Department of Public Health
University of Helsinki

Dissertationes Universitatis Helsingiensis 423/2025

COVID-19 vaccine effectiveness in Finland during the pandemic

Register-based cohort analyses

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in the auditorium PIII, Porthania, on 13 December 2025, at 12 noon.

Helsinki 2025

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Julkaisija (Publisher): Helsingin yliopisto
Sarja (Series): Dissertationes Universitatis Helsingiensis 423/2025

ISBN 978-952-84-1574-9 (print)
ISBN 978-952-84-1573-2 (online)
ISSN 2954-2898 (print)
ISSN 2954-2952 (online)

PunaMusta, Joensuu 2025

To my grandparents, Maire, Riitta, Paavo, and Kaino, with gratitude and love

Abstract

Background

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused outbreaks of severe pneumonia in Wuhan, China, leading into the coronavirus disease 2019 (COVID-19) pandemic which resulted in high mortality, particularly among the elderly and individuals with chronic conditions. To prevent SARS-CoV-2 infections and severe COVID-19, vaccines were introduced in December 2020 and rapidly rolled out across Finland and other Nordic countries. Although randomised controlled trials provided data on vaccine efficacy against symptomatic and severe COVID-19, policymakers required evidence on long-term effectiveness, protection against emerging variants (e.g. Omicron), and effectiveness in specific population groups, such as individuals aged 80 years and older. Therefore, vaccine effectiveness (VE) was continuously monitored in real time in Finland using nationwide register data throughout the pandemic. This thesis summarises five studies conducted between 2021 and 2023.

Methods

Population-based analyses were conducted by linking data from multiple national registers. The studies were conducted between January 2020 and August 2023, with the Omicron period beginning in January 2022. The study populations included the elderly aged 65 or 70 years or more, risk groups (i.e. people with conditions predisposing to severe COVID-19), and healthcare workers in Finland, as well as adolescents aged 12 to 17 years in the Nordic countries. The exposures of interest were COVID-19 primary vaccination schedules (two doses) and booster doses (third dose and bivalent BA.1 or BA.4–5 boosters), with the unvaccinated and those who had not received a bivalent booster considered unexposed. The outcomes of interest were SARS-CoV-2 infection, COVID-19 related hospitalisation, and death. VE was estimated using a single-cohort design as 1 minus the hazard ratio derived from Cox regression, and in a 1:1 propensity score–matched target trial emulation as 1 minus the risk ratio derived from the Kaplan–Meier estimator.

Results

Depending on the study, the study cohorts totalled at least 896,220 elderly, 774,526 people in risk groups, 427,905 healthcare workers, and 526,966 adolescents. The number of COVID-19 related hospitalisations ranged from 266 to 3,137 across the five studies.

During the pre-Omicron period, VE for primary schedules ranged from 70% to 80% against SARS-CoV-2 infection among adults but waned notably after 4–6 months. VE against hospitalisation was high (90–99%). The vaccines sustained high protection against hospitalisation among healthcare workers, while VE among the elderly waned after 3–6 months. However, the protection was restored with a booster dose.

Following the emergence of Omicron, VE against infection decreased significantly, but protection against severe COVID-19 was maintained. Among adolescents aged 12 to 17 years, VE against

hospitalisation ranged from 65% to 90% for primary schedules during 12 months of follow-up. Among the elderly, VE against hospitalisation was initially high for one booster dose but seemed to wane more rapidly compared to pre-Omicron period. Relative VE for bivalent BA.1 and BA.4-5 boosters was approximately 50% in autumn 2022 but waned during spring 2023.

Conclusions

Register-based analyses provided timely evidence to support policymaking during the COVID-19 pandemic. COVID-19 vaccines significantly reduced the number of SARS-CoV-2 infections and hospitalisations during the pre-Omicron period, helping to limit virus transmission and reduce the COVID-19 burden in hospitals. Although VE waned against COVID-19 related hospitalisation over time among the elderly, booster doses restored the protection. Following the emergence of Omicron, protection against SARS-CoV-2 infection was limited but the protection was maintained against severe COVID-19. As a result, booster roll-outs were targeted for those at high risk for severe COVID-19. The rollout of variant-adapted boosters further improved protection against severe COVID-19 among the elderly, with relative VE comparable to that of seasonal influenza vaccines providing approximately 40–60% VE against influenza hospitalisation.

Abstrakti

Tausta

Joulukuussa 2019 koronavirus (Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) aiheutti ryvästymän vaikeita keuhkokuumeita Wuhanissa Kiinassa, ja johti koronapandemiaan (Coronavirus disease 2019, COVID-19). Pandemia aiheutti korkeaa kuolleisuutta erityisesti iäkkäillä ja henkilöillä, joilla oli kroonisia sairauksia. SARS-CoV-2-infektioiden ja vaikean COVID-19-taudin ehkäisemiseksi kehitettiin rokotteita vuoden 2020 aikana, ja ne otettiin nopeasti käyttöön Suomessa ja muissa Pohjoismaissa joulukuussa 2020. Vaikka satunnaistetut kliiniset tutkimukset antoivat tietoa rokotteiden tehosta oireista ja vaikeaa tautia vastaan, päätöksentekijät tarvitsivat tietoa pitkäaikaissuojasta, suojatehosta uusia virusmuunnoksia (esimerkiksi Omikronia) vastaan, sekä suojasta eri väestöryhmissä, kuten 80 vuotta täyttäneissä. Tämän vuoksi rokotusten tehokkuutta arvioitiin Suomessa reaaliaikaisesti pandemian aikana hyödyntäen valtakunnallisia rekisteriaineistoja. Tämä väitöskirja kokoaa viisi vuosina 2021–2023 tehtyä tutkimusta.

Menetelmät

Väestöpohjaiset analyysit tehtiin yhdistämällä useita kansallisia rekisteriaineistoja, ja tutkimukset toteutettiin tammikuun 2020 ja elokuun 2023 välisenä aikana. Omikron-aika alkoi tammikuussa 2022. Tutkimusaineistoihin kuuluivat iäkkäät (yli 65- tai 70-vuotiaat), riskiryhmiin kuuluvat henkilöt (perussairauksien vuoksi vaikealle koronataudille alttiit henkilöt), terveydenhuollon ammattilaiset Suomessa sekä 12–17-vuotiaat nuoret Pohjoismaissa. Altisteina olivat COVID-19-rokotusten perussarja (kaksi annosta) ja tehosteannokset (kolmas annos sekä bivalentit varianttiräätälöidyt BA.1- tai BA.4/5-tehosteet). Rokottamattomat ja ne, jotka eivät olleet saaneet bivalenttia tehostetta, muodostivat verrokkiryhmän. Päätetapahtumat olivat SARS-CoV-2 infektio, COVID-19:ään liittyvä sairaalahoito ja kuolema. Rokotustehokkuus arvioitiin kahdella tutkimusasetelmalla: väestökohortissa Coxin regressiomallilla laskettuna tehokkuutena (1 – hasardisuhde) sekä 1:1 propensity score-kaltaistetussa asetelmassa käyttäen Kaplan–Meier-estimaattoria ja riskisuhdetta (1 – riskisuhde).

Tulokset

Tutkimuksesta riippuen tutkimusaineistoihin kuului vähintään 896,220 iäkästä, 774,526 riskiryhmäläistä, 427,905 terveydenhuollon ammattilaista ja 526,966 nuorta. COVID-19:ään liittyvien sairaalahoitojaksojen määrä vaihteli 266:sta 3,137:ään.

Ennen Omikron-aikaa perussarjan antama suojateho SARS-CoV-2-infektiota vastaan vaihteli aikuisilla 70–80 % välillä, mutta heikkeni 4–6 kuukauden kuluttua. COVID-19-sairaalahoitoa vastaan suoja oli erittäin hyvä (90–99 %). Terveydenhuollon ammattilaisilla suoja sairaalahoitoa vastaan säilyi hyvänä, kun taas iäkkäillä suojateho heikkeni 3–6 kuukauden jälkeen. Tehosteannos kuitenkin palautti suojan hyvälle tasolle iäkkäillä.

Omikronin ilmaantumisen jälkeen suoja infektiota vastaan heikkeni merkittävästi, mutta vakavaa tautia vastaan suoja säilyi paremmin. Iältään 12–17-vuotiailla nuorilla perussarjan tuottama suoja COVID-19-sairaalahoitoa vastaan oli 65–90 % 12 kuukauden seurannassa. Iäkkäillä tehosteannoksen antama suoja COVID-19-sairaalahoitoa vastaan oli aluksi hyvä, mutta heikkeni nopeammin kuin suojateho ennen Omikronia. Varianttiräätälöityjen BA.1- ja BA.4/5-tehosteiden suhteellinen suojateho COVID-19-sairaalahoitoa vastaan oli noin 50 % syksyllä 2022, mutta heikkeni keväällä 2023.

Johtopäätökset

Rekisteripohjaiset analyysit tarjosivat ajankohtaista näyttöä päätöksenteon tueksi koronapandemian aikana. Koronarokotukset vähensivät merkittävästi SARS-COV-2-infektioiden ja COVID-19-sairaalahoitojen määrää ennen Omikronin ilmaantumista, mikä osaltaan hidasti viruksen leviämistä ja vähensi sairaalakuormaa. Vaikka iäkkäiden rokotussuoja sairaalahoitoa vastaan heikkeni ajan myötä, tehosteannokset palauttivat suojan hyvälle tasolle. Omikronin ilmaantumisen jälkeen suoja infektiota vastaan oli vähäinen, mutta suoja vakavaa tautia vastaan säilyi paremmin. Tämän vuoksi tehosterokotukset kohdennettiin henkilöille, joilla oli suurin riski vakavaan COVID-19-tautiin. Varianttiräätälöidyt bivalenttitehosteet paransivat suojaa iäkkäillä. Niiden suhteellinen teho oli verrattavissa kausi-influenssarokotteisiin, joiden tehokkuus sairaalahoitoa vaativaa influenssaa vastaan on noin 40–60 %.

List of abbreviations

AI = Artificial intelligence
ARDS = Acute respiratory distress syndrome
CI = Confidence interval
COPD = Chronic obstructive pulmonary disease
COVID-19 = Coronavirus disease 2019
DK = Denmark
EMA = European Medicines Agency
FI = Finland
HIV = Human immunodeficiency virus
HR = Hazard ratio
ICD-10 = International Classification of Diseases, Tenth revision
ICU = Intensive care unit
KRAR = Finnish National Advisory Committee on Vaccines (Kansallinen Rokotusasiantuntijjaryhmä)
MERS-CoV = Middle East Respiratory Syndrome–related coronavirus
MISC = Multi-inflammatory syndrome in children
NNV = Number needed to vaccinate
OR = Odds ratio
PCR = Polymerase chain reaction
PYRS = Person years
RCT = Randomised control trial
RD = Risk difference
RR = Risk ratio
SARS-CoV-1 = Severe respiratory syndrome coronavirus 1
SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2
SE = Sweden
THL = Finnish Institute for Health and Welfare (Terveyden ja Hyvinvoinnin laitos)
UK = United Kingdom
VE = Vaccine effectiveness
VOC = Variant of concern
VOI = Variant of interest
VUM = Variant under monitoring
WHO = World Health Organization

Index

List of original publications

This thesis is based on the following publications:

I Baum U*, Poukka E*, Palmu A, Salo H, Lehtonen T, Leino T. Effectiveness of vaccination against SARS-CoV- 2 infection and Covid-19 hospitalisation among Finnish elderly and chronically ill-An interim analysis of a nationwide cohort study. PloS One. 2021 Nov 18;16(11):e0258704.

II Poukka E, Baum U, Palmu A, Lehtonen T, Salo H, Nohynek H, Leino T. Cohort study of Covid-19 vaccine effectiveness among healthcare workers in Finland, December 2020 - October 2021. Vaccine. 2022 Jan 31;40(5):701-705.

III Poukka E, Andersson N, Thiesson EM, Baum U, Starrfelt J, Ljung R, Hviid A. COVID-19 vaccine effectiveness among adolescents in Denmark, Finland, Norway and Sweden. Pediatrics. 2024 Jan 1;153(2):e2023062520.

IV Baum U*, Poukka E*, Leino T, Kilpi T, Nohynek H, Palmu A. High vaccine effectiveness against severe COVID-19 in the elderly in Finland before and after the emergence of Omicron. BMC Infect Dis. 2022 Nov 5;22(1):816.

V Poukka E, Perälä J, Nohynek H, Goebeler S, Auranen K, Leino T, Baum U. Bivalent booster effectiveness against severe COVID-19 outcomes in Finland, September 2022–August 2023. Eurosurveillance. 2024;29(37):pii=2300587.

* Contributed equally to the work

The publications are referred to in the text by their roman numerals.

1 Introduction

In December 2019, outbreaks of severe pneumonia of unknown aetiology occurred in Wuhan, China (1). Subsequently, a novel betacoronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of these pneumonia cases, and the resulting illness was termed coronavirus disease 2019 (COVID-19) (2). The virus spread rapidly worldwide, leading to the declaration of a global pandemic in March 2020 (3). By 2 February 2025 the reported COVID-19 death toll had exceeded 7 million (4).

