between first admission and last discharge. To estimate differences in our outcomes we calculated adjusted hazard ratios (aHR) using a Cox proportional hazards model. Explanatory variables included virus variant, sex, age, country of birth, underlying risk factors, regional health authority and vaccination status (see table 1). We also conducted subgroup analysis by age group and vaccination

status for subgroups with ≥50 omicron and ≥50 delta patients, and ≥10 outcomes. Estimates from the univariable model for all patients and all multivariable models are presented in supplement B.

We also assessed the representativeness of patients with known variant among all COVID-19 patients in the study period (supplementary material A, section 3).

Ethics

Ethical approval was granted by Regional Committees for Medical Research Ethics - Southeast Norway, reference number 249509.

Results

During the study period, 1747 patients were hospitalised with COVID-19 as the main cause of hospitalisation. Of these, 1710 (98%) had a national identity number, of which 1079 (63%) had known variant. Our study cohort comprised 409 Omicron (38%) and 666 Delta patients (62%). We excluded three patients reported to be infected with another variant, and one Delta patient with a date of positive test two months before hospitalisation. The median number of days from positive test to admission was 0 (interquartile range (IQR): 0–1) for Omicron patients and 4 (IQR: 0–7) for Delta patients. Detailed characteristics of the study cohort are presented in table 1. Descriptive results for each outcome by subgroup are presented in table 2.

Omicron patients had a 48% lower risk of ICU admission (aHR: 0.52, 95%CI: 0.34–0.80) and a 56% lower risk of in-hospital death (aHR: 0.44, 95%CI: 0.24–0.79), compared to Delta patients. By age subgroup, Omicron patients 18–79 years had a lower risk of ICU admission than Delta patients. We did not observe a difference in the risk of death between Omicron and Delta patients 65–79 years old. Patients ≥80 years were infrequently admitted to ICU, but Omicron patients had a lower risk of death than Delta patients. Omicron patients vaccinated with three doses had an 80% lower risk of

ICU admission (aHR: 0.20, 95%CI: 0.08–0.47), and a 70% lower risk of in-hospital death (aHR: 0.30, 95%CI: 0.11–0.83). Results tended in the same direction for unvaccinated patients (aHR for ICU admission or death: 0.51, 95%CI: 0.26–0.98). We did not observe a difference in the risk of ICU admission or death between Omicron and Delta patients who had completed primary vaccination with maximum two doses (table 3).

In the multivariable model including all patients, the variable 'variant' did not satisfy the proportional hazards assumption for either LoS outcome. However, our subgroup analysis suggested a shorter LoS (with or without ICU stay) for Omicron patients compared to Delta patients in the age subgroups 18–79 years and those who had completed primary vaccination. For example, for Omicron patients vaccinated with three doses the aHR for discharge overall was 1.58 (95%CI: 1.16–2.17). Assuming exponential distribution of the survival data (see supplement A, part 2.3), this translates into an expected 37% (95%CI: 14%–54%) shorter overall LoS for Omicron patients (1-(1/1.58)) (table 3).

Discussion

We find that hospitalised COVID-19 patients infected with the Omicron variant have a milder disease trajectory than patients infected with Delta in Norway. This supports the growing evidence of reduced disease severity among those infected with Omicron (2;4-8). Results from similar studies in South Africa, USA and France have also reported a reduction in the median LoS, risk of ICU admission and/or death among Omicron patients compared to Delta patients (9-12).

Our subgroup analyses generally supported the main results, although we did not observe any difference in the risk of ICU admission or death between Omicron and Delta patients who had completed primary vaccination with maximum two doses. This may be in line with evidence of reduced vaccine effectiveness against infection with Omicron (13-15), and in Norway we have

previously observed similar results when analysing the risk of hospitalisation among reported COVID-19 cases (2). However, we did not observe an interaction between variant and vaccination status in this study, while the size of each subgroup must be considered. Such relationships should be further explored in larger patient cohorts.

We have analysed national data from a cohort of patients with known variant data, encompassing 63% of all hospitalisations due to COVID-19 in the study period. One limitation with our study is that a higher proportion of patients admitted to ICU had known variant (see supplement A, part 3). Given the increased risk of ICU admission for Delta patients, we may have oversampled severely ill Delta patients, which may cause us to slightly overestimate the reduction in our outcomes for Omicron patients. Another important limitation is that we could not distinguish sublineage BA.1 and BA.2 for all Omicron patients. In Norway BA.2 has gradually begun to outcompete BA.1 (16). However, up to the end of the study period, BA.1 was still the dominant circulating Omicron sublineage, and our results were robust when we excluded 57 patients known to be infected with BA.2 (see supplement A, part 2.4). Further studies are needed to investigate whether disease severity differs between Omicron sublineages.

Evidence of lower disease severity among hospitalised Omicron patients in Norway and elsewhere is encouraging in the ongoing response to the COVID-19 pandemic. Analyses of circulating variants in a local context are important for informing decision-making on control measures and hospital capacity planning in different settings.

Notes and acknowledgements

Authors' contributions

All co-authors were involved in the conceptualisation of the study. RW coordinated the study. OH, RK, KB and EB contributed to the acquisition of data. LV, HB, JS, OH, NA, ES, KB and RW contributed to data cleaning, verification and/or preparation. ABK, JS, ES, HB, LV and RW had access to the final linked dataset. ABK conducted the statistical analysis in consultation with JS and RW. JS and RW drafted the manuscript. All co-authors contributed to the interpretation of the results. All co-authors contributed to the revision of the manuscript and approved the final version for submission.

Conflict of interest

The authors declare that they have no competing interests.

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Data sharing statement

The dataset analysed in the study contains individual-level linked data from various central health registries, national clinical registries and other national administrative registries in Norway. The researchers had access to the data through the national emergency preparedness registry for COVID-19 (Beredt C19), housed at the Norwegian Institute of Public Health (NIPH). In Beredt C19, only fully anonymised data (i.e. data that are neither directly nor potentially indirectly identifiable) are permitted to be shared publicly. Legal restrictions therefore prevent the researchers from publicly sharing the dataset used in the study that would enable others to replicate the study findings. However, external researchers are freely able to request access to linked data from the same registries from outside the structure of Beredt C19, as per normal procedure for conducting health

research on registry data in Norway. Further information on Beredt C19, including contact information for the Beredt C19 project manager, and information on access to data from each individual data source, is available at https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/.

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First and foremost, we wish to thank all those who have helped report data to the national emergency preparedness registry at the Norwegian Institute of Public Health (NIPH) throughout the pandemic. We also highly acknowledge the efforts that regional laboratories have put into establishing a routine variant screening procedure or whole genome sequencing at short notice and registration of all analysis in national registries for surveillance. Thanks also to the staff at the Virology and Bacteriology departments at NIPH involved in national variant identification and whole genome analysis of SARS-CoV-2 viruses. We also highly acknowledge the efforts of staff at hospitals around Norway to ensure the reporting of timely and complete data to the Norwegian Intensive Care and Pandemic Registry, as well as colleagues at the register itself. We would also like to thank Anja Elsrud Schou Lindman, project director for the national preparedness registry, and all those who have enabled data transfer to this registry, especially Gutorm Høgåsen at the NIPH, who has been in charge of the establishment and administration of the registry.

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Tables and figures

Table 1. Characteristics of patients hospitalised with COVID-19 as the main cause of hospitalisation and infected with the SASRS-CoV-2 omicron or delta variant, by variant, Norway, 6 December 2021 – 6 February 2022 (n=1075)

Characteristics		Variant		
		Omicron (n=409)	Delta (n=666)	p value
Sex	Male	196 (47.9%)	389 (58.4%)	<0.001
	Female	213 (52.1%)	277 (41.6%)	
Age group	0-17 years	44 (10.8%)	15 (2.3%)	<0.001
	18-29 years	31 (7.6%)	27 (4.1%)	
	30-44 years	68 (16.6%)	123 (18.5%)	
	45-54 years	61 (14.9%)	99 (14.9%)	
	55-64 years	46 (11.2%)	137 (20.6%)	
	65-79 years	91 (22.2%)	177 (26.6%)	
	≥80 years	68 (16.6%)	88 (13.2%)	
Median age	In years (IQR)	55 (35–75)	59 (45–73)	0.010
Born in Norway	Yes, with at least one parent born in Norway	257 (62.8%)	370 (55.6%)	<0.001
	Yes, two parents born outside of Norway	19 (4.6%)	14 (2.1%)	
	No	106 (25.9%)	250 (37.5%)	
	Unknown	27 (6.6%)	32 (4.8%)	
Underlying risk factors	Asthma	46 (11.2%)	62 (9.3%)	0.305
	Cancer [a]	51 (12.5%)	33 (5.0%)	<0.001
	Chronic lung disease, excluding asthma	65 (15.9%)	76 (11.4%)	0.035
	Chronic neurological or neuromuscular disease	31 (7.6%)	62 (9.3%)	0.367
	Diabetes (type 1 and 2)	68 (16.6%)	102 (15.3%)	0.327

	Heart disease, including hypertension	147 (35.9%)	232 (34.8%)	0.712
	Immunosuppression, including HIV and immunosuppressive treatment [b]	55 (13.4%)	65 (9.8%)	0.062
	Kidney disease, including kidney failure	58 (14.2%)	67 (10.1%)	0.041
	Liver disease, including liver failure	10 (2.4%)	12 (1.8%)	0.470
	BMI ≥30 [c]	57 (13.9%)	144 (21.6%)	0.119
	Pregnant	19 (4.6%)	15 (2.3%)	0.029
	Current smoker	22 (5.4%)	41 (6.2%)	0.598
Vaccination status [d]	Not vaccinated	99 (24.2%)	401 (60.2%)	<0.001
	One dose <21 days before positive test	4 (1.0%)	9 (1.4%)	
	Partially completed primary vaccination series ≥21 days before positive test	8 (2.0%)	10 (1.5%)	
	Completed primary vaccination series with maximum two doses 7–179 days before positive test	77 (18.8%)	63 (9.5%)	
	Completed primary vaccination series with maximum two doses≥180 days before positive test	69 (16.9%)	111 (16.7%)	

	Vaccinated with three doses ≥7 days before positive test	152 (37.2%)	71 (10.7%)	
	Unvaccinated, but previously diagnosed with COVID-19 6–12 months before positive test	0 (0.0%)	1 (0.2%)	
Week of admission	49/2021	2 (0.5%)	164 (24.6%)	<0.001
	50/2021	3 (0.7%)	168 (25.2%)	
	51/2021	6 (1.5%)	132 (19.8%)	
	52/2021	32 (7.8%)	97 (14.6%)	
	1/2022	49 (12.0%)	61 (9.2%)	
	2/2022	60 (14.7%)	28 (4.2%)	
	3/2022	56 (13.7%)	9 (1.4%)	
	4/2022	94 (23.0%)	5 (0.8%)	
	5/2022	107 (26.2%)	2 (0.3%)	
Regional health authority	South-East	248 (60.6%)	462 (69.4%)	<0.001
	West	70 (17.1%)	138 (20.7%)	
	Mid	70 (17.1%)	39 (5.9%)	
	North	21 (5.1%)	27 (4.1%)	
Admission to ICU	No	378 (92.4%)	501 (75.2%)	<0.001
	Yes	31 (7.6%)	165 (24.8%)	
Death [a]	Died in ICU	4 (1.1%)	20 (3.2%)	0.002
	Died in hospital, not in ICU	11 (2.9%)	43 (6.8%)	
	Alive at discharge	364 (96.0%)	568 (90.0%)	
Status at end of follow-up (14 February 2022)	In ICU	5 (1.2%)	8 (1.2%)	0.311
	In hospital, not in ICU	25 (6.1%)	27 (4.1%)	
	Discharged from hospital	379 (92.7%)	631 (94.7%)	

IQR: interquartile range; ICU: Intensive care unit; BMI: Body mass index. P values comparing patients with Omicron and Delta calculated using chi-squared tests or Wilcoxon rank sum tests as appropriate.

[a] Refers to cancer patients undergoing treatment or with regular controls (>1 per year).

[b] Includes ongoing use of steroids in doses equivalent to at least 5mg Prednisolone daily.

[c] In our dataset, 215 (52,6%) omicron patients and 264 (39,6%) delta patients had unknown information on height and weight, and thus unknown data on BMI. BMI ≥30 was therefore included as a three-level categorical variable in the models; yes, no and unknown.

[d] Data on vaccine type among vaccinated patients are presented in supplement A, part 1. Among the 298 Omicron and 245 Delta patients who had completed their primary vaccination series, 99% had received a homologous or mixed mRNA vaccine regimen.

[e] Excludes patients still in hospital at end of follow-up.

Table 2 Number of patients, median number of days from admission to discharge from hospital, admissions to ICU and deaths in hospital among patients admitted to hospital with COVID-19 as the main cause of hospitalisation, by variant and subgroup, Norway, 6 December 2021 – 6 February 2022

	Omicron						Delta					
	Number of patients	Median number of days from admission to discharge from hospital [IQR] [a]	Median number of days from admission to discharge, patients not admitted to ICU [IQR] [a]	Number admitted to ICU [%]	Number of deaths in hospital [%] [b]		Number of patients	Median number of days from admission to discharge from hospital [IQR] [a]	Median number of days from admission to discharge, patients not admitted to ICU [IQR] [a]	Number admitted to ICU [%]	Number of deaths in hospital [%] [b]	
All patients	409	2.82 (1.49–6.24)	2.64 (1.30–4.94)	31 (7.6%)	15 (4.0%)		666	5.93 (3.01–11.98)	4.61 (2.50–7.77)	165 (24.8%)	70 (10.5%)	
Age groups												
– <18 years	44	[c]	[c]	[c]	[c]		15	[c]	[c]	[c]	[c]	
– 18–44 years	99	1.81 (0.83–3.00)	1.80 (0.82–2.92)	4 (4.0%)	0 (0%)		150	4.68 (2.67–8.12)	3.61 (1.93–5.90)	27 (18.0%)	1 (0%)	
– 45–64 years	107	2.79 (1.67–7.64)	2.63 (1.53–6.69)	9 (8.4%)	3 (3.1%)		236	7.22 (3.27–15.10)	4.61 (2.50–8.00)	78 (33.1%)	5 (2.3%)	

– 65–79 years	91	4.16 (2.10–7.84)	3.97 (2.06–6.52)	11 (12.1%)	5 (6.2%)	177	7.42 (3.88–13.65)	6.08 (3.15–9.76)	48 (27.1%)	23 (12.6%)		
– ≥80 years	68	3.82 (2.05–7.66)	3.82 (2.05–8.08)	3 (4.4%)	7 (11.1%)	88	5.24 (2.76–8.31)	4.56 (2.72–7.77)	11 (12.5%)	36 (40.9%)		
Vaccination status												
– Unvaccinated	99	2.27 (0.88–4.31)	2.13 (0.83–3.71)	8 (8.1%)	3 (3.2%)	401	6.68 (3.15–12.35)	4.87 (2.76–7.88)	117 (29.2%)	81 (8.4%)		
– One dose <21 days before positive test	4	"	"	"	"	9	"	"	"	"		
– Partially completed primary vaccination series ≥21 days before positive test	8	"	"	"	"	10	"	"	"	"		
– Completed primary vaccination series with maximum two doses 7–179 days before positive test	77	1.88 (0.97–2.92)	1.83 (0.92–2.72)	6 (7.6%)	1 (1.4%)	63	4.40 (1.38–6.93)	3.16 (1.21–6.08)	11 (17.5%)	5 (5.2%)		
– Completed primary vaccination series with maximum two doses≥180 days before positive test	659	3.82 (2.06–6.94)	3.05 (1.86–6.07)	9 (13.0%)	3 (4.6%)	111	4.88 (2.71–10.80)	4.00 (2.09–7.77)	15 (13.5%)	16 (16.0%)		
– Vaccinated with three doses≥7 days before positive test	152	3.79 (1.90–7.57)	3.61 (1.86–7.12)	7 (4.6%)	8 (5.8%)	71	6.94 (3.20–13.22)	5.24 (2.56–9.76)	18 (25.4%)	10 (14.9%)		

–	Unvaccinated, but previously diagnosed with COVID-19 6–12 months before positive test	0	"	"	"	"	"	1	"	"	"	"

IQR: interquartile range; ICU: intensive care unit.

[a] Estimates from univariable Cox regression.

[b] Crude proportions calculated excluding those still admitted at the end of the study period. All patients: 30 Omicron, 35 Delta; 18–44 years: 2 Omicron, 6 Delta; 45–64 years: 11 Omicron, 19 Delta; 65–79 years: 10 Omicron, 10 Delta; ≥80 years: 5 Omicron, 0 Delta; Unvaccinated: 6 Omicron, 21 Delta; Completed primary vaccination series with maximum two doses 7–179 days before positive test: 4 Omicron, 5 Delta; Completed primary vaccination series with maximum two doses≥180 days before positive test: 4 Omicron, 5 Delta; Vaccinated with three dose≥27 days before positive test: 15 Omicron, 4 Delta.

[c] Subgroup analysis not conducted due to small sample size (<50 omicron and/or <50 delta patients and/or <10 outcomes).

Table 3 Crude and adjusted hazard ratios for discharge from hospital with and without stay in intensive care, intensive care admission and/or in-hospital death from a Cox proportional hazards model, patients admitted to hospital with omicron variant compared with patients admitted with delta variant of SARS-CoV-2, overall and by subgroup, Norway, 6 December 2021 – 6 February 2022

	Discharge from hospital		Discharge from hospital, patients not admitted to ICU		Admission to ICU		Death in hospital		ICU admission OR death in hospital	
	Crude hazard ratio (95%CI)	Adjusted hazard ratio (95%CI)	Crude hazard ratio (95%CI)	Adjusted hazard ratio (95%CI)	Crude hazard ratio (95%CI)	Adjusted hazard ratio (95%CI)	Crude hazard ratio (95%CI)	Adjusted hazard ratio (95%CI)	Crude hazard ratio (95%CI)	Adjusted hazard ratio (95%CI)
All patients	**1.77 (1.55–2.02)**	[a]	**1.44 (1.26–1.65)**	[a]	**0.33 (0.23–0.49)**	**0.52 (0.34–0.80)**	0.83 (0.47–1.47)	**0.44 (0.24–0.79)**	**0.38 (0.27–0.53)**	**0.45 (0.32–0.64)**
Age groups										
– <18 years	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	
– 18-44 years	**2.32 (1.78–3.03)**	**1.98 (1.44–2.71)**	**1.98 (1.50 -2.61)**	**2.40 (1.80–3.19)**	**0.31 (0.11–0.90)**	**0.31 (0.11-0.90)**	[b]	[b]	**0.31 (0.11–0.90)**	**0.31 (0.11-0.90)**
– 45-64 years	**1.87 (1.46–2.39)**	**1.56 (1.14–2.13)**	**1.33 (1.02–1.73)**	1.26 (0.92–1.72)	**0.25 (0.13–0.50)**	**0.38 (0.17–0.83)**	[b]	[b]	**0.27 (0.14–0.52)**	**0.35 (0.17–0.78)**
– 65-79 years	**1.47 (1.12–1.92)**	1.19 (0.87–1.64)	**1.33 (1.00–1.78)**	**1.13 (1.00–1.78)**	**0.47 (0.24–0.90)**	**0.47 (0.24–0.90)**	0.92 (0.34–2.47)	0.67 (0.24–1.88)	**0.55 (0.31–0.98)**	0.73 (0.37–1.14)
– ≥80 years	1.20	1.20	1.09	1.05	0.37	0.31	**0.32**	**0.26**	**0.33**	**0.31**

Vaccination status																					
– Unvaccinated		**2.42**			**1.97**																**0.51**
		(1.92–3.05)			**(1.54–2.50)**																**(0.26–0.98)**
– One dose <21 days before positive test		[a]			[a]			[a]			[a]			[a]			[a]			[a]	[a]
– Partially completed primary vaccination series ≥21 days before positive test		[a]			[a]			[a]			[a]			[a]			[a]			[a]	[a]
– Completed primary vaccination series with maximum two doses 7–179 days before positive test		**1.80**		1.46	**1.97**		**1.63**		0.57		0.73		1.17		0.44		0.50		0.78		0.48
		(1.26–2.55)		(0.99–2.14)	**(1.35–2.88)**		**(1.10–2.42)**		(0.21–1.58)		(0.25–2.12)		(0.51–2.67)		(0.13–1.50)		(0.14–1.74)		(0.38–1.61)		(0.31–1.39)
– Completed primary vaccination series with maximum two doses ≥180 days before positive test		1.32		1.34	1.32		**1.41**		1.17		1.17		1.17		0.44		0.50		0.78		0.48
		(0.96–1.80)		(0.98–1.83)	(0.95–1.83)		**(1.01–1.97)**		(0.51–2.67)		(0.51–2.67)		(0.51–2.67)		(0.13–1.50)		(0.14–1.74)		(0.38–1.61)		(0.31–1.39)

–	Vaccinated with three doses≥7 days before positive test	**1.58 (1.18–2.14)**	"	**1.58 (1.16–2.17)**	"	1.17 (0.85–1.62)	"	1.22 (0.88–1.68)	**0.19 (0.08–0.46)**	"	**0.20 (0.08–0.47)**	0.67 (0.26–1.74)	**0.30 (0.11–0.83)**	**0.28 (0.15–0.54)**	**0.28 (0.15–0.54)**
–	Unvaccinated, but previously diagnosed with COVID-19 6–12 months before positive test	"	"	"	"	"	"	"	"	"	"	"	"	"	"

ICU: intensive care unit; 95%CI: 95% confidence interval. Bold text = statistically significant results. Estimates from the univariable model for all patients and all multivariable models are presented in supplement B.