The development of COVID-19 vaccines started immediately after the identification of the SARS-CoV-2. The first COVID-19 vaccine (Comirnaty, tozinameran, BNT162b2) based on mRNA technology was authorised by the European Medicine Agency (EMA) on 21 December 2020 (5). In January 2021, two other vaccines, an mRNA-based (Spikevax, elasomeran, mRNA-1273) and an adenovirus vector vaccine (Vaxzevria, COVID-19 Vaccine (ChAdOx1-S [recombinant]), AZD1222), were authorised (6,7). Despite the development of other vaccines during the pandemic (8), these three vaccines were the most frequently administered in European countries, including Finland.

In Finland, the COVID-19 vaccination rollout started on 27 December 2020 with the vaccination of healthcare workers working in intensive care units (ICU) (9). Initially, the COVID-19 vaccination series included two doses; however, waning immunity and the emergence of immune-evasive variants led to booster rollouts and the development of variant-tailored COVID-19 vaccines in the following years (10,11).

The efficacy of COVID-19 vaccines was first evaluated in randomised controlled trials (RCT) (12–16). Although these RCTs were pivotal at the time of introduction of COVID-19 vaccines, understanding of protection against a broader variety of COVID-19 outcomes and SARS-CoV-2 variants as well as the effectiveness of booster doses were primarily derived from observational studies. These studies, including test-negative design (TND) and register-based cohort studies, played a significant role in decision making of COVID-19 vaccination rollout. In Finland, register-based evaluation of COVID-19 vaccine effectiveness (VE) began at the Finnish Institute for Health and Welfare (THL) in March 2021 using multiple data sources including real-time data on laboratory-confirmed SARS-CoV-2 infections, hospitalisations, intensive care unit (ICU) admissions, COVID-19 deaths and COVID-19 vaccinations.

This dissertation summarises the research resulting from these efforts to evaluate VE. In the literature review, the COVID-19 pandemic and the vaccine rollout are described first. This is followed by an overview of the most common study designs for evaluating vaccine

effectiveness — RCTs, the TND, and the cohort design — as well as common methods for addressing confounding. Then, the methods and main results of Studies I–V are presented. In the discussion, the findings are compared with those of other studies that estimated VE in real time during the pandemic, along with a discussion of the strengths and limitations of Studies I–V.

2 Literature Review

2.1 COVID-19

2.1.1 SARS-CoV-2 and clinical picture of COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus and belongs to a wide family of coronaviruses, some of which cause mild seasonal respiratory infections while others, such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East Respiratory Syndrome–related coronavirus (MERS-CoV), can cause severe and potentially fatal infections (2). Emergence of SARS-CoV-1 led to an outbreak in 2002 with most of the cases localised in China and Hong Kong (2,17). MERS-CoV was identified in 2012 and has thereafter caused outbreaks mostly affecting the Middle East (18). Human to human transmission of MERS-CoV is rare although possible and most of the cases are caused by zoonotic transmission from dromedary camels (19). The likely original reservoir of SARS-CoV-1 and MERS-CoV are bats (20,21).

The exact source of SARS-CoV-2 remains uncertain, but researchers linked the initial human outbreak to individuals who visited the animal market in Wuhan in late 2019. The emergence of the virus is believed to have resulted from animal-to-human transmission (22,23), although alternative theories exist (24).

SARS-CoV-2 is capable of transmission from human to human via aerosols, droplets, or mucous membrane contact (25). SARS-CoV-2 uses angiotensin-converting enzyme 2 as a receptor and binds to epithelial cells in the respiratory tract with a spike protein (2). The incubation time of the original strain was on average five days, generally ranging from 1 to 14 days (2). Pre-symptomatic transmission, where SARS-CoV-2 spreads before the symptoms begin, is a documented characteristic of this virus (26) which underscores the critical importance of detecting pre-symptomatic cases in order to effectively control the spread of SARS-CoV-2 (27,28).

SARS-CoV-2 infection results in an illness known as coronavirus disease 2019 (COVID-19). The initial symptoms of COVID-19 are commonly mild respiratory symptoms such as fever, dry cough, or fatigue (2,29,30). The diagnosis of COVID-19 is usually based on the detection of SARS-CoV-2 from nasopharyngeal or nasal swabs with molecular testing (i.e. polymerase chain reaction [PCR]) or alternatively with antigen tests. It is worth mentioning that during the COVID-19 pandemic, the so-called self-taken antigen tests (i.e. home tests) were developed and used widely after 2022 (31). The measurement of antibody

concentrations can also be used to assess whether an individual has previously been infected with SARS-CoV-2 (32).

COVID-19 typically causes only mild acute respiratory symptoms or is asymptomatic. The clinical presentation varies depending on the infecting SARS-CoV-2 variant (see section 2.12). Some individuals with COVID-19 may experience progression to severe illness characterised by symptoms such as shortness of breath and reduced oxygen saturation in the blood. For the original SARS-CoV-2 virus severe symptoms usually occurred after 7–14 days from symptom onset and often caused hospitalisation (2). COVID-19 can progress to even more severe complications, such as acute respiratory distress syndrome or multi-organ failure, leading to ICU admission or death (Figure 1).

The ballpark infection fatality ratio for the original SARS-CoV-2 infection was 0.5–1% in an immune-naïve population (2,33–37). Notably, the infection fatality ratio of SARS-CoV-2 depends on several factors, such as immunity level and prevalence of risk factors for severe COVID-19 (Figure 2). For example, the risk of severe COVID-19 increases exponentially among the oldest; among those aged 80 years or older, the fatality ratio due to COVID-19 was notably higher than that of 70–79-year-olds (38,39).

In children and adolescents, COVID-19 is rarely severe although SARS-CoV-2 infection can lead to multi-inflammatory syndrome in children (MIS-C). This rare syndrome was first described in April 2020 (40,41) and resembles Kawasaki Disease (42). MIS-C is characterized by intense systemic inflammation, typically manifesting 2–6 weeks after infection and affecting multiple organs. Cardiovascular complications, including hypotension, heart failure, and peri- or myocarditis, are common. Most affected children require hospitalization for management (43–46).

COVID-19 is also associated with long-term symptoms. If these symptoms – such as fatigue, anosmia, dyspnea and headache – persist for more than three months, the condition is referred to as long-COVID (47). Severe post-acute complications such as myocardial infarction and stroke are also considered part of the long-COVID syndrome (48–50). In a Swiss study conducted in 2020 among outpatients, approximately 30–40% of participants had some symptom after 7–9 months after the SARS-CoV-2 infection (51). The risk of developing long-COVID is higher in individuals who have experienced severe COVID-19; however, even mild or asymptomatic SARS-CoV-2 infections can lead to the condition. Other risk factors include female sex, age between 40–70 years and comorbidities (52,53). Among the children long-COVID is rare compared to adults (54).

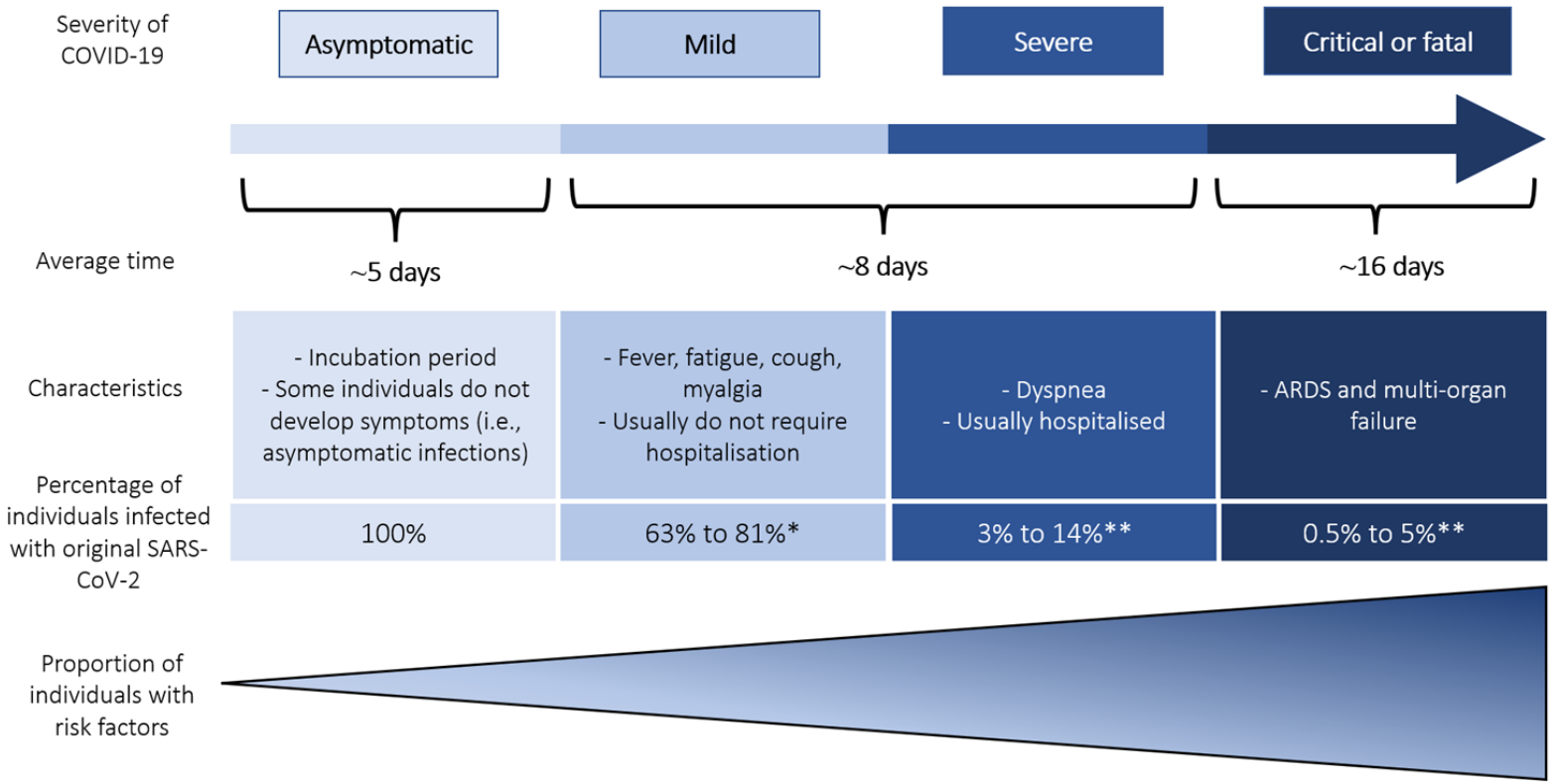


Figure 1 Clinical picture of COVID-19 caused by the original SARS-CoV-2. * Based on reviews by Oran et al. (55) and Hu et al. (2). Figure adapted from Hu et al. (2). ** Based on studies evaluating proportion of critical or fatal COVID-19 by Hu et al. (2), Marziano et al. (35), Verity et al. (37) and Russell et al. (34). ARDS = Acute respiratory distress syndrome.

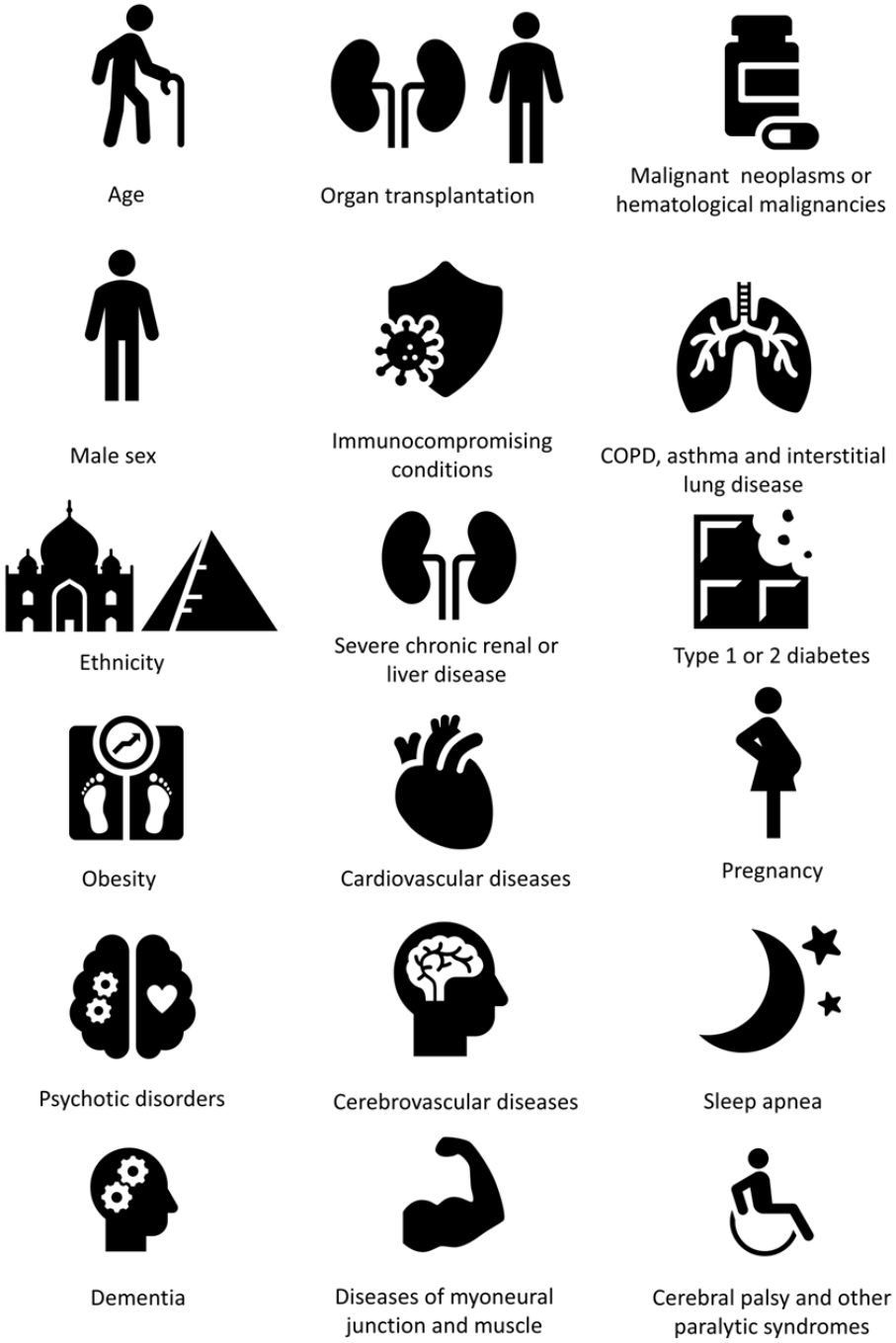


Figure 2 Selected risk factors for severe COVID-19. Studies referred (38,39,56,57). COPD = Chronic obstructive pulmonary disease.