[a] Adjusted estimates not presented as the variable 'variant' had to be stratified in this model to satisfy the proportional hazards assumption.

[b] Subgroup analysis not conducted due to small sample size (<50 omicron and/or <50 delta patients and/or <10 outcomes).

9.2 Study protocol for papers III – VI

Versjon 4. *11.04.2022*

Prosjekt i Team Overvåking i Beredt C19:
Sykdomsforløpet blant påviste tilfeller av SARS-CoV-2 infeksjon i Norge

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Formål

Det første tilfellet av påvist SARS-CoV-2-infeksjon i Norge ble bekreftet 21. februar 2020. Per april 2022 har over 11000 pasienter blitt innlagt i sykehus med covid-19 som hovedårsak og over 2500 covid-19-relaterte-dødsfall har blitt varslet (1). Forekomst av alvorlig sykdom og den følgende belastningen i helsetjenesten er en av de viktigste og alvorligste konsekvensene av covid-19 pandemien. I begynnelsen av pandemien viste risikoen for alvorlig sykdom og dødsfall seg til å være høyere for eldre personer, menn, personer med visse underliggende sykdommer, og visse innvandrergrupper (2-5). Gjennom pandemien har ytterligere faktorer begynt å påvirke denne risikoen f.eks. vaksinasjon mot covid-19, samt hvilken variant av SARS-CoV-2 som er dominerende (6-9). Vaksinasjon og hvilken variant av SARS-CoV-2 som er dominerende påvirker også risikoen for å bli reinfisert med SARS-CoV-2 (10, 11). Per april 2022 har over 50000 SARS-CoV-2 reinfeksjoner blitt registrert ved Folkehelseinstituttet (FHI) (1).

Vårt formål er å undersøke ulike utfall og tidsintervaller relatert til sykdomsforløpet blant påviste tilfeller av SARS-CoV-2 infeksjon i Norge, i ulike grupper og over tid, for å bedre forstå påvirkningen epidemien har på de smittede og på helsetjenesten, for planlegging ved sykehusene, og for videre håndteringen av epidemien i landet.

Problemstillinger:

1. Hva er risikoen for reinfeksjon og/eller alvorlig sykdom hos personer smittet med SARS-CoV-2 i Norge, og hvordan varierer disse risikoer mellom ulike grupper?
2. Hvilke faktorer predikerer utfall hos personer som har vært innlagt i sykehus med covid-19 sykdom i Norge?

Metode

Studiepopulasjon

Personer som har fått påvist SARS-CoV-2 infeksjon i Norge siden begynnelsen av covid-19-epidemien i landet.

Studiedesign

Register-basert kohortstudie i Beredskapsregistret Beredt C19.

Datakildene

Denne studien vil være basert på en kobling av Meldingssystemet for smittsomme sykdommer (MSIS), MSIS-labdatabase, Norsk intensiv- og pandemiregister (NIPaR), Folkeregistret, Nasjonalt vaksinasjonsregister (SYSVAK), Beredt C19 sin datatabell om risikogrupper (Risikogruppe-tabellen), Beredt C19 sin tabell om helsepersonell (Helsepersonell-tabellen), Norsk pasientregister (NPR), Statistisk sentralbyrå (SSB) og Dødsårsaksregistret (DÅR). Alle registrene/datatabeller inngår i Beredt C19, opprettet ved FHI (8).

MSIS: et sentralt helseregister. Fra MSIS henter Beredt C19 daglig informasjon om positive covid-19-tilfeller og opplysninger som prøvedato, alder, kjønn, bosted, smittested og fødeland. Kriterier for melding er påvisning av SARS-CoV-2 ved isolering, nukleinsyreundersøkelse eller antigenpåvisning i klinisk prøvemateriale (12).

MSIS-labdatabase: I forbindelse med covid-19-pandemien har FHI opprettet en nasjonal laboratoriedatabase som mottar koronaprøvesvar fra samtlige diagnostiske laboratorier og helsetjenester i Norge (13). I Beredt C19 inngår opplysninger om prøver og prøveresultat for covid-19 (både virus, antigen og antistoff). FHI helgenomsekvenserer virus i prøver som sendes inn til det nasjonale referanselaboratoriet for overvåking av pandemien. I tillegg gjør

diagnostiske laboratorier i Norge PCR screeninger, delgenom- og helgenomsekvensering. Underliggende metode for variantresultatet kan både være PCR screening eller gensekvensanalyser. Tabellene LabC19Virus_Resultat, LabC19Antigen_Resultat, LabC19Variant_Resultat og LabC19Antistoff_Resultat i Beredt C19 inneholder prøvesvar på henholdsvis PCR, antigen, variant og antistoff. Nye bekymringsvarianter vil inkluderes som separate verdier i datasettet etter hvert når de blir oppdaget og kategorisert.

NIPaR: et nasjonalt medisinsk kvalitetsregister. Registret samler inn data om pasienter innlagt i sykehus og intensivavdelinger med covid-19. Alle sykehus i landet har rapporteringsplikt til registret. På nettsidene til Helse Bergen kan man lese om formålet med registeret. Her finner man også informasjon om hva som registreres for henholdsvis intensivdelen (NIR) og pandemidelen (NoPaR – dvs. sykehusinnleggelser) (14).

- https://helse-bergen.no/norsk-pandemiregister
- https://helse-bergen.no/norsk-intensivregister-nir

Folkeregistret: inneholder informasjon om alle som er bosatt eller har bodd i Norge. Disse dataene vil hjelpe oss til å identifisere hvis personer ikke fremkommer i de andre registre, fordi de manglet fødselsnummer eller D-nummer (og derfor ikke kan bli koblet). De vil også hjelpe oss til å kontrollere for 1. (født utenfor Norge) og 2. (født i Norge til foreldre født i utlandet) generasjons innvandrere i analysen.

SYSVAK: et landsdekkende elektronisk vaksinasjonsregister, og et sentralt helseregister. Disse dataene er nødvendige for å kunne ta hensyn til hver persons vaksinasjonsstatus i analysen. Registret sender data om personer vaksinert mot covid-19 til Beredt C19. Den første covid-19-vaksinedosen ble satt 27. desember 2020.

Risikogruppe-tabellen: Denne tabellen inneholder en liste over alle personer registrert med fødselsnummer i folkeregistret, som er i medisinsk risikogruppe for alvorlig covid-19 sykdom, og hvilken risikogruppe(r) de tilhører. Datasettet lages internt i Beredt C19, basert på ICD-10 and ICPC-2 koder fra NPR og Kommunalt pasient- og brukerregister. Risikogruppene er definert etter risikogruppene til covid-19-vaksinasjonsprogrammet. Dataene trengs for å kunne kontrollere for risikogrupper i analyser der alle som har fått påvist SARS-CoV-2 er utvalget, fordi disse dataene ikke er tilgjengelig i MSIS eller MSIS-labdatabase. Tilsvarende analyser om innlagte pasienter med NPR som utvalgsdatasettet vil også kreve bruk av risikogruppe-tabellen. I analyser basert på NIPaR data kan data om risikofaktorer registrert direkte i NIPaR benyttes.

NPR: inneholder helseopplysninger om alle personer som har fått behandling, eller som venter på behandling i spesialisthelsetjenesten i Norge. Data fra NPR vil være viktige for å kunne identifisere personer som har blitt innlagt i sykehus med covid-19, og tilfeller av MIS-C (Multisystem inflammatory syndrome in children), en alvorlig sykdomstilstand etter covid-19 smitte blant barn. ICD-10 kodene for covid-19 er U071 og U072. ICD-10 koden for MIS-C er U109, men andre koder (f.eks. M303, A483, I412 og D761) blant pasienter som også var positiv for SARS-CoV-2 virus eller antistoff kan også identifisere MIS-C tilfeller tidligere i pandemien før U109 kom i bruk i ca. oktober 2020. Prosedyrekoder GXAV (GXAV01, GXAV10, GXAV20 og GXAV30) fra kodeverk NCSP/NCMP/NCRP vil være nødvendige for å identifisere pasienter på ventilasjonsstøtte. Den nye særkoden B0050 (innlagt i intensivenhet) vil inkluderes dersom det blir tilgjengelig i Beredt ved et senere tidspunkt. Analyseteams i Beredt har kun tilgang til et fåtall diagnose- og prosedyrekoder fra NPR jf. prinsippet om dataminimering i Beredt C19.

Helsepersonell-tabellen: lages internt i Beredt C19, og er basert på Arbeidsgiver- og arbeidstakerregisteret. Tabellen har opplysninger om arbeidsforhold i Norge (yrke, arbeidssted og arbeidstid). Opplysninger fra helsepersonell-tabellen er nødvendige for at vi blant annet skal kunne skille helsearbeidere fra andre i analysene om risiko for reinfeksjon.

SSB: Data om trangboddhet er inkludert slik at vi kan se på om denne faktoren er assosiert med risiko for reinfeksjon.

DÅR: inneholder opplysninger om dødsårsaker i Norge. Data fra DÅR vil være nødvendige for å identifisere covid-19-relaterte dødsfall. Fra mars 2022 er covid-19-relaterte dødsfall i Norge kun definert basert på data fra DÅR (Dødsfall hvor ICD-10 kode U071, U072, U099 eller U109 er angitt på dødsattesten). Se https://www.fhi.no/nyheter/2022/endring-i-registreringen-av-covid-19-assosierte-dodsfall/

Datainnsamling

Datainnsamlingen skjer fortløpende. Per april 2022, er data fra MSIS, NoPaR, NIR, SYSVAK, risikogruppe-tabellen og NPR oppdatert daglig i Beredt C19. Data fra MSIS-Labdatabasen oppdateres to ganger per uke. Folkeregistret og DÅR oppdateres ukentlig. SSB data om trangboddhet var sist oppdatert i Beredt i mars 2021. Helsepersonell-tabellen oppdateres med uregelmessig mellomrom.

Registerkoblingsprosedyren

Registerkoblingen skal gjøres i Team Overvåking i Beredt C19. Individdata benyttes i Beredt C19, men uten direkte personidentifiserende kjennetegn. Medlemmer i ulike team i Beredt C19 med tilgang til Beredt C19-databasen, kan via databasen koble datakilder som det er innvilget koblingsrett for. Koblingsnøkler, laget med en irreversibel hash-algoritme basert på fødselsnummer eller D-nummer, er unike for hvert team, og det skal ikke kobles data ut over de det er innvilget koblingsrett for. Prosjektgruppen vil ikke ha tilgang til direkte identifiserende personopplysninger, som fødselsnummer eller D-nummer. Team Overvåking er innvilget koblingsrett for data fra bl.a. MSIS (gjennom variabel Fnr_hash), MSIS-lab (Fnr_hash), NoPaR (PasientGUID_hash), NIR (PatientInRegistryGuid_hash), Folkeregistret (Fnr_hash), SYSVAK (Fnr_hash), risikogruppe-tabellen (Fnr_hash), NPR (persId_hash), helsepersonell tabellen (Fnr_hash) og DÅR (Fnr_hash). I Beredt C19 er NPR data delt opp i ulike datatabeller som også må kobles sammen via andre koblingsnøkler som nprProsedyreId. Koblingen vil bli utført av medarbeiderne fra FHI som har tilgang til dataene gjennom Team Overvåking. Medarbeiderne fra utenfor Team Overvåking vil ikke ha mulighet til å koble datakildene, eller få tilgang til det koblete datasettet. De vil kun ta del av anonymiserte resultat. Per april 2022 har Team Overvåking ikke tilgang til data fra Beredt tabellen SSB om trangboddhet (boforhold). Data fra denne tabellen vil kun inkluderes i prosjektet dersom Team Overvåking får innvilget koblingsrett for denne tabellen av styringsgruppen i Beredt.

Analyseplan

Variabler

Variablene i Beredt C19 som foreløpig er nødvendige for vask av dataene og/eller analysene per april 2022 er:

- MSIS
  - Fnr_hash
  - Innsykningsdato
  - Innsykningsdatokvalitet
  - Indikasjon
  - Prøvedato
  - Prøvedatokvalitet
  - Metode
  - AlderÅr
  - Kjønn

  - Fødeland
  - Bostedskommune
  - Smittested
  - DødsDato
  - Utfall
  - ErReinfeksjon
- MSIS-labdatabase (tabell LabC19Virus_Resultat, tabell LabC19Antigen_Resultat, tabell LabC19Variant_Resultat, tabell LabC19Antistoff_Resultat)
  - Fnr_hash
  - Fødselsdato
  - Laboratorium
  - LabId
  - Prøvedato
  - Opprettettidspunkt
  - Svardato
  - Prøvenummer
  - Resultat
  - Beskrivelse
  - Helgenomsekvensert
  - Kode
  - ErPositiv
  - Bostedskommune
  - Bostedskommunenummer
  - AlderIÅr
  - KjønnKode
  - Identtype
- NoPaR
  - PasientGUID_hash
  - PatientAge
  - PatientGender
  - FormDate
  - FormDateUt
  - Utskrivningsdato
  - FormStatus
  - FormStatusUt
  - ArsakInnleggelse
  - Helseforetak (HF)
  - Regionalt helseforetak (RHF)
  - Astma
  - Diabetes
  - Gravid
  - Hjertesykdom
  - KjentRisikofaktor
  - Kreft
  - KroniskLungesykdom
  - KroniskNevro
  - Leversykdom
  - Municipal (bostedskommune)

  - NedsattimmunHIV
  - Nyresykdom
  - Royker
  - Hoyde
  - Vekt
  - StatusVedUtskriving
  - FoerstePositivProeve
- NIR
  - PatientInRegistryGuid_hash
  - PatientAge
  - PatientGender
  - Diagnosis
  - FormDate
  - DateDischargedIntensive
  - FormStatus
  - HF
  - RHF
  - Municipal (bostedskommune)
  - Astma
  - Diabetes
  - Kreft
  - ImpairedImmuneSystemIncHiv
  - HeartDiseaseIncHypertension
  - IsObesePatient
  - IsChronicLungDiseasePatient
  - KidneyDiseaseIncFailure
  - LiverDiseaseIncFailure
  - ChronicNeurologicNeuromuscular
  - Graviditet
  - IsActivSmoker
  - MechanicalRespirator
  - MechanicalRespiratorStart
  - MechanicalRespiratorEnd
  - IsEcmoTreatmentAdministered
  - EcmoStart
  - EcmoEnd
  - Morsdato
  - DischargedIntensivStatus
- Folkeregistret
  - Fnr_hash
  - FodselsnummerType_Beskrivelse
  - RegisterStatus_Beskrivelse
  - RegTypeDato
  - MorsFodselsnummer_hash
  - FarsFodselsnummer_hash
  - Fodeland
  - Fødselsdato/år
  - Bostedskommune/fylke

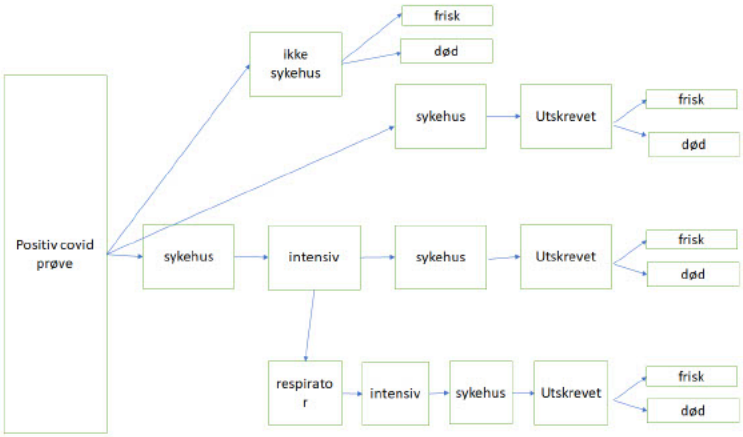
- SYSVAK
  - Fnr_hash
  - FødselsnummerType
  - Konsultasjonsdato (= vaksinasjonsdato)
  - Vaksinekode
  - Vaksinebeskrivelse
- Risikogruppe-tabellen
  - Fnr_hash
  - AnnenAktivKreftsykdom
  - Demens
  - Diabetes
  - Fedme
  - HematologiskKreft
  - Hjerneslag
  - HjerteKar
  - Immunsviktsykdommer
  - KroniskLunge1
  - Leversvikt
  - NedsattImmunforsvar
  - Nevrolidelser
  - Nyresvikt
  - Organtransplantasjon
- NPR
  - persId-hash
  - nprPasientId
  - nprProsedyreId
  - nprEpisodeId
  - nprTilstandId
  - nprTiltakId
  - nprTjenesteId
  - nprInstitusjonsId
  - kjonn
  - fodselsår
  - KodeVerdi
  - Kodenr
  - Kodeverk
  - innDatoTid
  - utDatoTid
  - startDatoTid
  - sluttDatoTid
  - innTilstand
  - utTilstand
  - behandlingssted_nprEnhetID
  - helseforetakOrgNr
  - helseforetakKortBeskrivelse
  - institusjonKortBeskrivelse
  - institusjonsID
  - fodselsår

  - omsorgsnivå
  - innmateHast
  - komNrHjem
- Helsepersonel-tabellen
  - Fnr_hash
  - ansatt_fra
  - ansatt_til
  - yrke
  - yrkeskategori
  - helsetjeneste
  - kommunenr
- SSB (trangboddethet)
  - PersId_hash
  - trangbodd
  - Periode
- DÅR
  - Fnr_hash
  - dødsdato
  - daar_alle_koder
  - diagnose_underliggende_k

Prosjektutvalg og utfall

I figur 1 presenteres ulike utvalg og utfall i studien, der pilene angir flytt mellom ulike stadier. Utfallet kan inkludere tid til eller forekomst av et stadia, f.eks. tid fra innleggelse i sykehus til innleggelse i intensivavdeling, eller risikoen for innleggelse i intensivavdeling blant pasienter innlagt i sykehus. Analysene vil bli utført med enten alle personer som har fått påvist SARS-CoV-2 (MSIS og/eller MSIS-lab som utvalgsdatasettet), alle personer som har blitt innlagt i sykehus med påvist SARS-CoV-2 (NoPaR og/eller NPR som utvalgsdatasett), eller alle som har blitt innlagt i intensivavdeling med påvist SARS-CoV-2 (NIR og/eller NPR som utvalgsdatasett) som utvalg. Både NIPaR og NPR kan brukes som utvalgsdatasettet, eller for å definere utfall når det gjelder innlagte pasienter. Dette for å kunne kvalitetssikre resultatene ved behov, gitt ulike styrker og svakheter med begge registrene. DÅR, Folkeregistret og MSIS kan brukes for å identifisere dødsfall med og på grunn av covid-19. NIPaR og NPR kan også brukes for å identifisere dødsfall blant personer innlagt i spesialisthelsetjenesten. Til analysen om risiko for reinfeksjon vil utvalget være personer som har blitt smittet minst én gang, med utfallet en andre positiv SARS-CoV-2 test utført en viss tid etter første positiv test. Visse personer kan har blitt reinfisert mer enn én gang i studieperioden.

Startdato for analysene kan være f.o.m. begynnelsen av epidemien (første tilfelle påvist 21. februar 2020). Epidemien er pågående, og datainnsamlingen skjer fortløpende. Derfor er det ikke satt en sluttdato når datasettene vil bli lukket for de ulike analysene, fordi analysene vil måtte bli tilpasset til utviklingen i epidemien, og dets håndtering.



Figur 1: Model for analysene i prosjektet. NB: 'MIS-C' og 'reinfeksjon' er ikke med i figur 1, men inkluderes også som utvalg, forklaringsvariabel og/eller utfall i prosjektet. For eksempel, risiko for MIS-C blant meldte tilfeller av SARS-CoV-2 infeksjon blant barn, risiko for innleggelse i sykehus etter reinfeksjonsstatus eller risiko for reinfeksjon blant tilfeller av SARS-CoV-2 infeksjon.

Deskriptiv analyse

Vi vil utføre en deskriptiv analyse av våre utvalg og utfall etter ulike forklaringsvariabler, både kontinuerlige og kategoriske. Dataene kan bli presentert som f.eks. antall, andel, median og gjennomsnitt hvor hensiktsmessig. Forklaringsvariabler vil inkludere bl.a. alder, kjønn, fødeland, risikogruppe/risikofaktorer, vaksinasjonsstatus, reinfeksjon, yrke, trangboddhet, hovedårsak til innleggelsen, virus-variant, smitteland, RHF, HF, bostedsfylke og bruk av ventilasjonsstøtte. Vi vil i tillegg utføre en deskriptiv analyse av datakvaliteten i hver datakilde og det koblete datasett, spesielt mtp. kompletthet av variablene.