2.1.2 SARS-CoV-2 variants

Since the start of the pandemic, SARS-CoV-2 has mutated, and new strains have emerged (58). Usually, mutations have not changed the characteristics of SARS-CoV-2 or COVID-19; however, occasionally, SARS-CoV-2 genomic changes can lead to increased disease severity of COVID-19 or improved ability to escape the immunity produced against earlier circulating viruses. For these reasons, SARS-CoV-2 strains have been monitored, and the World Health Organization (WHO) has classified the most worrisome variants into variants under monitoring (VUM), variants of interest (VOI), or variants of concern (VOC) depending on transmissibility, virulence, immune escape, susceptibility to therapeutics, detectability, and impact on healthcare (59).

In Finland, the main VOC lineages circulating between 2021 and 2023 were Alpha, Beta, Delta, and Omicron lineages. The characteristics of these lineages are described in Table 1. Globally, also other VOC lineages circulated during the pandemic; for example, the Gamma variant spread in South America in 2021 (60).

The emergence of Omicron in 2021 changed the course of the COVID-19 pandemic. While the exact origin of Omicron remains unclear, some researchers have suggested that its emergence could be linked to extended infections among immunocompromised individuals (61,62).

Omicron has a large number of mutations that changed the properties of the variant compared to previous variants, as outlined in Table 1 (63,64). Importantly, the spike protein of Omicron was different at several locations, increasing both binding to the angiotensin-converting enzyme 2 receptor and immune escape capabilities. Mutations in the spike protein and near the furin cleavage site also increased Omicron's tendency to use endosomal (i.e. cathepsin dependent) pathway for cell entry, whereas the pre-Omicron variants primarily relied on cell surface fusion (i.e. TMPRSS2 dependent) pathway. As a result, Omicron infects cells in the upper respiratory tract more efficiently, while pre-Omicron variants infect mostly the lower respiratory tract. This difference is thought to have contributed to Omicron's enhanced transmissibility and reduced intrinsic severity (65,66). The virulence, transmissibility and immune escape varied across Omicron subvariants (Table 1).

Table 1 Main SARS-CoV-2 variants circulating in Finland between 2021 and 2023.

	Alpha (B.1.1.7)	**Beta (B.1.351)**	**Delta (B.1.617.2)**	**Omicron (B.1.617.2)**			
Notable sublineages	-	-	-	BA.1	BA.2	BA.5	XBB.1.5
First time detection	September 2020	May 2020	October 2020	October 2021	October 2021	January 2022	October 2022
Spread in Finland	Dominant variant February – May 2021	Approximately 10–20% of SARS-CoV-2 infections between March and April 2021	Dominant variant between June and December 2021	Dominant variant between December 2021 and February 2022	Dominant variant March and June 2022	Dominant variant June 2022 and February 2023	XBB-lineages dominant variant between March and December 2023
Location of main genetic mutations	Several deletions and mutations in spike protein	Mutations in spike protein	Mutations in spike protein and furin cleavage	Some deletions and several mutations in spike protein. Furthermore, mutations outside the spike protein (affecting pathogenicity)			
Transmissibility	↑	(↑)	↑↑	↑↑↑	↑↑↑↑	↑↑↑↑	↑↑↑↑↑
Severity	↑	↑	↑↑	↓↓↓	↓↓↓	↓↓(↓)	↓↓↓
Generation interval (95% CI)[1]	4.35 days (3.91–4.80)	-	3.65 days (3.25–4.05)	2.99 days (2.48–3.49)	-		-
Immune escape	+/-	(↑)	↑	↑↑↑	↑↑↑	↑↑↑↑	↑↑↑↑

Table based on articles published by Scovino et al. (63), Markov et al. (64), Shrestha et al. (67), Pather et al. (68), Relan et al. (69) and Vogel (70). The arrows up and down refer to increased or decreased capability compared to the original SARS-CoV-2 strain.
[1] Based on the meta-analysis conducted by Xu et al. (71). Generation interval = time interval between infections of infectors and infections
* XBB.1.5 was not considered as variant of concern but was included in the table because of its significance.

2.1.3 COVID-19 pandemic worldwide

As of 2 February 2025, over 750 million confirmed SARS-CoV-2 infections and more than 7 million COVID-19 related deaths have been reported globally (4). After SARS-CoV-2 was identified as the causative agent of COVID-19, the virus spread rapidly across countries. In Europe, the first confirmed SARS-CoV-2 cases were detected in France on 24 January 2020 (72), while Northern Italy experienced a major outbreak between January and March 2020 (73).

Globally, the number of reported SARS-CoV-2 cases remained relatively low before the emergence of Omicron, largely due to non-pharmaceutical interventions (4,74,75) and rollouts of COVID-19 vaccines (76). However, cases surged worldwide following the emergence of Omicron (4,77) , due to its higher transmissibility, higher immune escape, and shorter generation interval (Table 1).

The pandemic's trajectory varied across regions. In Asia, SARS-CoV-2 spread was more limited than in Europe and North America, particularly before Omicron's emergence (78). For example, China's stringent non-pharmaceutical interventions, named as Zero-COVID policy, significantly restricted SARS-CoV-2 transmission in the country (78). Interestingly, the overall impact of the COVID-19 pandemic on mortality in Africa was relatively limited compared to Europe and North America (79). This may have been influenced by the younger population structure in the continent, although underreporting of cases likely contributed to this observed difference as well (80).

2.1.4 COVID-19 pandemic in Finland

In Finland, the first SARS-CoV-2 case was confirmed in a Chinese tourist in Lapland on 29 January 2020 (81), and the first COVID-19 related death occurred on 20 March 2020 (82). During the first wave of COVID-19 in spring 2020, testing of severe COVID-19 cases was prioritised due to limited resources (83,84). Later, testing capacity was improved, and testing for SARS-CoV-2 was performed with a low threshold among all symptomatic to increase the detection of cases, with the objective of limiting the spread of the virus (Figure 3). As a result, most of the SARS-CoV-2 cases were likely detected and registered from autumn 2020 onwards until the emergence of Omicron. In particular, testing of healthcare workers was done in vast numbers to limit the spread of SARS-CoV-2 in hospitals and long-term care units (85). At the start of the COVID-19 vaccination rollout in late 2020, non-pharmaceutical interventions were common, including contact tracing, quarantine of exposed individuals, restaurant restrictions, recommendation of face masks, and remote working (86–89). Similarly, travelling abroad or entering Finland required SARS-CoV-2 sampling under certain circumstances (90), and unvaccinated individuals were also recommended to limit situations with a high risk of SARS-CoV-2 infection in 2021 by THL (91).

The emergence of Omicron caused unprecedented numbers of SARS-CoV-2 infections between December 2021 and April 2022 (Figure 4) and different Omicron subvariants circulated in Finland between 2021 and 2023 (Table 1). Although the severity of COVID-19 decreased with the emergence of Omicron, the vast number of SARS-CoV-2 infections led to a high number of COVID-19 deaths in Finland (Figure 5). Omicron's rapid spread overwhelmed testing capacities, making it impossible to test every infection. Consequently, home testing became widespread and the primary method for detecting mild SARS-CoV-2 infections in the general population (31,92). The emergence of Omicron reduced the effectiveness of non-pharmaceutical interventions (93,94), which were eventually lifted in 2022 in Finland (95).

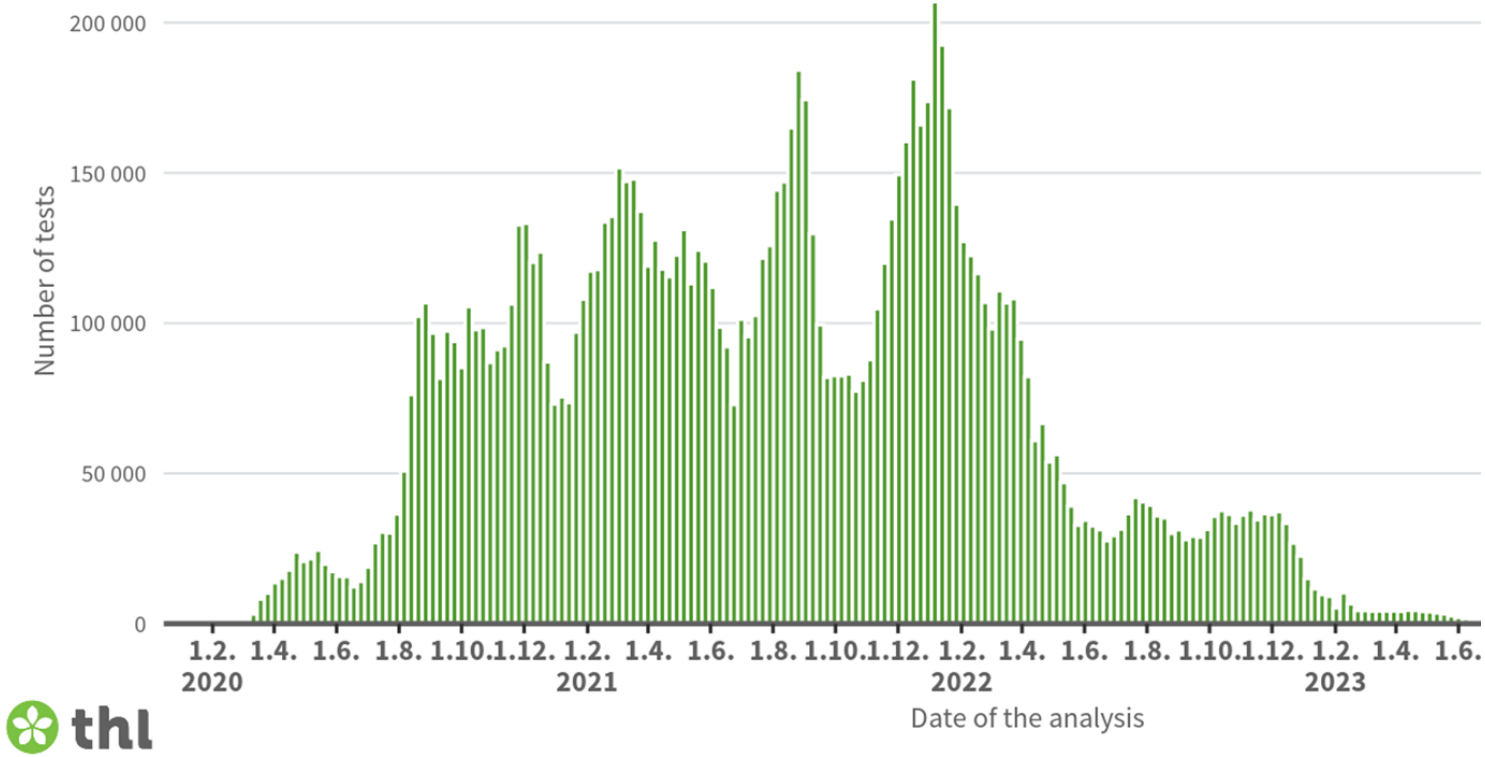


Figure 3 Weekly number of SARS-CoV-2 tests in Finland. Source: Finnish Institute for Health and Welfare.