Statistiske analyser

Vi vil for ulike problemstillinger bruke en passende statistisk modell til analysen. For eksempel, for analyser av tidsintervaller som liggetid i sykehus vil overlevelsesanalyse (Cox Proportional Hazards model) brukes i utgangspunkt. Cox-regresjon med tidsavhengige kovariater vil benyttes for å se på risiko for reinfeksjon etter smitte med ulike virusvarianter. For å beregne prosentandelen av utvalget som ender opp i hver av de mulige utfallene vil modeller som logistisk, binomial eller poisson regresjon også kunne benyttes. Andre regresjonsmodeller kan være aktuelle, dersom dataene tilsier at det er nødvendig (f.eks. ved brudd av antakelsen av 'proportional hazard' i overlevelsesanalysen). Vi vil i modelleringen først se på univariable modeller for å observere hvilke forklaringsvariabler som skal inkluderes i en endelig modell.

Sensitivitetsanalyse

For variabler med lavere kompletthet vil vi utføre en sensitivitetsanalyse av forskjeller mellom personer med og uten data for de variablene. Vi vil inkludere 'kjent data for variabel X' som forklaringsvariabel, og se om den gir signifikant forklaringskraft, i overlevelsesmodellene, og

regresjonsmodellene. Vi vil i tillegg utføre sensitivitetsanalyser der vi justerer bl.a. vår studieperiode/utvalg/definisjon av utfallene for å sjekke om våre resultat er robuste.

Analyseverktøy

Dataanalysen vil bli utført med bruk av R og STATA.

Etikk og personvern

Personvern

Dette prosjektet skal utføres i Team Overvåking i Beredt C19. FHI opprettet Beredt C19 med hjemmel i helseberedskapsloven paragraf 2-4. Slike registre kan etableres for å gi oversikt og kunnskap om utbredelse, årsakssammenhenger og konsekvenser ved miljøhendelser, ved mistanke om utbrudd av sykdom relatert til eksponering for helseskadelige miljøfaktorer og ved andre typer kriser og beredskapssituasjoner. Overordnet er formålet med analysene i Beredt C19 å fremskaffe oversikt og kunnskap om hvordan pandemien og tiltakene som er iverksatt, påvirker befolkningens helse, bruk av helsetjenester og helserelaterte atferd, som angitt i DPIA'en til Beredt C19.

Individdata benyttes i Beredt C19, men uten direkte personidentifiserende kjennetegn. Dataene kan ikke under noen omstendighet flyttes bort fra Team Overvåkings dedikerte område på FHI sin interne sikkersone, og kun data som er anonyme (dvs. umulig å bakveisidentifisere) kan deles med andre/publiseres jf. DPIA'en for Beredt C19. Det er straffbart å ta ut informasjon som kan knyttes direkte eller indirekte til faktiske enkeltpersoner. Beredt C19 er midlertidig, og opplysningene skal slettes eller anonymiseres når pandemien er over og evaluert.

Koblingen i dette prosjektet vil bli utført av medarbeiderne fra FHI som har tilgang til dataene gjennom Team Overvåking. Andre medarbeidere fra utenfor Team Overvåking vil ikke ha mulighet til å koble datakildene, eller få tilgang til det koblete datasettet. De vil kun ta del av anonymiserte resultat.

Behov for godkjenning fra regional etisk komité (REK)

Prosjektleder anser at prosjektet er helsefagligforskning. Forhåndsgodkjenning fra REK foreligger (REK sør-øst B #249509).

Prosjekt planlegging

Planlagt prosjektstart og slutt

Start i april 2021. Det kan være behov for å gjenta analysene i fremtiden ift. utviklingen i, og håndteringen av, epidemien, og prosjektets slutt er knyttet til sletting/anonymisering av data i Beredt C19 (se '*Personvern*'). I det formålet er prosjektets sluttdato foreløpig satt til tre år etter prosjekt start (31. mars 2024), men det kan være behov for å forkorte eller forlenge den tiden ift. sletting/anonymisering av data i Beredt C19, og behov for analysene for håndteringen av epidemien.

Bruk av resultatene

Resultatene av denne studien vil bli delt internt på FHI og NIPaR, og eksternt med relevante aktører, som Helsedirektoratet og Helse- og Omsorgsdepartementet, umiddelbart dersom resultatene vurderes som nyttige for myndighetenes og helsevesenets håndtering av beredskapssituasjonen. Dette kan være gjennom ulike format som rapporter og presentasjoner på møter. Resultatene vil bli offentliggjort gjennom rapporter, nettsaker, presentasjoner eller fagfellevurderte artikler, og vurderes for innsending til vitenskapelige konferanser.

Fagfellevurderte artikler knyttet til prosjektet som er blitt publisert, eller akseptert for publisering, i medisinsk tidsskrift per 11. april 2022 er:

- Veneti L, Seppala E, Larsdatter Storm M, Valcarcel Salamanca B, Alnes Buanes E, Aasand N, et al. Increased risk of hospitalisation and intensive care admission associated with reported cases of SARS-CoV-2 variants B.1.1.7 and B.1.351 in Norway, December 2020 - May 2021. PLoS One. 2021;16(10):e0258513.
- Whittaker R, Kristofferson AB, Seppala E, Valcarcel Salamanca B, Veneti L, Storm ML, et al. Trajectories of hospitalisation for patients infected with SARS-CoV-2 variant B.1.1.7 in Norway, December 2020 - April 2021. J Infect. 2021;83(4):e14-e7.
- Veneti L, Valcarcel Salamanca B, Seppala E, Starrfelt J, Storm ML, Bragstad K, et al. No difference in risk of hospitalization between reported cases of the SARS-CoV-2 Delta variant and Alpha variant in Norway. Int J Infect Dis. 2022;115:178-84.
- Veneti L, Boas H, Brathen Kristoffersen A, Stalcrantz J, Bragstad K, Hungnes O, et al. Reduced risk of hospitalisation among reported COVID-19 cases infected with the SARS-CoV-2 Omicron BA.1 variant compared with the Delta variant, Norway, December 2021 to January 2022. Euro Surveill. 2022;27(4).
- Whittaker R, Kristofferson AB, Valcarcel Salamanca B, Seppala E, Golestani K, Kvåle R, et al. Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a register-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients. Clin. Microbiol. Infect. doi: https://doi.org/10.1016/j.cmi.2022.01.033.

Finansieringskilder

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6. Veneti L, Boas H, Brathen Kristoffersen A, Stalcrantz J, Bragstad K, Hungnes O, et al. Reduced risk of hospitalisation among reported COVID-19 cases infected with the SARS-CoV-2 Omicron BA.1 variant compared with the Delta variant, Norway, December 2021 to January 2022. Euro Surveill. 2022;27(4).
7. Veneti L, Valcarcel Salamanca B, Seppala E, Starrfelt J, Storm ML, Bragstad K, et al. No difference in risk of hospitalization between reported cases of the SARS-CoV-2 Delta variant and Alpha variant in Norway. Int J Infect Dis. 2022;115:178-84.
8. Whittaker R, Brathen Kristofferson A, Valcarcel Salamanca B, Seppala E, Golestani K, Kvale R, et al. Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a register-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients. Clin Microbiol Infect. 2022.
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9.3 Data from the prospective follow-up study to paper I

Appendix table 9.3-a: Number of COVID-19 patients admitted to hospital, by day and health trust, Norwegian intensive care and pandemic registry, Norway, 19 November 2020[1] – 30 June 2021

Date	Akershus University Hospital	Diakonhjemmet	Finnmark	Haraldsplass	Helgeland	Bergen	Fonna	Førde	Møre Romsdal	Nord Trøndelag	Stavanger	Lovisenberg	Nordland	Oslo University Hospital	St Olav	Innlandet	Telemark	Vestfold	Østfold[2]	Sørlandet	University Hospital of North Norway	Vestre Viken[2]	Sunnaas	Ukjent
19.11	39	10	0	6	0	15	2	0	3	0	2	18	0	29	5	11	2	2	0	5	2	7	-	1
20.11	35	10	0	5	0	13	2	0	3	0	2	18	0	25	5	12	1	2	0	5	2	5	-	1
21.11	22	7	0	3	0	13	1	0	2	0	1	17	0	27	6	12	1	6	0	5	2	5	-	1
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08.01	26	6	0	1	0	2	2	0	5	4	14	5	1	20	6	7	6	3	14	1	4	9	-	3
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20.04	58	11	0	4	2	7	5	0	8	0	19	11	1	46	1	10	1	9	19	4	3	26	0	1
21.04	44	11	0	3	4	9	4	1	9	1	18	11	1	42	1	12	1	7	17	4	3	20	0	1
22.04	43	10	0	4	3	8	2	1	12	1	15	11	1	39	2	11	1	7	9	4	3	26	0	1
23.04	41	6	0	5	3	8	3	1	10	1	17	13	1	37	2	10	1	8	11	6	3	27	0	1
24.04	41	6	0	5	1	10	3	1	9	0	18	14	1	38	3	9	1	6	11	8	3	24	0	1
25.04	39	6	0	5	1	14	3	1	9	0	18	14	1	37	3	9	1	7	11	7	3	23	0	1
26.04	27	6	0	5	0	14	3	1	10	0	18	19	1	39	3	9	1	7	9	6	3	26	0	1