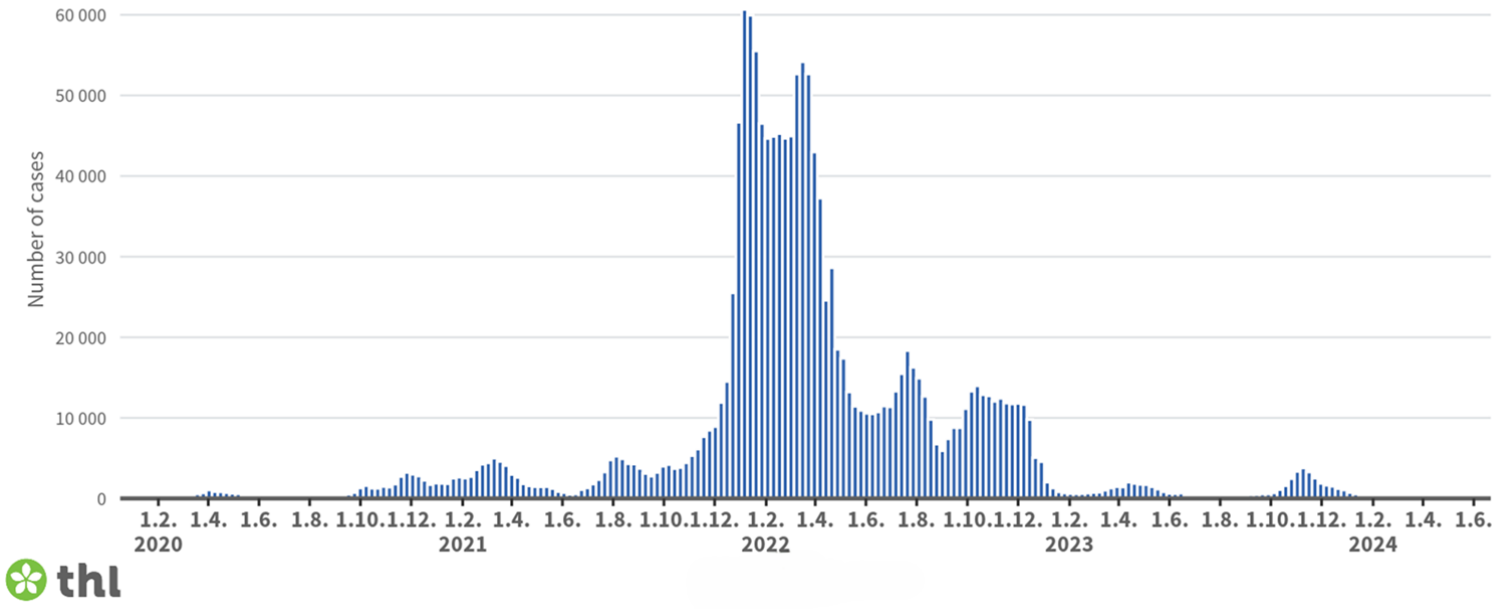


Figure 4 Weekly number of laboratory-confirmed SARS-CoV-2 infections in Finland. Source: Finnish Institute for Health and Welfare.

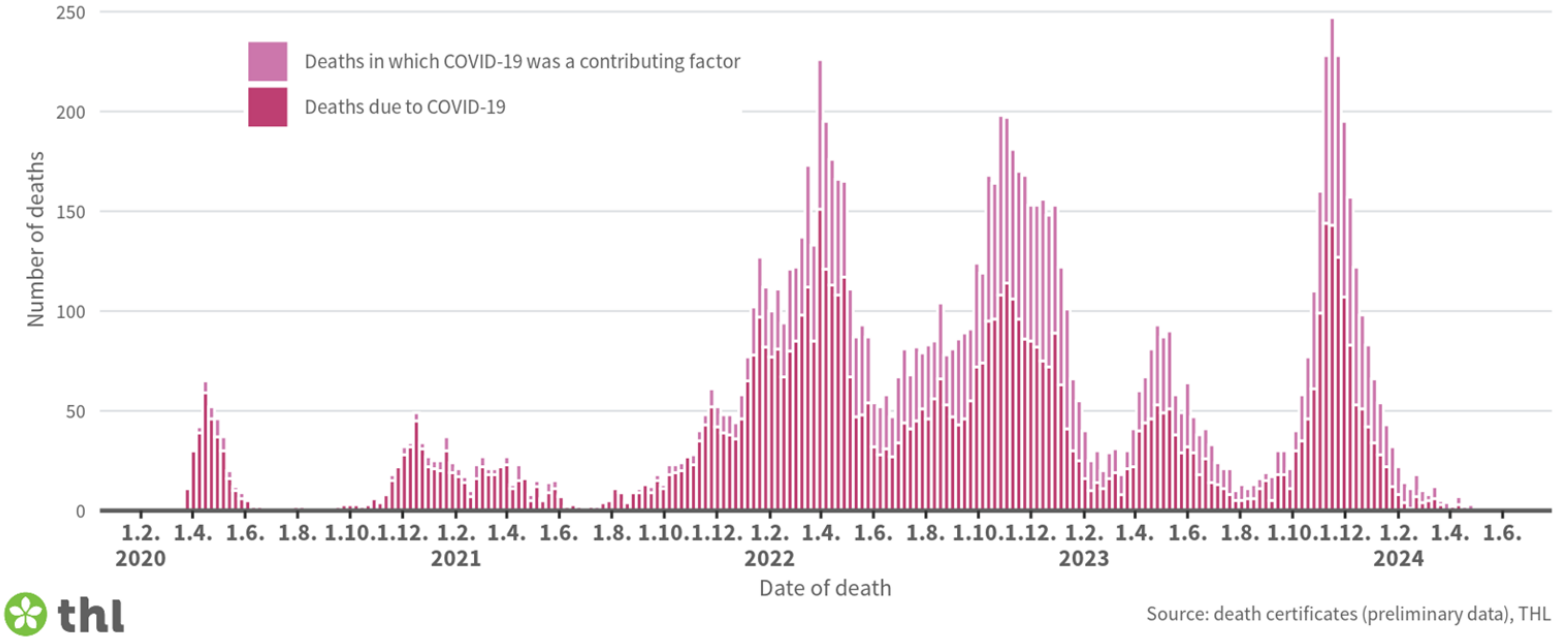


Figure 5 Weekly number of COVID-19 deaths in Finland. Source: Finnish Institute for Health and Welfare.

2.2 COVID-19 vaccines

2.2.1 COVID-19 vaccine induced immune response

The human immune system comprises several components, which can be categorised into innate and adaptive immune responses. The innate immune response serves as the initial defence against microbes; however, it recognises only a limited number of antigens and does not generate microbe-specific immune memory. During microbial invasion, an adaptive immune response is essential for growth suppression. The adaptive immune system includes B and T cells, which possess the capacity to specifically memorise antigens (96). Adaptive immune memory for COVID-19 can be acquired through exposure to SARS-CoV-2 antigens either via SARS-CoV-2 infection or COVID-19 vaccination. This adaptive immune memory can be translated into immunity against COVID-19 which reduces the risk of SARS-CoV-2 infection and severe COVID-19 (97).

After encounter with SARS-CoV-2 antigen, such as COVID-19 vaccination, it takes approximately 21 days to produce adaptive immune response indicated by an increase in neutralizing antibodies (98–100). Therefore, COVID-19 vaccination provides no (or possibly little protection) protection against SARS-CoV-2 infection during the initial days (100). The encounter with antigen induces naïve B cells to be transformed into plasma cells that start to produce neutralising antibodies. For most COVID-19 vaccines, the antigen is the SARS-CoV-2 spike protein. The concentration of neutralising antibodies peaks after a few months and then gradually decreases over time (101,102) (Figure 6). A subset of B cells undergo differentiation into antigen-specific memory B cells, which exhibit enhanced capacity for rapid antibody production upon subsequent exposure to the SARS-CoV-2 antigen (96). Therefore, if an individual receives second COVID-19 dose, the adaptive immune response is more rapid compared to the initial encounter (98–100). The neutralizing antibodies protect from SARS-CoV-2 infection and the level of neutralizing antibodies can be used as a proxy of protection against SARS-CoV-2 infection (Figure 6) (98,99,101). The immune escape of SARS-CoV-2 variants is partly due to reduced neutralisation of antibodies (103).

T cells are another part of the immune memory. Although T cells can be divided into several classes, CD8 or CD4 T cells are regarded the most important components of the adaptive immune system for protection against viral infections (103,104). CD4 T cells assist other immune cells, whereas CD8 T cells are a component to control the spread of the virus in the body (105). While B cell immunity can be easily evaluated through antibody assays, the quantification of T cell immunity is more complex and includes methods such as the analysis of cytokine release (96). In fact, T cell immunity is thought to be more persistent and less susceptible to immune escape (101,104,106). Immunity induced by seasonal coronaviruses may even provide cross-protection against SARS-CoV-2 through T cell-mediated mechanisms (104). Moreover, T cell immunity is considered an important component of protection against severe COVID-19 (105) and offers longer-lasting immune memory than B cells (Figure 6).

Evidence suggests that SARS-CoV-2 infection produces stronger immune protection against COVID-19 outcomes than vaccination. However, immunity from SARS-CoV-2 infection can be further enhanced by COVID-19 vaccination, this "hybrid immunity" providing more robust immune protection than solely infection- or vaccination-induced immunity (107,108).

While each exposure to SARS-CoV-2 antigen alters immunity, the first encounter with the antigen plays a crucial role in shaping the immune response. This phenomenon is called immune imprinting (or original antigen sin) and has been observed with influenza (109) and COVID-19 antigens (103). For example, if a person with prior exposure for original SARS-CoV-2 antigens encounters antigens from new variant (e.g. BA.4-5) the neutralizing antibodies and T cell response might be stronger against the original SARS-CoV-2 strain compared to the currently encountered variant (103).

There are plenty of other factors that affect the protection provided by COVID-19 vaccination, such as the time since vaccination (101,103), age and comorbidities of the vaccinated (102), the type of vaccine used, the dosing interval (110–112), and the variant that is encountered (Table 1).

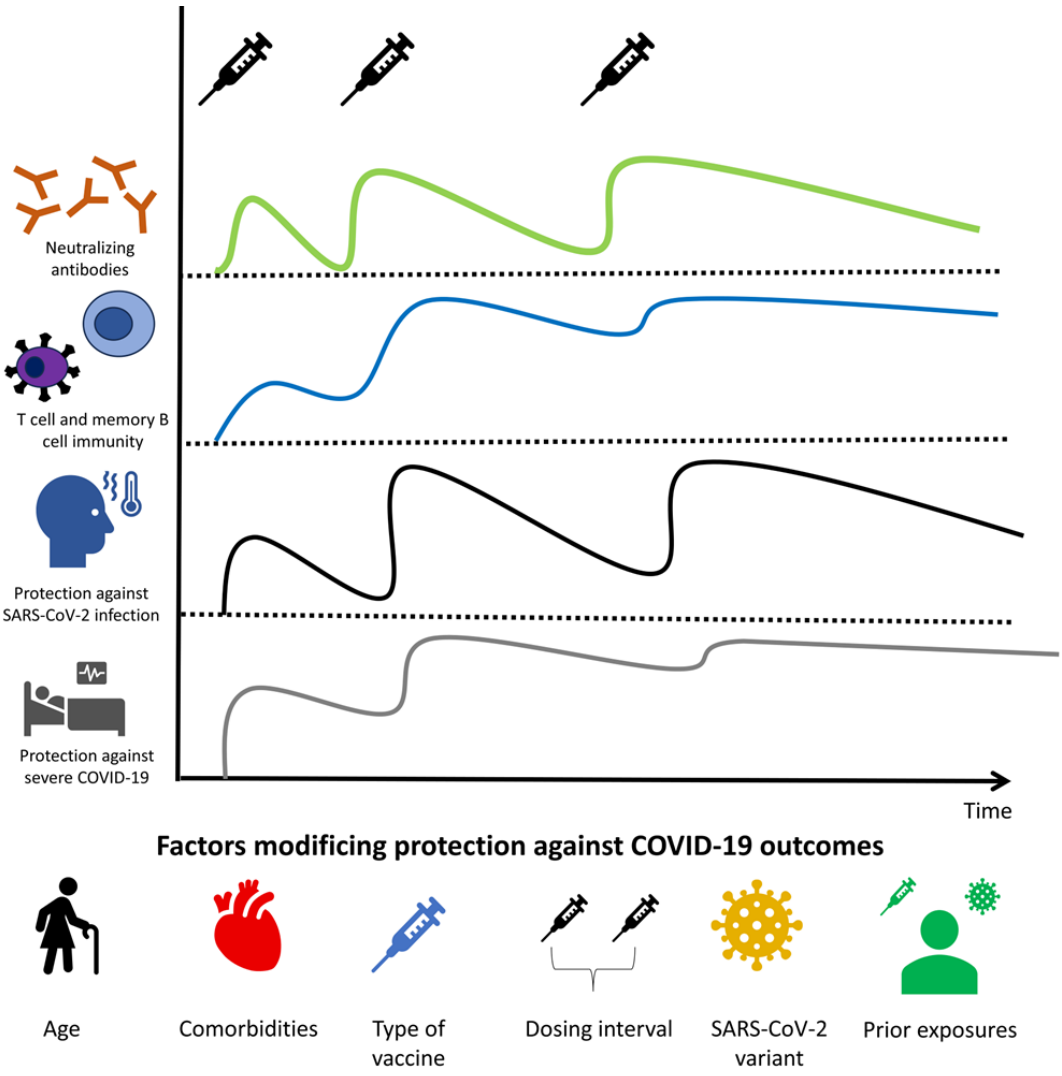


Figure 6 Schematic illustration of COVID-19 vaccine protection over time and the factors influencing it.

2.2.2 COVID-19 vaccine rollout

Protective and safe vaccines against COVID-19 were developed in less than 12 months from the first outbreaks in China, with the first vaccines authorized before the end of 2020. To date, over 13 billion COVID-19 vaccine doses have been administered worldwide (4). Several COVID-19 vaccines have been used globally (8), while many others progressed to clinical trials but were never authorized for use (113).

COVID-19 vaccines have been developed using traditional, recently developed, and novel platforms including inactivated or live-attenuated, protein subunit and mRNA-, DNA-, and vector-based vaccines, respectively (8,114). In Western countries, the most commonly used vaccines were mRNA vaccines (Comirnaty manufactured by BioNTech/Pfizer and Spikevax manufactured by Moderna), adenovirus vector vaccines (Vaxzevria manufactured by AstraZeneca and Jcovden manufactured by Janssen) and a recombinant nanoparticle vaccine (Nuvaxovid manufactured by Novavax) (5–7,12–14,115–119). Initially, COVID-19 vaccines were only authorised for adults aged 18 years or more (120–122) but vaccines for children and adolescents were eventually authorised in 2021–2022 (123–125) (Figure 7).

The first authorised COVID-19 vaccines were monovalent vaccines – meaning that the vaccine included only antigens from one SARS-CoV-2 strain – based on the original SARS-CoV-2 strain (12,98). Most of COVID-19 vaccine schedules included two doses (i.e. primary schedule), although some one-dose schedules were also authorised (115). As discussed later, the primary schedules did not provide long-term protection, and this led to the rollout of booster doses in autumn 2021 (126) and in later years (127,128).

During the initial phase the COVID-19 vaccination, rollout was marked by a significant shortage of vaccine availability. In numerous countries, due to the limited availability of COVID-19 vaccines, specific groups such as healthcare workers and elderly individuals were given priority to optimise the use of these scarce resources (129). Similarly, COVID-19 vaccinations were often administered based on availability, meaning that individuals received whichever vaccines were on hand at the time of their appointment. This led to many individuals receiving heterologous vaccination schedules, where the vaccine brand changed across the vaccine schedule.

2.2.3 COVID-19 vaccinations in Finland

In Finland, the COVID-19 vaccination rollout started on 27 December 2020 with the vaccination of healthcare workers in ICU, emergency departments, and pulmonary disease departments (120). Vaccinations were then continued among the elderly and the population at high risk of severe COVID-19 (Table 2) (130). Healthcare workers treating COVID-19 patients were also prioritised to receive the primary schedule and first booster dose to protect the healthcare workers themselves and their patients; however, additional doses were not recommended for healthcare workers after the emergence of Omicron owing to the

low vaccine-induced protection against SARS-CoV-2 infections caused by this variant (131,132).

In Finland, the most used COVID-19 vaccines were Comirnaty, Spikevax and Vaxzevria. Jcovden and Nuvaxovid vaccines were also introduced, but their uptake in the population remained low. In the spring of 2021, Vaxzevria was observed to cause thrombotic thrombocytopenia, a severe life-threatening adverse effect (133,134). This adverse effect appeared to be more prevalent among young adults; consequently, in Finland, the administration of Vaxzevria was suspended for individuals under 65 years of age (135) and subsequently discontinued in November 2021. Another safety concern was observed in autumn 2021, when mRNA vaccinations were associated with an increased risk of peri- and myocarditis (136–138). This risk was highest among young male adults and adolescents, and in a Nordic register-based study, it seemed that the risk was higher after Spikevax vaccination compared to Comirnaty (136). Therefore, in Finland, Spikevax vaccinations were halted in males aged 30 years or younger in October 2021 (139).

The standard dosing interval – used in the RCT – for Comirnaty and Spikevax primary schedule were 21 and 28 days, respectively (12,13) but for Vaxzevria the standard dosing interval was 4 to 12 weeks (140). Finland was also one of the few countries to use an extended dosing interval for the primary schedule (e.g. using over 28 days dosing interval for mRNA vaccines). The rationality of the decision was that

1) An extended dosing interval enabled more people to receive the first dose due to vaccine shortage (i.e. vaccines were used for first doses and not second doses)
2) Typically vaccinations offer higher protection with extended dosing interval (141,142).

The first COVID-19 boosters (i.e. third doses) were introduced in autumn 2021 for priority groups and first boosters were eventually recommended in December 2021 for all adults (143) (Figure 7 and 8). The rationale was to limit the spread of Omicron, which had recently emerged, (144) and increase the protection against severe COVID-19. However, boosters could not halt the spread of Omicron (93), and the objective of the vaccination rollout was shifted towards decreasing the number of severe COVID-19 cases instead of SARS-CoV-2 infection and spread of the virus. Therefore, second and additional boosters, such as BA.1 and BA.4-5 bivalent variant-adapted boosters in autumn 2022 and an XBB.1.5 variant-adapted booster in autumn 2023 (131), were only recommended to the elderly and high-risk groups.

Table 2 Target groups for COVID-19 vaccination due to presence of comorbidities and treatments predisposing to severe COVID-19 in Finland.

Risk group 1	Risk group 2
Organ or stem cell transplant	Asthma with continuous treatment
Active cancer treatment	Severe heart disease
Severe disorder of immune system	Neurological illness or condition that affects breathing
Severe chronic renal disease	Immunosuppressive drug therapy
Severe chronic lung disease	Selected autoimmune diseases
Type 2 diabetes requiring medication	Severe chronic liver disease
Down syndrome	Type 1 diabetes
	Adrenal insufficiency
	Sleep apnea
	Psychotic disorder

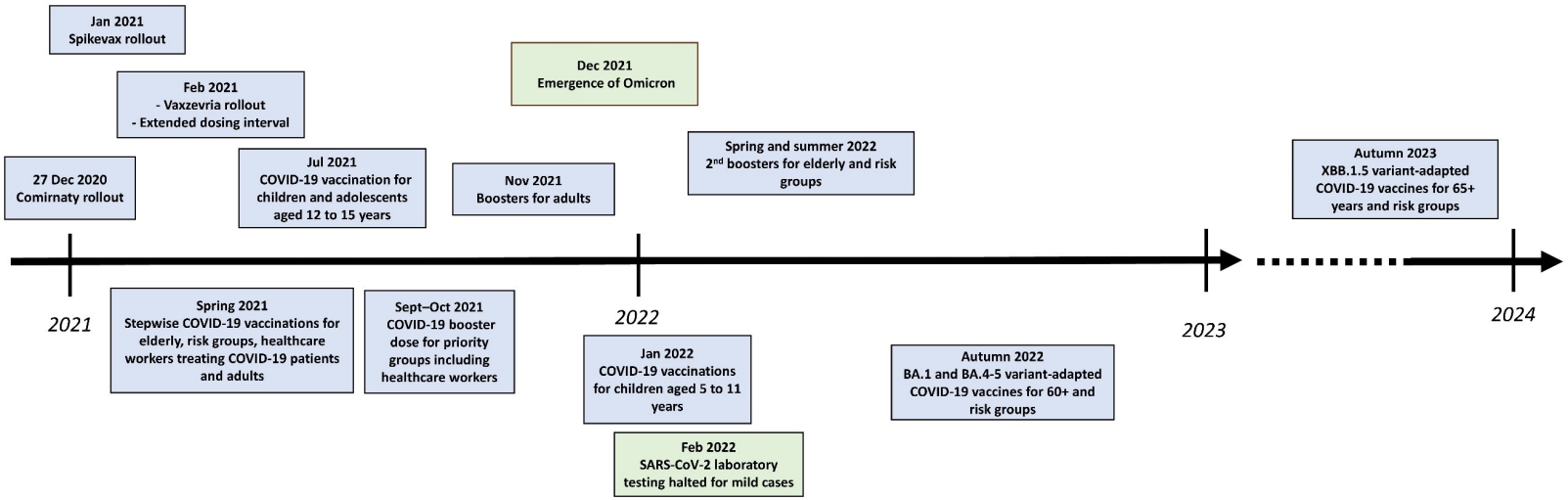


Figure 7 COVID-19 vaccination rollout in Finland from December 2020 to January 2024.

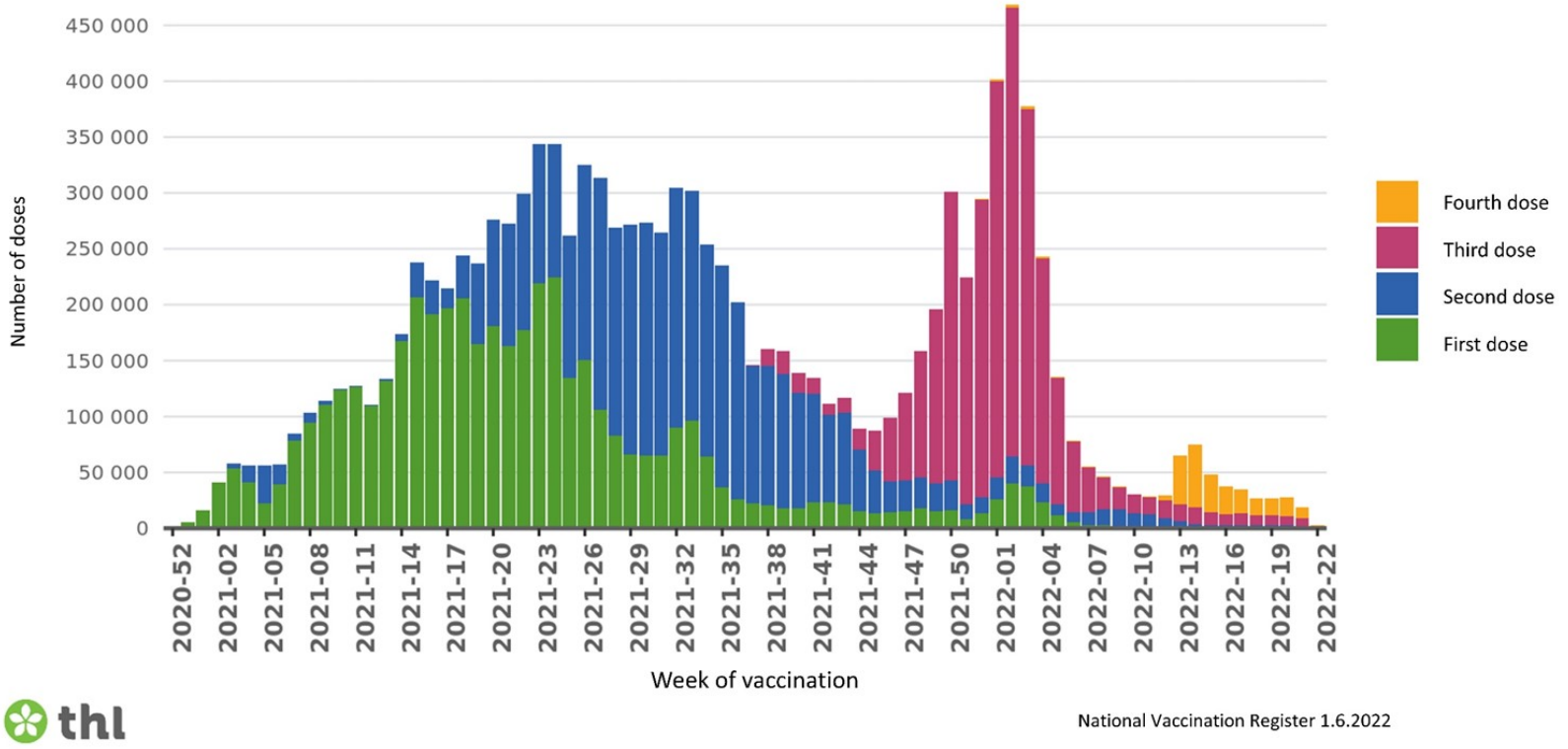


Figure 8 Weekly number of COVID-19 vaccine doses in Finland. Source: Finnish Institute for Health and Welfare.