27.04	33	8	0	3	0	10	2	1	10	0	21	19	1	39	3	11	2	7	8	5	3	27	0	0
28.04	44	9	0	3	1	11	2	1	10	0	19	17	1	38	2	14	3	7	9	7	3	22	0	0
29.04	39	8	0	3	1	7	1	2	9	1	20	16	1	37	2	14	3	7	9	8	3	20	0	0
30.04	39	6	0	4	0	7	0	2	7	1	20	16	1	31	2	15	3	7	10	8	3	17	0	0
01.05	39	6	0	4	0	7	0	2	6	1	19	16	1	32	2	11	3	7	10	8	3	15	0	0
02.05	39	6	0	4	0	7	0	2	6	1	19	15	1	30	2	11	3	7	10	9	3	16	0	0
03.05	36	6	0	4	0	7	0	2	4	1	19	13	1	30	2	11	4	6	9	11	3	16	0	0
04.05	38	8	0	4	0	7	1	0	4	1	15	15	1	31	2	11	5	5	10	9	3	17	0	0
05.05	23	7	0	4	0	6	0	0	4	0	14	8	1	29	2	9	5	6	7	7	3	14	0	0
06.05	21	4	0	3	0	6	0	0	3	0	15	6	1	24	2	7	5	6	7	7	3	14	0	0
07.05	22	6	0	2	0	6	0	1	4	0	16	6	1	19	2	9	6	7	11	8	3	14	0	0
08.05	22	7	0	2	0	6	0	1	4	0	14	7	1	15	1	9	6	8	10	9	3	16	0	0
09.05	22	7	0	2	0	6	0	1	4	0	14	6	1	16	1	8	3	7	9	8	3	16	0	0
10.05	22	7	0	2	0	7	0	1	4	0	14	6	1	18	1	8	3	10	9	8	3	16	0	0
11.05	26	5	0	2	0	8	0	1	4	0	14	6	1	18	1	9	4	9	10	8	3	17	0	0
12.05	19	5	0	1	0	9	0	2	4	0	14	5	1	19	1	9	4	9	9	8	3	20	0	0
13.05	19	6	0	1	0	7	0	2	5	0	13	5	1	22	1	9	4	9	11	4	4	20	0	0
14.05	23	6	0	1	0	7	0	2	5	0	13	5	1	19	1	9	4	10	11	3	4	18	0	0
15.05	23	9	0	1	0	3	0	2	3	0	13	4	0	22	1	10	7	8	11	6	4	16	0	0
16.05	19	7	0	1	0	3	0	2	3	0	13	4	0	22	1	10	6	8	11	5	6	17	0	0
17.05	14	6	0	1	0	4	0	2	4	0	13	4	0	18	1	8	5	7	13	5	6	15	0	0
18.05	14	6	0	1	0	5	0	2	4	0	13	4	0	17	1	9	5	7	12	5	6	16	0	0
19.05	14	6	0	0	0	5	0	1	4	0	13	5	0	19	1	9	9	9	13	5	7	13	0	0
20.05	11	2	0	0	0	4	0	0	4	0	13	5	0	19	1	7	9	8	12	5	5	12	0	0
21.05	9	2	0	0	0	5	0	0	3	0	3	3	0	17	1	7	8	8	14	8	5	14	0	0
22.05	11	1	0	0	0	6	0	0	3	1	3	3	0	17	1	7	9	9	10	6	2	14	0	0
23.05	11	1	0	0	0	5	0	0	3	1	3	3	0	17	1	7	9	13	10	6	2	13	0	0
24.05	15	2	1	0	0	4	0	0	3	1	3	2	0	19	1	8	9	14	8	8	1	13	0	0
25.05	14	3	3	0	0	3	0	0	3	1	3	3	0	21	1	8	11	14	7	9	1	14	0	0
26.05	14	2	1	0	0	3	0	0	3	0	3	5	0	21	2	8	11	11	6	9	2	14	0	0
27.05	13	2	1	0	0	4	0	0	3	0	3	5	0	19	2	10	8	11	9	7	2	11	0	0
28.05	14	1	2	0	0	2	0	0	2	0	3	2	0	17	2	11	8	12	8	9	2	10	0	0
29.05	14	1	3	0	0	2	0	0	2	0	3	2	0	17	3	10	6	10	7	5	3	10	0	0
30.05	14	1	3	0	0	2	0	0	2	0	3	2	0	12	6	10	7	10	7	5	2	11	0	0
31.05	14	1	4	0	0	2	0	0	2	0	3	4	0	12	7	10	6	11	6	5	2	10	0	0
01.06	11	1	4	0	0	2	0	0	2	0	5	4	0	12	6	11	6	8	5	4	1	9	0	0
02.06	10	1	3	0	2	2	0	0	3	1	4	3	0	12	3	9	6	8	5	5	2	9	0	0
03.06	7	1	4	0	2	2	0	0	3	1	2	3	1	12	4	9	5	8	5	5	2	8	0	0
04.06	8	2	3	0	1	2	0	0	2	3	2	3	2	12	2	8	5	7	5	5	2	5	0	0
05.06	8	2	3	0	1	2	0	0	1	4	2	3	3	9	2	7	5	9	4	5	3	5	0	0
06.06	9	2	3	0	1	2	0	0	1	4	2	3	3	10	3	7	5	8	4	5	3	5	0	0
07.06	10	1	3	0	1	2	0	0	2	2	2	3	3	11	4	10	5	8	4	2	4	5	0	0
08.06	12	1	2	0	1	2	0	0	3	2	3	2	2	10	5	8	5	6	3	3	5	4	0	0
09.06	10	2	2	0	0	2	0	0	2	2	2	2	2	9	5	8	1	5	3	4	7	3	0	0
10.06	10	2	2	0	0	2	0	0	2	0	1	2	1	10	6	7	1	5	3	4	7	2	0	1
11.06	6	1	1	0	0	2	0	0	2	0	1	2	1	8	5	8	1	5	2	1	7	2	0	1
12.06	6	1	1	0	0	2	0	0	1	0	1	2	1	8	5	8	1	7	2	3	6	3	0	1
13.06	7	0	1	0	0	2	0	0	1	1	1	2	1	8	5	8	1	7	2	3	6	3	0	1
14.06	7	0	1	0	0	2	0	0	2	1	1	3	2	8	5	10	1	7	2	3	6	3	0	1
15.06	6	0	0	0	0	2	0	0	2	1	1	3	2	6	4	9	1	10	2	4	6	3	0	1
16.06	6	0	0	0	0	2	0	0	2	1	1	3	2	7	3	8	1	12	1	4	5	3	0	1
17.06	5	0	0	0	0	2	0	0	3	1	1	3	2	8	2	7	0	6	0	4	4	3	0	1
18.06	3	0	0	0	0	2	0	0	2	0	1	3	2	9	2	5	0	8	0	4	4	2	0	1
19.06	3	0	0	0	0	2	0	0	1	0	1	3	2	9	2	5	0	9	0	4	4	2	0	1
20.06	3	0	0	0	0	2	0	0	1	0	1	3	2	7	2	5	0	8	0	3	4	2	0	1
21.06	3	1	0	0	0	2	0	0	1	0	1	2	4	8	2	5	0	8	0	3	4	2	0	0
22.06	3	2	0	0	0	2	0	0	1	0	1	3	4	7	2	4	0	9	1	3	4	2	0	0
23.06	3	0	0	0	0	2	0	0	1	0	1	3	3	7	3	4	0	9	1	2	3	2	0	0
24.06	3	0	0	0	0	0	0	0	1	0	1	3	3	6	4	6	0	5	0	2	3	3	0	0
25.06	4	0	2	0	0	0	0	0	1	0	1	2	3	2	4	6	1	6	0	2	3	2	0	0
26.06	4	0	2	0	0	0	0	0	1	0	1	2	3	2	4	6	1	5	0	3	3	3	0	0
27.06	4	0	2	0	0	0	0	0	1	0	1	3	3	2	4	6	1	5	0	3	3	4	0	0

28.06	4	0	2	0	0	0	0	0	1	0	3	1	3	1	4	6	1	5	0	3	2	6	0	0
29.06	4	0	3	1	0	0	0	0	1	0	2	2	3	2	2	5	1	4	0	3	2	6	0	0
30.06	4	0	3	1	0	0	0	0	1	0	2	2	3	2	2	5	1	4	0	3	2	6	0	0

-: missing data. [1] *Data extraction by health trust started on 19 November 2020. During the period 1 September 2020 – 18 November 2020 data were extracted by regional health authority. During this period, most COVID-19 patients admitted to hospital nationally were in the South-Eastern regional health authority.* [2] *From 19 November – 19 December 2020, data for the number of COVID-19 patients admitted to hospital in Vestre Viken and Østfold health trust were affected by an artefact in the estimation of patients (discharge determined by registration of discharge form, not registration of discharge date). Thus, the number of patients for these two health trusts during this period are underestimated. From 20 December 2020, discharge was determined by discharge date.*

Appendix table 9.3-b: Number of COVID-19 patients admitted to hospital, by day and health trust, linkage Norwegian Patient Registry-Norwegian Surveillance System for Communicable Diseases, Norway, 20 November 2020 – 30 June 2021

Date	Akershus University Hospital	Diakonhjemmet	Finnmark	Haraldsplass	Helgeland	Bergen	Fonna	Førde	Møre Romsdal	Nord Trøndelag	Stavanger	Lovisenberg	Nordland	Oslo University Hospital	St Olav	Innlandet	Telemark	Vestfold	Østfold	Sørlandet	University Hospital of North Norway	Vestre Viken	Private, West regional health authority	Private, unknown health trust
20.11	22	7	1	2	0	11	2	0	0	0	1	13	0	24	5	8	0	3	3	6	1	14	-	-
21.11	22	4	2	2	0	10	1	1	1	0	1	8	0	26	5	8	0	6	5	5	1	15	-	-
22.11	21	3	3	1	0	10	1	1	1	0	2	8	0	26	6	8	0	7	7	5	1	15	-	-
23.11	24	6	3	2	0	10	1	1	1	0	3	9	0	26	6	9	0	6	5	5	1	14	-	-
24.11	25	7	3	2	0	11	1	1	1	0	3	9	0	26	7	9	0	6	5	5	1	17	-	-
25.11	21	6	2	1	1	11	2	0	1	0	3	7	1	26	6	6	3	5	5	4	0	18	-	-
26.11	22	6	2	0	1	11	1	0	1	0	4	7	1	25	6	9	3	5	9	5	0	17	-	-
27.11	20	8	2	0	1	11	1	1	2	0	3	9	1	26	5	8	3	5	10	5	0	22	-	-
28.11	18	8	2	1	1	8	2	2	2	0	1	5	1	26	5	7	4	5	10	5	0	24	-	-
29.11	20	9	2	1	2	8	1	1	1	0	1	6	1	23	4	7	3	7	11	4	0	24	-	-
30.11	22	11	2	1	2	8	1	1	1	0	1	9	1	24	4	8	3	8	13	4	0	22	-	-
01.12	22	9	2	1	2	12	1	1	1	0	1	9	1	24	3	7	3	8	14	2	0	21	-	-
02.12	23	7	1	0	2	12	2	2	1	0	1	7	0	25	3	8	2	6	15	2	0	25	-	-
03.12	25	5	1	0	2	8	1	2	1	0	1	9	0	22	3	6	1	6	11	2	0	28	1	-
04.12	24	6	1	1	2	6	1	2	1	0	3	9	0	24	1	8	1	7	14	3	0	29	1	-
05.12	24	7	1	0	2	6	1	1	1	0	5	7	0	25	1	8	1	10	13	5	0	29	1	-
06.12	27	5	1	0	1	7	1	2	1	0	5	7	0	29	0	10	3	11	13	6	1	33	1	-
07.12	31	6	1	1	0	7	1	2	2	0	3	8	0	26	0	8	3	10	8	6	2	29	1	-