2.3 Evaluation of vaccine efficacy and effectiveness

2.3.1 Concept of vaccine efficacy and effectiveness

Measurements of immunological responses, such as antibody production by B cells or cytokine activity of T cells, can serve as surrogates of the protection afforded by vaccinations. However, these measurements do not provide a precise estimate of actual protection (145). To evaluate the benefits of vaccination, it is necessary to estimate the reduction in incidence of an infection-related outcome attributable to vaccination. This estimate is referred to as vaccine efficacy when derived from a controlled trial and as vaccine effectiveness when derived from an observational study (96,145). They are usually estimated as

$$1 - Risk\ Ratio\ (RR) = 1 - \frac{Risk\ of\ the\ outcome\ among\ exposed}{Risk\ of\ the\ outcome\ among\ unexposed}$$

$$1 - Hazard\ ratio\ (HR) = 1 - \frac{Hazard\ of\ the\ outcome\ among\ exposed}{Hazard\ of\ the\ outcome\ among\ unexposed}$$

$$1 - Odds\ ratio\ (OR) = 1 - \frac{Odds\ of\ the\ outcome\ among\ exposed}{Odds\ of\ the\ outcome\ among\ unexposed}$$

$$1 - Incidence\ rate\ ratio\ (IRR) = 1 - \frac{Incidence\ rate\ of\ the\ outcome\ among\ exposed}{Incidence\ rate\ of\ the\ outcome\ among\ unexposed}$$

Both vaccine efficacy and effectiveness are relative measures of protection. However, the absolute effects of vaccination are similarly important (Figure 9). The absolute effect of vaccination can be measured as

$$Risk\ reduction\ (RD) = Risk\ of\ the\ outcome\ among\ unexposed - Risk\ of\ the\ outcome\ among\ exposed$$

The RD can also be used to estimate the number needed to vaccinate (NNV). NNV indicates how many individuals must be vaccinated in a study to prevent one outcome under a specified time period (146). NNV can be estimated as

$$Number\ needed\ to\ vaccinate\ (NNV) = \frac{1}{RD}$$

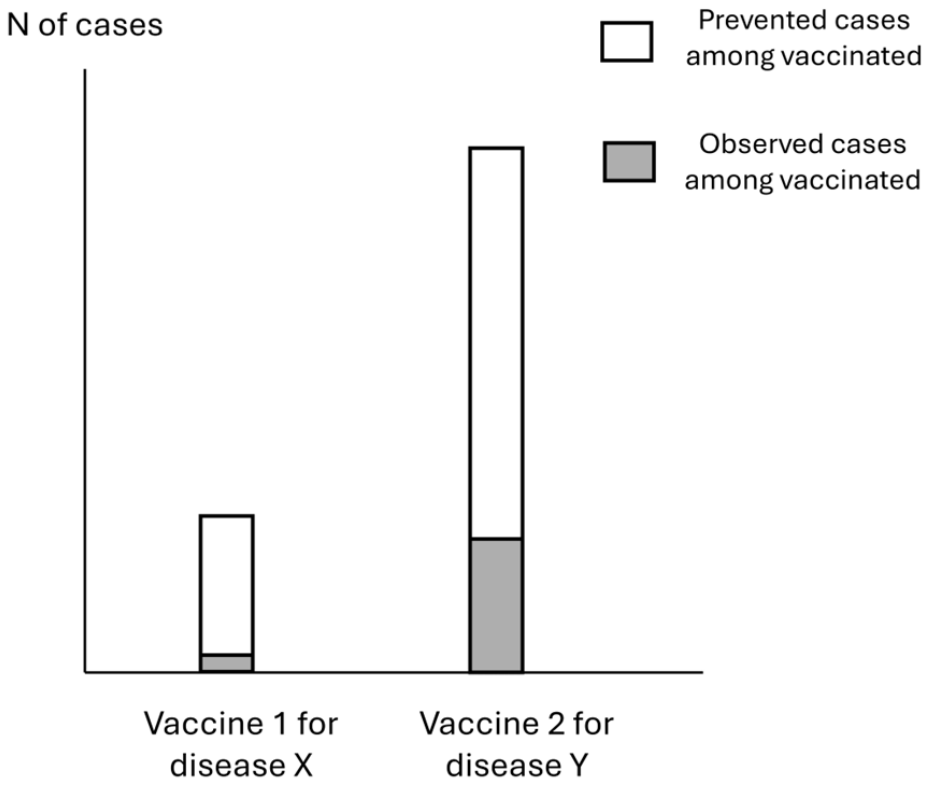


Figure 9 Absolute and relative effect of vaccination for two vaccines for diseases X and Y. Although the VE of vaccine 1 is higher, the absolute effect presented as prevented cases among vaccinated is larger for vaccine 2. This can be explained by e.g. higher incidence of disease Y. For example, VE of bivalent vaccines against COVID-19 related hospitalisation was comparable between individual aged 50 to 69 years and those aged 70 years or more. However, the absolute reduction of COVID-19 related hospitalisations was considerably higher among the latter group (147).

2.3.2 Study designs

2.3.2.1 Randomized controlled trial

In a randomised control trial (RCT), treatment is randomly allocated to study subjects (active arm), while the other subjects are allocated to receive a placebo or active control (control arm). Treatment effects are estimated by comparing these groups. An RCT can also be blinded which decreases the risk of bias. For instance, in the absence of blinding, the behaviour of study participants might be altered given their knowledge on whether they received the treatment or not, or research personnel might differentially evaluate the outcome of interest across the study arms. For RCTs evaluating vaccines, the common

problem is the side effects of vaccination (i.e. fever or rash due to vaccination) which might reveal the allocation to the study subject or researchers. This can be avoided by using active vaccines with similar side effects and known effects on the outcome of interest in the control arm (145).

For new vaccines, RCTs have two key goals: 1) to estimate the protective effect of the vaccine, and 2) to evaluate its safety before wider implementation. The benefit of RCTs is that, on average, they balance the measured and unmeasured confounders (see: Confounders and residual confounding) between groups at baseline and, therefore, are the gold standard design for evaluating the protective effect and safety of vaccines (145,148). Moreover, the research question is usually precise and data quality is high (149).

RCT has some limitations including

- *Ethical concerns*. When highly effective and safe treatment is available, placebo-controlled trials are usually regarded unethical (150). Therefore, RCTs might be inappropriate for estimating the protective effect of vaccination after the vaccine rollout, although this data could be needed for decision making, for example due to a newly emerged virus variant.
- *Reduced timeliness*. In some cases, observational studies might provide evidence for policymaking more rapidly than RCTs, when vaccination has been introduced. For example, observational studies enabled assessments of waning effectiveness and vaccine protection against newly emerged SARS-CoV-2 variants almost in real time (151,152).
- *Lack of power for rare outcomes*. Although the phase III RCTs of Comirnaty and Spikevax provided robust data on vaccine efficacy against COVID-19 and severe COVID-19, they lacked the power to estimate long-term vaccine efficacy against severe COVID-19 (12,13,153,154). Therefore, it was not known whether vaccine efficacy against severe COVID-19 waned over time. Moreover, some rare – but clinically significant – adverse effects of COVID-19 vaccines were not identified in RCTs but were later confirmed in observational studies after mass roll-out of COVID-19 vaccines (134,136).
- *Exclusion of high-risk groups*. Usually, in RCTs, the study population lacks elderly individuals and those with comorbidities. For example, in the phase III RCT of Comirnaty, only individuals "*who were healthy or had stable chronic medical conditions*" were enrolled (12).
- *Post-randomisation confounding*. Although, on average, randomisation balances confounders at the baseline, confounding might be present in an RCT due to loss to follow-up, non-compliance, missing data, and differences in the rate of diagnosis or treatment (155–157). The risk of post-randomisation confounding is considered higher in trials with long follow-up or trials estimating intervention in real-world routine practice setting (i.e. pragmatic trials) (157).

Moreover, clinical trials are conducted in ideal settings, and the storage and transport of vaccines are closely monitored which might not be possible in mass rollout. For example, the transportation of mRNA vaccines requires cold conditions, and in real-world settings,

vaccine storage might fail, causing vaccine failure. For example, the initial transportation of Comirnaty required temperatures from -90° to -60° Celsius (158), but the transportation temperatures could be later relaxed with more data on the stability of the vaccine (159). Close monitoring can be viewed as both a strength and limitation in an RCT. RCTs can reveal the ideal efficacy of vaccination, which might be difficult to obtain from observational studies. On the other hand, RCT might overestimate the protection provided in mass vaccination settings where logistical or administrative errors can result in vaccine failure.

2.3.2.2 Test-Negative Case-Control Design

A test-negative case-control design (TND) is a modified case-control design used to estimate VE. A study evaluating pneumococcal vaccine efficacy published in 1980 is usually considered the first which utilised the TND (160), although the concept of TND was formalised in 1985 by Olli Miettinen (161), a Finnish-born epidemiologist who acted as a professor at Harvard University from 1974 to 1986 (162). The design was further developed to monitor seasonal influenza VE and was first used for this purpose in Canada in 2005 (148,163). Thereafter, it has been used to estimate the VE of other vaccines such as rotavirus and COVID-19 vaccines (164,165).

In a TND estimating the effectiveness of COVID-19 vaccines, the study includes those who seek medical care for acute respiratory infection and who are tested for SARS-CoV-2. Based on the laboratory test results the participants are divided into cases (positive result for SARS-CoV-2) and controls (negative result for SARS-CoV-2) (Figure 10). The control group in the TND includes those infected with other viruses than SARS-CoV-2 that cause similar clinical presentations (e.g. adenovirus, respiratory syncytial virus). The enrolment of cases and controls at the time of testing makes the TND a relatively simple design compared to the traditional case-control study design (164). Moreover, by limiting the study participants to those tested for the disease, the TND inherently addresses confounding due to health-seeking behaviour, although this behaviour may not be fully controlled without adequate adjustment. Addressing confounding due to health-seeking behaviour is a major advantage in estimating VE against symptomatic SARS-CoV-2 infection (166).

For the validity of the TND, it is crucial that the cases and controls are derived from the same source population (e.g. symptomatic ARI patients seeking medical care) and that the enrolment of controls is independent of the exposure status. Usually, enrolment criteria include the time of symptom onset (e.g. <10 days) and a list of symptoms (e.g. at least two symptoms of ARI) to ensure the derivation of unexposed and exposed from the same source population (165). If these are fulfilled, the relative frequency of test-negative results among the exposed and unexposed participants should be similar to the source population, enabling the estimation of VE (see Figure 10) (148).

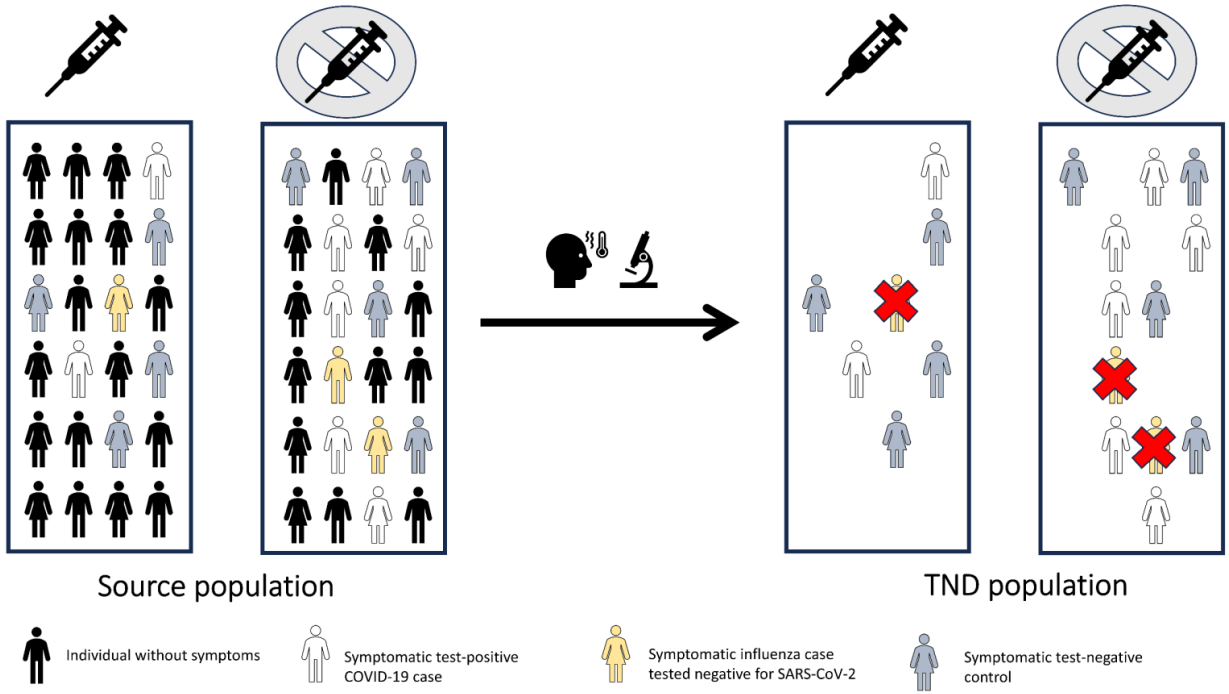
In addition to confounding, TND is subject to other potential sources of bias. One concern is the possible dependency between the severity of infection and the exposure status. If severity of symptoms varies between vaccinated and unvaccinated, the source

population from which the subjects are enrolled might differ between the two exposure groups causing bias (164). Furthermore, correlation between COVID-19 and influenza vaccination might also induce bias (167). The correlation results in an alteration in the enrolment of influenza cases into a TND estimating VE against COVID-19; consequently, unexposed controls have a higher probability of being infected with influenza than exposed controls, thus altering the source population. However, this bias can be addressed by either excluding influenza cases from the control group (Figure 10) or adjusting the analysis for influenza vaccination (167,168).

Another source of bias is the imperfect diagnostic accuracy of laboratory tests, which may result in the misclassification of controls or cases (166). It is noteworthy that imperfect diagnostic accuracy causes misclassification bias in other study designs, including RCTs; however, in the TND, misclassification has a slightly more profound effect (169). If the accuracy of the laboratory test is high, as is the case for SARS-CoV-2 confirmation by PCR, misclassification bias in the TND is generally relatively small and clinically insignificant (169).

As a limitation, the TND approach is suitable only for selected outcomes and estimation of VE against e.g. MIS-C or mortality due to COVID-19 might be difficult. Furthermore, TND does not facilitate the quantification of absolute risks, thereby limiting its benefits in policymaking.

TND can be based on clinical or surveillance data. In a clinic-based design, participants are enrolled in a clinic by researchers at the time of testing, and data on vaccination status and other variables are collected from sources such as questionnaires or patient records. In this setting, the researcher is blinded to the case-control status of the participant, and the case-control status is revealed prospectively from the time of enrolment. In a TND based on surveillance data, researchers typically have access to data on positive and negative test results from medical registers or other databases, and the case-control status is defined retrospectively from the time of enrolment (i.e. testing). This methodology can potentially introduce bias through two mechanisms. Firstly, register data usually do not include precise information on the symptomatology of tested individuals. If the severity of symptoms differs between cases and controls, bias may be induced (164). Moreover, asymptomatic testing was frequent during the COVID-19 pandemic, causing potential bias if such cases were included in the TND (170). Exclusion of these asymptomatic cases might not be possible with register data. Secondly, the TND based on surveillance data might utilise data gathered after the baseline (e.g. diagnosis codes from registers). For instance, if VE is estimated against hospitalisation due to acute respiratory infection caused by COVID-19, the researcher might enrol patients with diagnosis codes related to acute respiratory infection. It is probable that positive or negative test results have some impact on the recorded diagnosis codes, causing dependency between case-control status and enrolment of the participants, thereby altering the source population and potentially introducing bias (171). The strengths of the TND based on surveillance data is its low price and capability of enrolling large study populations.



$$VE = 1 - OR = 1 - \frac{\frac{Vaccinated\ symptomatic\ test-positive\ COVID\text{-}19\ cases}{Vaccinated\ symptomatic\ test-negative\ controls}}{\frac{Unvacciated\ symptomatic\ test-positive\ COVID\text{-}19\ cases}{Unvaccinated\ symptomatic\ test-negative\ controls}}$$

Figure 10 Test-negative case-control design. Figure adapted from Tchetgen Tchetgen et al. (168). In a TND estimating VE against symptomatic SARS-CoV-2 infection, individuals who present with symptoms and undergo SARS-CoV-2 testing are enrolled in the study. The test-negative controls represent the source population, enabling the VE estimation. The correlation between COVID-19 and influenza vaccination results in a differential enrolment of influenza cases as negative controls between COVID-19 vaccinated and unvaccinated, potentially introducing bias (167). This correlation can be addressed by either excluding influenza cases as presented in the figure or adjusting for influenza vaccination (167). TND = Test-negative design, VE = Vaccine effectiveness, OR = Odds ratio.

2.3.2.3 Cohort designs

A cohort is defined as a group of individuals who share common experiences, conditions, or characteristics (172). For instance, Finnish residents aged 18 years or older constitute a nationwide cohort of adults. In COVID-19 VE studies, some cohorts with active enrolment were utilised (173); however, this study design is resource-intensive and costly. Consequently, the most pragmatic approach typically involves identifying a cohort using registers or databases, which facilitates the inclusion of large cohorts, thereby enhancing statistical power. A limitation of this method is that registers or databases may contain inaccuracies, potentially affecting the identification of data such as exposures, outcomes, or covariates (171). In the context of COVID-19 VE estimation, register-based studies have primarily adopted two methodological approaches: a single cohort with time-varying exposure, and target trial emulation (174).

2.3.2.4 A single cohort with time-varying exposure

VE can be assessed using a single cohort approach with vaccination as a time-varying exposure (174). In this approach, each individual initially enters the cohort as unexposed, and subsequently some individuals receive vaccination, at which point their exposure status is altered from unexposed to exposed. This allows individuals to be prospectively followed over time, accommodating changes in exposure status at any time point, as shown in Figure 11. VE can be assessed by comparing hazards or incidence rates among unvaccinated and vaccinated (174). The confounder-adjusted VE can be estimated utilising Cox or Poisson regression models. In these models, calendar time can be accounted for by selecting it as an underlying time scale (Cox regression model) or incorporating it as a covariate (Poisson regression model). This adjustment is crucial, as hazard or incidence rates and vaccination coverage fluctuate over time, potentially confounding the analysis.

One advantage of this design is its relative simplicity. The study population size is also usually large because the inclusion criteria for the study can be wide, which might increase statistical power. Furthermore, findings from this approach can often be generalized to the broader population.

However, this approach is not without limitations. Firstly, at the time of vaccination, significant time-varying confounding may occur, as individuals with respiratory symptoms are less likely to seek vaccination. This presents methodological challenges (174). Secondly, the comparability of vaccinated and unvaccinated individuals may decrease over time, as SARS-CoV-2 infections or other acute medical conditions are more likely to occur in unvaccinated individuals. This imbalance might be complicated to address in a single-cohort design, although other study designs – including RCTs – might as well be subject to similar bias (175). Thirdly, this methodology does not easily facilitate a reliable assessment of absolute risk reduction, in contrast to some other designs (e.g. target trial emulation) (174).

Lastly, the statistical methods used to estimate confounder-adjusted VE have inherent limitations, which are discussed later (176,177).

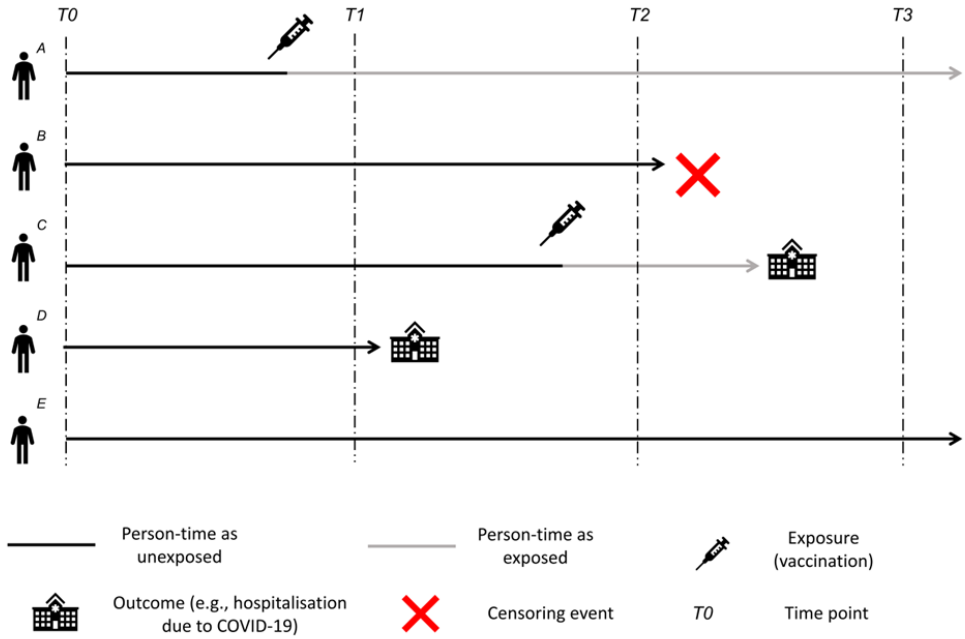


Figure 11 Illustration of a single cohort with time-varying exposure. Individuals are followed over time. Follow-up data are presented for five individuals (A, B, C, D, E) at four different time points (T0, T1, T2, T3) during the study.

2.3.2.5 Target trial emulation

Many observational studies have design flaws that introduce biases, which can be mitigated through a precise research question and appropriate study design (178–180). One common bias is immortal time bias, which arises when either the exposed or unexposed group have a period due to study design during which the outcome cannot occur. This bias has been estimated to affect nearly half of observational studies (181). In some cases, study design flaws may introduce greater bias than confounding (180). To address these issues, the target trial emulation framework has been introduced. This approach utilizes observational data to mimic a hypothetical RCT. By systematically specifying the causal question, eligibility criteria, treatment assignment, and follow-up, researchers can minimize biases in observational studies due to inappropriate study design (Table 3) (180,182).

When estimating VE, the target trial emulation framework helps identify potential flaws in the study design. For instance, one common observational study design for evaluating VE against long-COVID has been to compare the risk of long-COVID between vaccinated and unvaccinated individuals who have been infected with SARS-CoV-2 (183,184). In this design, the exposure (COVID-19 vaccination) occurs some time before the infection, such as three months earlier. However, only vaccinated individuals who become infected after vaccination are included in the vaccinated (i.e. exposed) group. In other words, vaccinated individuals who never become infected are excluded from the study.

This approach does not align with a hypothetical RCT where the exposure would be randomly assigned at the start of the study, and all participants—regardless of subsequent SARS-CoV-2 infection—would be followed from exposure until a censoring event. Crucially, an RCT would not condition inclusion on SARS-CoV-2 infection. Conditioning on infection can introduce collider bias in the VE estimate—bias that arises when conditioning on a variable that is influenced by the exposure and by another factor related to the outcome (176) (Figure 12).

When the study population includes only individuals who became SARS-CoV-2 infected, the vaccinated group may disproportionately include individuals who were more susceptible for SARS-CoV-2 infection than those in the unvaccinated group. This susceptibility could be an immunocompromising condition or poor immunological response for vaccination, both of which might also increase the risk for long-COVID. Consequently, the vaccinated group is restricted to a subpopulation at higher risk for long-COVID, potentially leading to a misleading conclusion that vaccination increases the risk—even if it actually reduces it (185). Although previous studies using this design have not reported an increased risk of long-COVID among vaccinated individuals (183,184), this does not mean that the design is free from methodological challenges related to collider bias.

Moreover, in a target trial emulation framework, eligibility criteria can be incorporated more easily into the study compared to other observational designs. For example, the eligibility criteria for a vaccine X are outlined in Table 2. The first two criteria can be easily adapted to a single cohort with time-varying exposure or TND by excluding individuals who do not fulfil the criteria. However, implementing the third (individual is not hospitalized at the time of treatment assignment) and fourth criterion (individual does not have symptoms related to disease X) might be challenging. In a target trial emulation, ensuring that individuals meet these eligibility criteria at the start of follow-up is easily adapted reducing the risk of bias in the analysis.

Table 3 An example of target trial emulation for vaccine X among adults aged 18 years or more. Table adapted from Andersson et al. (186).

Protocol	RCT specification	Target Trial Emulation
Eligibility criteria	1) Individual is aged 18 years or more 2) Individual has not experienced an anaphylactic or allergic reaction caused by vaccine Y with similar conjugate to vaccine X 3) Individual is not hospitalised at the time of treatment assignment 4) Individual does not have symptoms related to disease X	Same as for the target trial.
Treatment strategies	1) Individual receives a vaccine X at baseline 2) Individual does not receive a vaccine X at baseline and continue being unvaccinated during follow-up	Same as for the target trial.
Treatment assignment	Randomisation 1:1 at baseline	Exact 1:1 matching with confounders at baseline
Outcomes	Hospitalisation due to disease X with laboratory confirmation	Same as for the target trial.
Follow-up	Follow-up from the baseline until censoring event, including outcome of interest, death or end of study period.	Same as for the target trial.
Causal contrast of interest	Per-protocol analysis	Same as for the target
Statistical analysis	Cumulative incidences are estimated with Kaplan-Meier estimator and are used for evaluating risk ratios and differences across the treatment assignments.	Same as for the target trial.

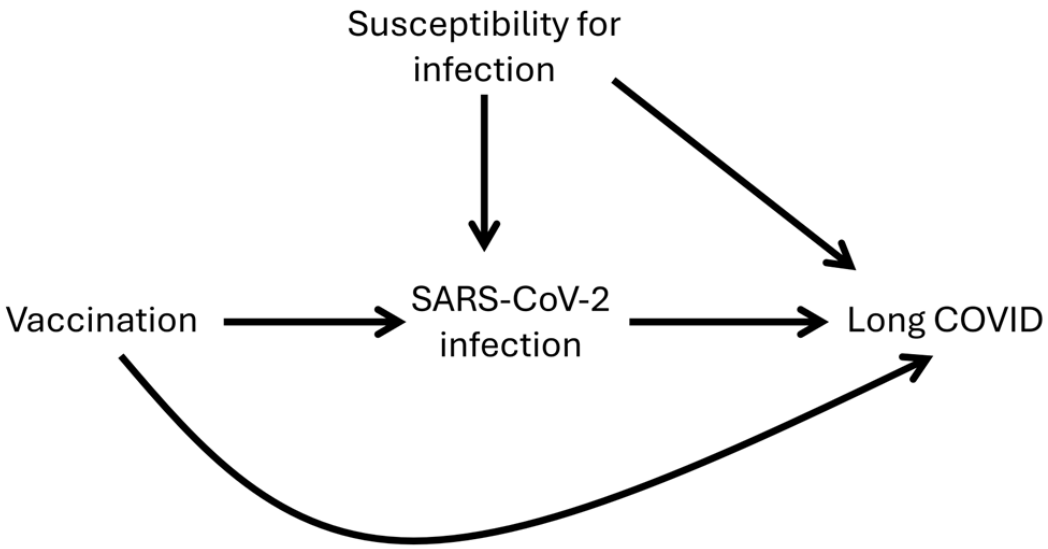


Figure 12 Collider bias due to conditioning on SARS-CoV-2 infection when estimating vaccine effectiveness against long-COVID among SARS-CoV-2 infected individuals (185).