08.12	32	1	1	1	0	8	0	2	2	0	3	7	1	28	0	9	3	8	8	6	1	24	1	-
09.12	32	1	1	2	0	9	0	1	2	0	3	9	1	28	0	7	3	7	10	6	1	25	1	-
10.12	25	2	1	3	0	8	0	1	2	0	3	9	1	25	0	8	4	7	9	5	2	24	1	-
11.12	20	2	1	2	0	8	0	1	1	0	1	6	1	24	0	9	4	4	10	4	1	23	0	-
12.12	20	1	1	2	0	7	0	0	1	0	1	8	1	24	0	10	7	5	9	4	1	21	0	-
13.12	30	2	1	2	0	7	0	0	1	0	1	9	0	24	0	10	7	3	9	4	1	22	0	-
14.12	34	2	0	2	0	6	0	0	1	0	1	9	0	23	0	10	8	3	7	1	2	23	0	-
15.12	35	4	0	1	0	7	0	0	1	0	1	7	0	23	1	11	11	3	12	2	2	23	0	-
16.12	31	4	0	1	0	8	0	0	1	0	1	7	0	17	1	11	11	4	10	2	4	20	0	-
17.12	31	3	0	1	0	9	0	0	1	0	1	6	0	16	0	10	10	3	10	2	3	21	0	-
18.12	31	7	0	0	0	9	0	0	1	0	1	3	0	17	2	10	9	3	15	2	4	25	0	-
19.12	32	7	0	0	0	9	0	0	1	0	1	2	0	17	3	8	12	4	15	2	5	24	0	-
20.12	33	8	0	0	0	9	0	0	1	0	2	2	0	17	5	9	13	4	18	2	3	27	0	-
21.12	32	5	0	0	0	9	0	0	1	1	2	2	0	17	5	11	13	4	15	2	3	27	0	-
22.12	33	5	0	0	0	9	0	0	1	1	3	1	0	15	4	11	14	4	15	1	3	27	0	-
23.12	31	5	0	0	0	9	0	0	1	0	3	1	0	16	1	9	12	4	17	1	2	22	0	-
24.12	26	3	0	0	0	9	0	0	1	0	4	2	0	16	1	9	10	4	16	1	2	16	0	-
25.12	30	4	0	0	0	9	0	0	2	0	2	2	0	17	2	9	10	4	15	1	2	15	0	-
26.12	34	3	0	0	0	9	0	0	4	0	2	2	0	19	1	10	11	4	17	1	2	17	0	-
27.12	36	4	0	0	0	9	1	0	3	0	4	6	0	19	2	9	12	3	17	1	2	18	0	-
28.12	31	7	0	0	0	9	1	0	5	1	4	6	0	16	3	9	17	3	19	1	2	18	0	-
29.12	33	6	0	0	0	9	2	0	8	1	5	4	0	15	4	9	14	3	22	2	3	16	0	-
30.12	30	4	0	0	0	9	2	0	8	0	4	3	0	13	4	10	14	3	27	2	3	13	0	-
31.12	22	4	-	0	-	9	2	0	8	1	5	1	-	14	4	6	13	3	27	1	4	10	0	-
01.01	26	4	-	0	-	9	2	0	8	1	6	4	-	13	5	4	9	4	25	1	4	10	0	-
02.01	27	4	-	0	-	9	2	0	8	1	6	6	-	19	5	4	8	4	24	1	5	8	0	-
03.01	26	4	1	0	-	9	2	0	7	2	8	6	-	20	5	4	8	4	22	1	4	7	0	-
04.01	25	4	1	0	-	4	1	-	8	3	11	5	1	20	6	4	6	5	22	1	4	6	0	-
05.01	27	6	0	0	-	4	1	-	6	3	11	5	1	18	6	4	7	5	22	1	4	8	0	-
06.01	29	6	0	1	-	3	1	-	6	3	11	5	1	15	6	4	7	4	17	1	4	7	-	-
07.01	34	7	0	2	-	3	1	-	7	3	11	5	1	18	6	2	6	5	14	1	4	6	-	-
08.01	36	8	0	1	0	10	2	0	5	4	13	4	1	17	5	4	5	5	15	1	4	9	0	-
09.01	41	10	0	1	0	12	3	0	4	5	13	6	1	18	6	5	5	6	19	1	4	11	0	-
10.01	42	10	0	1	0	12	4	0	5	2	13	7	1	17	7	3	5	7	21	1	4	15	0	-
11.01	45	8	0	1	0	12	4	0	4	2	13	8	1	19	7	3	6	8	19	2	3	16	0	-
12.01	47	7	0	1	0	12	2	0	4	2	13	8	1	17	7	4	5	7	22	2	3	17	0	-
13.01	48	9	0	0	0	11	3	0	3	3	15	7	1	18	6	6	4	9	20	2	6	19	0	-
14.01	42	8	0	0	0	4	4	1	3	4	19	9	1	20	4	4	2	8	20	2	5	18	0	-
15.01	41	8	0	0	0	4	3	1	2	5	22	8	1	21	4	3	2	6	18	2	4	19	0	-
16.01	40	10	0	0	0	4	3	1	2	5	19	8	1	19	5	3	2	7	16	1	5	21	0	-
17.01	44	9	0	0	0	4	3	1	1	5	19	9	1	17	4	3	3	7	17	1	5	19	0	-
18.01	40	9	0	0	0	4	2	1	2	4	17	8	1	15	3	3	3	10	14	1	2	18	0	-
19.01	31	9	0	0	0	4	2	1	2	5	14	7	1	14	2	4	3	9	17	1	2	19	0	-
20.01	31	9	0	0	0	4	1	1	1	3	12	7	1	14	3	5	3	9	15	1	2	25	0	-
21.01	31	9	0	0	0	5	1	0	1	3	15	7	1	11	2	6	3	9	16	1	2	23	0	-
22.01	37	8	0	0	0	4	1	0	1	3	15	7	1	14	2	4	3	10	17	1	1	17	0	-
23.01	36	9	0	0	0	5	1	0	1	3	14	7	1	12	2	4	3	9	20	1	1	15	0	-
24.01	39	8	0	0	0	5	1	0	1	3	14	7	1	13	2	4	3	9	17	3	1	16	0	-
25.01	34	8	0	0	0	5	1	0	1	2	12	7	1	13	2	5	2	8	19	3	1	15	0	-
26.01	33	8	0	0	0	5	0	0	0	2	11	7	1	14	2	5	2	7	16	3	1	13	0	-
27.01	31	8	0	0	0	3	0	0	0	0	11	7	2	14	3	6	2	6	15	3	1	12	0	-
28.01	27	8	0	0	0	5	0	1	0	0	10	7	2	11	3	5	2	4	11	3	1	14	0	-
29.01	27	8	0	0	0	5	0	0	0	0	7	7	2	8	2	5	2	2	9	2	1	12	0	-
30.01	26	8	0	0	0	4	0	0	0	0	8	7	2	9	2	5	2	2	9	3	1	14	0	-
31.01	31	9	0	0	0	3	0	0	0	0	8	7	2	9	3	5	2	2	9	3	1	14	0	-
01.02	27	5	0	0	1	2	0	0	0	0	10	7	2	11	4	4	2	3	9	4	1	14	0	-
02.02	26	6	0	0	1	3	0	0	0	0	10	7	2	9	4	4	2	3	10	4	1	14	0	-
03.02	22	4	0	0	0	5	1	0	0	0	9	7	0	9	3	3	2	2	13	4	1	15	0	-
04.02	21	4	0	2	0	5	1	0	2	0	7	7	0	11	3	3	2	2	18	5	1	20	0	-
05.02	18	5	0	4	0	8	2	1	0	0	6	6	0	12	4	3	1	3	18	5	2	17	0	0
06.02	16	4	0	2	0	6	2	1	0	0	6	6	0	12	4	3	1	3	18	8	2	17	0	0
07.02	17	4	0	2	0	6	2	1	1	0	6	6	0	11	3	3	1	2	18	9	2	19	0	0

08.02	17	3	0	2	0	6	2	1	1	0	6	4	0	9	4	3	1	1	18	6	2	18	0	0
09.02	17	3	0	2	0	6	2	1	1	0	6	6	0	9	4	2	1	1	18	6	2	21	0	0
10.02	17	4	0	2	0	6	2	1	1	0	6	6	0	10	4	2	1	3	18	7	2	19	0	0
11.02	17	3	0	2	0	6	2	1	0	0	6	7	0	9	3	3	1	2	18	5	2	18	0	0
12.02	17	4	0	2	0	6	2	1	0	0	6	7	2	10	3	3	1	2	18	5	2	14	0	0
13.02	17	3	0	2	0	6	2	1	0	0	6	7	3	10	3	3	1	2	18	5	2	16	0	0
14.02	18	3	0	2	0	6	2	1	0	0	6	10	3	10	3	3	1	2	18	5	2	16	0	0
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17.02	26	4	0	2	0	7	3	0	1	0	4	8	2	13	2	4	1	4	15	3	2	13	0	0
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25.02	33	7	0	0	0	6	2	1	0	0	2	10	2	18	3	2	1	5	20	2	1	15	0	0
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02.03	34	7	0	0	0	5	3	0	0	0	2	10	2	35	4	4	1	10	23	5	1	15	0	0
03.03	37	8	0	0	0	5	3	1	0	0	3	10	7	37	4	4	1	15	21	5	2	15	0	0
04.03	40	8	0	0	0	4	4	1	0	0	2	13	5	36	4	5	0	12	19	4	3	18	0	0
05.03	44	8	0	0	0	4	1	1	0	0	2	13	5	38	4	4	0	12	20	4	3	18	0	0
06.03	46	8	0	0	0	4	2	2	0	0	2	11	5	43	5	4	0	15	22	5	3	20	0	0
07.03	50	8	0	0	0	4	5	2	0	0	2	14	5	43	5	5	0	14	25	6	3	22	0	0
08.03	61	8	0	0	0	5	6	2	0	0	2	16	7	41	5	6	0	17	24	7	4	25	0	0
09.03	63	8	0	0	0	7	7	1	0	0	2	17	8	42	4	8	0	14	23	7	3	30	0	0
10.03	68	16	0	0	0	7	7	1	1	0	2	17	8	42	4	8	1	17	23	5	1	30	0	0
11.03	58	19	0	1	0	7	7	1	3	0	2	18	7	38	3	8	2	15	24	5	2	28	0	0
12.03	61	21	0	1	0	7	9	1	4	0	2	19	6	43	1	8	2	18	25	4	3	28	0	0
13.03	51	17	0	1	2	6	9	0	6	0	2	18	7	40	2	10	3	21	27	5	3	29	0	0
14.03	52	17	0	1	2	6	8	0	6	0	2	19	6	40	2	10	3	20	27	5	4	33	0	0
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16.03	67	17	0	1	1	8	9	1	7	0	2	19	7	42	2	11	3	20	26	4	3	40	0	0
17.03	57	23	0	1	0	8	9	1	5	0	3	18	6	45	1	13	4	18	29	4	3	45	0	0
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19.03	55	21	1	1	0	10	10	2	5	0	5	20	4	48	1	13	0	18	22	1	3	40	0	0
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25.03	58	22	0	1	0	9	10	2	10	0	5	24	5	61	1	16	2	14	26	2	2	47	0	1
26.03	63	20	0	0	0	9	9	2	10	0	3	22	5	61	0	15	1	14	27	2	2	48	0	1
27.03	68	19	0	0	0	9	9	2	8	0	5	26	5	65	1	16	1	14	28	2	2	46	0	1
28.03	71	16	0	0	0	12	9	1	7	1	5	26	5	65	1	16	1	16	29	2	2	48	0	1
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02.04	76	13	0	1	0	9	9	0	8	0	10	26	3	63	0	12	1	10	25	1	3	56	0	1
03.04	77	17	0	1	0	9	10	1	7	0	11	24	3	61	0	11	2	9	26	2	3	53	0	1
04.04	81	13	0	0	0	8	10	1	7	0	10	25	3	61	0	10	3	9	27	1	3	50	0	0
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09.04	64	11	0	3	0	9	11	0	9	0	12	20	3	53	0	9	4	10	22	5	3	33	0	0
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15.04	60	11	0	3	4	9	4	1	11	1	19	18	2	38	0	10	2	6	10	6	3	32	0	1
16.04	52	8	0	4	2	9	3	1	8	1	18	18	2	41	1	11	1	7	12	6	4	28	0	1
17.04	51	9	0	2	2	12	3	0	9	0	19	18	1	42	1	11	1	5	10	7	4	26	0	1
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19.04	54	10	0	2	2	13	2	1	10	0	18	23	1	39	2	11	1	6	10	6	3	30	0	1
20.04	55	7	0	2	1	10	1	2	10	0	18	21	1	39	3	12	3	6	9	6	3	28	0	1
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23.04	50	7	0	3	1	7	0	2	8	1	19	18	1	31	2	12	4	4	11	8	3	19	0	1
24.04	44	9	0	4	0	7	1	2	6	1	12	14	1	35	2	10	4	5	11	9	3	19	0	1
25.04	41	9	0	3	0	7	1	1	6	1	12	16	1	34	2	10	5	4	10	12	3	18	0	1
26.04	40	7	0	3	0	8	1	0	4	1	12	16	1	34	2	11	5	3	9	11	3	20	0	1
27.04	38	9	0	3	0	6	1	0	4	0	10	9	1	33	2	10	6	3	9	13	3	19	0	1
28.04	40	7	0	2	0	6	0	0	4	0	10	8	1	31	2	6	6	5	9	12	3	19	0	1
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01.05	37	6	0	1	0	6	0	1	4	0	7	9	1	26	1	5	3	7	9	10	3	18	0	1
02.05	37	6	0	1	0	6	0	1	4	0	7	9	1	26	1	6	3	7	9	9	3	19	0	1
03.05	35	6	0	1	0	6	0	1	5	0	7	9	1	27	1	6	3	9	10	7	3	19	0	1
04.05	33	5	0	0	0	8	0	2	5	0	6	9	1	25	2	7	5	8	11	9	3	20	0	1
05.05	35	6	0	0	0	8	0	2	4	0	7	9	1	25	2	6	5	9	11	7	4	23	0	1
06.05	34	7	0	0	0	7	0	2	4	0	6	8	2	26	3	7	5	10	10	5	3	21	0	1
07.05	34	10	0	0	0	5	0	2	4	0	6	8	1	26	3	7	7	10	9	6	3	20	0	1
08.05	30	8	0	0	0	3	0	2	4	0	5	7	1	26	1	6	7	8	11	11	2	18	0	1
09.05	26	8	0	0	0	4	0	2	5	0	4	6	1	24	1	5	5	8	14	9	2	17	0	1
10.05	25	7	0	0	0	4	0	2	5	0	4	6	1	23	1	5	5	7	13	7	4	18	0	1
11.05	26	8	0	0	0	4	0	2	4	1	5	7	1	24	1	6	7	8	11	8	4	18	0	1
12.05	23	4	0	0	0	5	0	1	4	0	5	7	1	27	1	7	9	10	14	8	5	15	0	1
13.05	19	4	0	0	0	6	0	1	4	0	4	5	1	26	1	7	8	9	13	8	4	16	0	1
14.05	19	3	0	0	0	6	0	0	3	1	5	5	1	26	1	8	8	9	12	9	2	16	0	1
15.05	19	3	0	0	0	5	0	0	3	1	5	4	1	22	1	6	9	10	12	9	2	15	0	1
16.05	23	4	0	0	0	5	0	0	3	1	4	4	1	25	1	7	9	14	10	10	1	14	0	1
17.05	24	5	1	0	0	5	0	0	3	0	4	4	1	29	1	8	11	15	7	11	1	14	0	1
18.05	26	5	3	0	0	3	0	0	3	0	4	6	1	30	1	8	9	14	7	11	2	15	0	1
19.05	23	3	1	0	0	4	0	1	4	1	4	8	1	28	2	10	9	12	7	9	2	14	0	1
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21.05	21	2	3	0	0	2	0	1	2	0	3	7	1	21	3	11	7	9	9	9	3	10	0	1
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26.05	16	2	3	0	2	2	0	1	2	1	4	6	1	16	5	10	2	7	7	7	3	9	0	1
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28.05	17	3	4	1	1	2	0	1	2	3	2	6	2	15	4	5	2	5	8	7	2	8	0	1
29.05	19	2	2	0	1	2	0	1	1	3	4	6	3	15	3	7	1	7	6	5	3	7	0	1
30.05	19	2	3	0	1	2	0	1	1	3	3	6	3	16	4	6	1	6	5	4	3	7	0	1
31.05	19	2	3	0	1	2	0	1	2	2	3	6	2	16	5	8	1	5	5	4	4	8	0	1
01.06	20	2	3	0	1	2	0	2	3	1	3	6	2	14	7	8	1	5	4	5	5	5	0	1
02.06	20	3	3	0	1	2	0	1	2	0	3	5	2	15	8	7	1	5	4	7	6	3	0	1
03.06	19	3	3	0	0	2	0	1	2	0	3	5	1	14	8	7	1	4	4	5	7	3	0	1
04.06	15	2	3	0	0	2	0	1	2	0	3	5	1	15	6	6	1	3	3	3	7	3	0	1
05.06	16	1	2	0	0	2	0	1	2	0	3	5	1	15	6	8	1	6	3	4	6	4	0	1
06.06	16	1	2	0	0	2	0	1	1	0	3	5	1	13	6	8	1	7	3	4	6	4	0	1
07.06	16	1	2	0	0	2	0	1	1	1	3	5	2	13	6	9	1	7	3	4	6	4	0	1
08.06	17	1	2	0	0	2	0	1	2	1	1	5	2	12	5	8	1	7	3	6	6	3	0	1
09.06	15	2	1	0	0	2	0	1	2	1	1	5	2	11	5	9	1	9	2	7	5	3	0	1
10.06	12	1	1	0	0	2	0	1	3	1	2	5	2	13	4	5	1	12	1	6	4	3	0	1
11.06	11	1	1	0	0	3	0	0	3	1	1	5	2	13	3	5	2	7	1	7	4	3	0	1

12.06	12	1	1	0	0	3	0	0	1	0	1	4	2	15	3	3	2	7	1	5	4	2	0	1
13.06	12	1	1	0	0	3	0	0	1	0	1	4	2	16	3	3	2	8	1	5	5	2	0	1
14.06	12	2	1	0	0	3	0	0	1	0	1	5	4	12	3	3	2	8	1	5	5	2	0	1
15.06	10	2	1	0	0	3	0	0	1	0	1	6	3	10	3	2	1	7	2	5	5	2	0	1
16.06	10	1	2	0	0	2	0	1	1	0	1	5	3	11	3	2	2	8	2	3	4	2	0	1
17.06	9	1	2	0	0	2	0	1	1	0	0	6	2	9	4	2	1	7	1	3	4	3	0	1
18.06	9	1	3	0	0	2	0	1	1	0	0	5	2	8	4	4	1	4	1	3	4	3	0	1
19.06	9	1	3	0	0	0	0	1	1	0	0	5	2	6	4	4	1	5	1	4	3	5	0	1
20.06	9	1	3	0	0	0	0	1	1	0	0	5	2	6	4	3	1	4	1	4	3	6	0	1
21.06	9	1	3	0	0	0	0	1	1	0	2	5	2	6	4	3	1	4	1	4	3	6	0	1
22.06	8	1	4	0	0	0	0	1	2	0	1	4	2	6	4	4	1	4	1	2	3	8	0	1
23.06	8	1	4	1	0	0	0	1	2	0	1	4	2	5	4	3	1	3	0	2	3	7	0	1
24.06	2	0	0	0	0	0	0	0	0	0	2	1	0	3	1	2	1	0	1	0	1	1	0	0
25.06	2	0	0	0	0	0	0	0	0	0	2	1	0	3	1	2	1	0	1	0	1	1	0	0
26.06	2	0	1	0	0	0	0	0	0	0	2	1	0	2	1	2	1	1	1	0	1	1	0	0
27.06	2	0	1	0	0	0	0	0	0	0	2	1	0	2	1	2	1	1	1	0	1	1	0	0
28.06	2	0	1	0	0	0	0	0	0	0	2	1	0	2	1	2	1	1	1	0	1	1	0	0
29.06	2	0	1	0	0	0	0	0	0	0	2	1	0	1	1	2	1	1	1	0	1	1	0	0
30.06	2	0	1	0	0	0	0	0	0	0	2	1	0	1	1	2	1	1	1	0	1	1	0	0

-: missing data. [1] *Data extraction by health trust started on 20 November 2020. During the period 1 September 2020 – 19 November 2020 data were extracted by regional health authority. During this period, most COVID-19 patients admitted to hospital nationally were in the South-Eastern regional health authority.*

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