2.4 Methods for addressing confounding

2.4.1 Confounders, confounding, and residual confounding

Confounding occurs when a factor—known as a confounder or common cause—influences both the exposure (independent variable) and the outcome (dependent variable), creating a spurious association between these variables (176). In RCTs, the distributions of both measured and unmeasured confounders are, on average, similar across treatment arms. Therefore, if conducted appropriately, RCTs are generally free from confounding. In observational studies, however, confounding is present (176). In the context of COVID-19 VE, confounding can be simplified into two main sources:

1) **Age and comorbidities.** Elderly individuals and those with comorbidities are more likely to receive vaccinations than the general population. Compared with others, they also have a different baseline risk of COVID-19. This risk may be lower if they avoid situations with a high risk of SARS-CoV-2 exposure (biasing VE estimates upward, toward 100%), or higher if transmission is widespread among the elderly (biasing VE estimates downward, toward 0%). This relationship introduces confounding, as illustrated by the directed acyclic graph in Figure 13.

2) **Health-seeking behaviour.** Individuals who are more concerned about their health tend to seek vaccinations more frequently. Such health-seeking behaviour may also reduce the risk of SARS-CoV-2 infection through protective measures such as mask use (biasing VE estimates upward, toward 100%). Alternatively, it may increase the likelihood of SARS-CoV-2 testing (biasing VE estimates downward, toward 0%).

To obtain accurate VE estimates, confounding must be rigorously addressed in studies. Various techniques exist to address measured confounders. This thesis focuses on two key techniques: the Cox regression model and matching.

Even after applying these methods, unmeasured confounding may still exist, introducing bias (172,176). This remaining bias is known as residual confounding (187). Methods for assessing residual confounding are discussed in later sections.

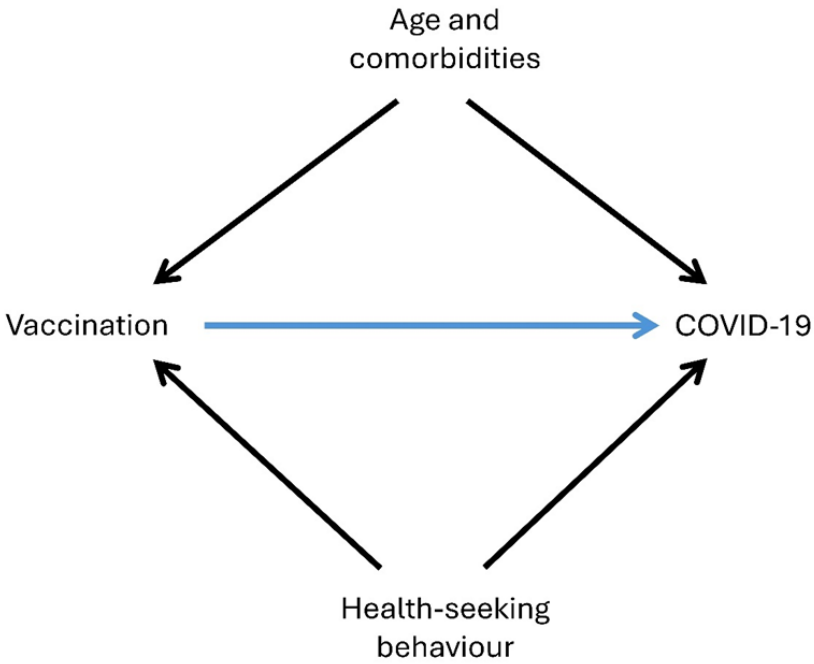


Figure 13 Confounding due to comorbidities and medical conditions and health-seeking behaviour in the estimation of COVID-19 vaccine effectiveness (blue arrow) presented in a direct acyclic graph.

2.4.2 Cox regression model

The Cox regression model, also known as proportional hazards model, was developed by Sir David Cox in 1972 (188) and is widely used in survival data analysis (172). The Cox regression

model can be used to semi-parametrically estimate the hazard ratio (HR) for an exposure. The hazard is an incidence rate in a split second (172).

The equation for the hazard of a group with the covariate vector $\bar{X}$ at time t is

$$h(t|\bar{X}) = h_0(\mathrm{t})\exp\left(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n\right)$$

where

$$h(t|\bar{X}) = Hazard\ function\ at\ time\ t$$
$$h_0(\mathrm{t}) = Baseline\ hazard$$
$$\beta_p = Coeffecient\ for\ variable\ p$$
$$X_p = Independent\ variable\ p$$

The baseline hazard represents the hazard when all covariates have zero values. When comparing two groups with different covariate profiles $\bar{X}_v$and $\bar{X}_u$, the ratio of their hazards is

$$\frac{h(t|\bar{X}_v)}{h(t|\bar{X}_u)} = \frac{h_0(\mathrm{t})\exp\left(\beta_1 X_{1,v} + \beta_2 X_{2,v} + \ldots + \beta_n X_{n,v}\right)}{h_0(\mathrm{t})\exp\left(\beta_1 X_{1,u} + \beta_2 X_{2,u} + \ldots + \beta_n X_{n,u}\right)}$$

The baseline hazard cancels out, and the formula can be simplified to

$$\frac{h(t|\bar{X}_v)}{h(t|\bar{X}_u)} = \exp\left(\beta_1(X_{1,v} - X_{1,u}) + \beta_2(X_{2,v} - X_{2,u}) + \ldots + \beta_n(X_{n,v} - X_{n,u})\right)$$

Suppose now that the two groups differ only in the covariate X_1, with the group v having $X_1 = 1$ and the group u having $X_1 = 0$, and all other covariates being equal. Then we get:

$$\frac{h(t|\bar{X}_v)}{h(t|\bar{X}_u)} = \exp\big(\beta_1(1-0) + \beta(0) + \ldots + \beta_n(0)\big) = \exp\beta_1$$

If the covariate X_1 is the vaccination status, then the exponential of the coefficient β_1 estimates the HR between vaccinated and unvaccinated individuals. This hazard ratio estimated with Cox regression is interpreted conditionally: it compares two groups that differ in vaccination status but are otherwise identical in terms of the covariates included in the model. If the covariates are the confounders, the Cox regression model enables estimation of confounder-adjusted HR between vaccinated and unvaccinated individuals.

2.4.2.1 Limitations

A key assumption of the Cox regression model is that the hazards are proportional over time meaning that the HRs of all covariates are constant over the underlying time scale (172). Notably, this assumption is violated in many cases (189). In studies evaluating VE using a Cox regression model, a major concern is that the vaccine protection changes over time due to waning or newly emerged variants, thereby violating this assumption. One approach to account for this is to divide the exposure into smaller intervals where the proportional hazard assumption might hold (176). However, the HR (and VE) might also vary within these intervals depending on their length.

Moreover, the Cox regression model provides a weighted average over the studied interval which interpretation might be problematic as presented in Figure 14. Even dividing the interval into two separate smaller intervals might not solve the problem. In Figure 14, if the interval is divided into intervals of 14–90 and 91–180 days since vaccination, the HR is over 1.0 in the latter period indicating that the vaccination would increase the risk of outcome during 91–180 days since vaccination. However, this interpretation would be incorrect. If at any point during the 91–180 days since vaccination, cumulative hazards were compared from day 14 onward, the cumulative hazard among the vaccinated would be lower than among the unvaccinated.

In RCTs, this problem is usually solved by drawing a survival curve with the Kaplan-Meier estimator from the time of randomisation (177). In the example shown in Figure 14, comparison of the survival curves reveals that the cumulative risk since vaccination is lower among vaccinated individuals at every time point until day 180 since vaccination. For HR estimation in observational studies, the cumulative hazard curves are not traditionally obtained because of the use of regression modelling to address confounding which makes drawing confounder-adjusted survival curves more laborious, although not impossible (177).

An additional limitation of the Cox regression model is that it cannot reliably estimate VE in the presence of time-varying confounders that either affect or are affected by the exposure. All traditional methods are subject to this issue, and in such cases, more advanced statistical approaches are required (172). The bias introduced by traditional methods is typically either overadjustment or collider stratification bias (190). Overadjustment bias can occur when time-varying confounders act as both confounder and mediator (176). A mediator is a variable that is influenced by the exposure and that also affects the outcome—essentially explaining part of the causal effect of the exposure on the outcome. If such a mediator is adjusted for using traditional statistical methods, part of the exposure's effect on the outcome may be blocked, biasing the estimation (176).

Collider stratification bias is caused by traditional methods' failure to handle colliders if they are adjusted for in the model (176). In principle, all traditional methods are based on stratification, meaning that they condition on covariates. However, conditioning on a collider induces an association between its causes, leading to bias as discussed in the Target Trial Emulation section (176).

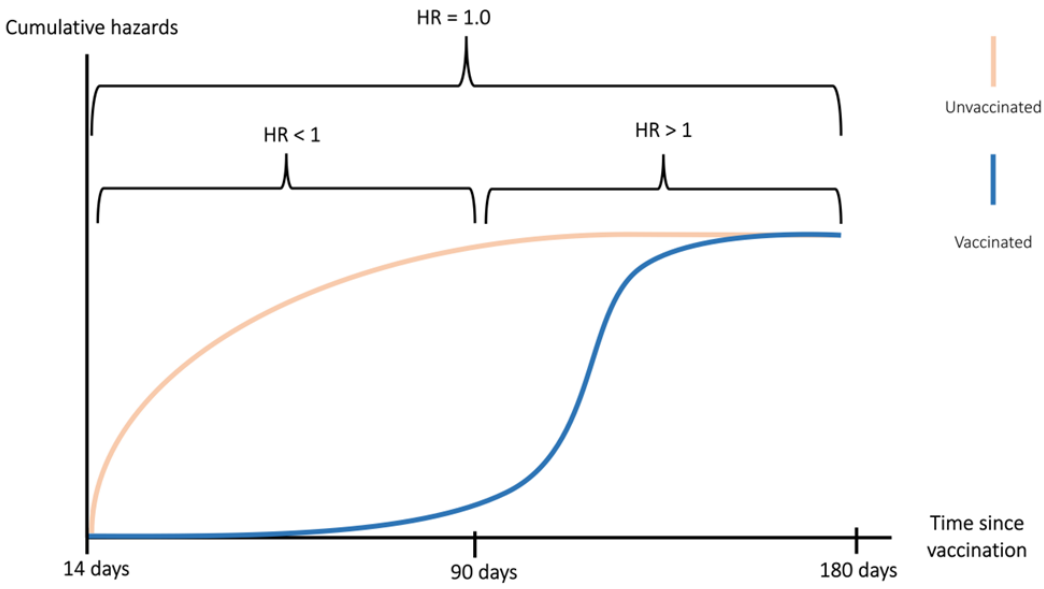


Figure 14 Hazards of hazard ratio.

2.4.3 Matching

The goal of matching is to construct a population of unexposed and exposed individuals with similar distributions of confounders. Ideally, all confounders should be measured and either incorporated into the matching procedure or accounted for afterwards using alternative methods (e.g. regression modelling). The classical example is 1:1 matching by the nearest neighbour, but weighting and sub-classification are also considered as matching methods (191).

One advantage of matching is its ability to accurately control for the confounding effects of the matched variables at baseline. Additionally, this approach reduces model dependency compared to parametric methods such as regression models (191). Parametric methods rely on assumptions that are often violated, and the consequences of these violations can be difficult to interpret (192). Another limitation of parametric modelling is the lack of transparency regarding how results are obtained. Researchers often run multiple statistical models using different sets of covariates but typically publish only one or a few estimates. The rationale behind selecting these specific estimates is often unclear. Were they chosen because they were believed to be the closest approximation of the true causal effect, or because they produced the most striking results (193)?

Several methodologies exist for implementing nearest-neighbour matching with the most precise approach being matching exposed and unexposed subjects with identical

variable values (i.e. exact matching) (191). Although this technique is considered optimal, it becomes increasingly complex when multiple variables are applied for matching purposes. An alternative approach to mitigate this issue is to employ a different matching method, such as propensity score matching (191).

The propensity score introduced by Rosenbaum and Rubin in 1983 (194) is a balancing score that represents the probability of receiving treatment (191,194). By design, individuals with the same propensity score exhibit, on average, similar distributions of covariates that influence the treatment probability. Confounding can thus be addressed by matching the exposed to unexposed subjects based on their propensity scores (194,195).

In an observational setting, the propensity score is unknown and must be estimated for each subject as the conditional probability of receiving a treatment given the individual's covariates. The model to obtain this probability is usually a logistic regression. Identifying individuals with identical propensity scores is improbable; therefore, matching is typically conducted for individuals with proximate, albeit not identical, propensity scores. For example, a male aged 72 years with coronary disease might have a similar probability of COVID-19 vaccination, i.e. a similar propensity score, as a female 81-year-old without any comorbidities and thus they might qualify as a match in a VE study.

2.4.3.1 Limitations

In matched study designs, the study population is restricted to a subset of the source population, thereby reducing the size of the study population and statistical power. This limitation constitutes a significant drawback of the matched designs (172). Furthermore, identifying suitable matches is frequently more challenging in subpopulations with high (or low) vaccination coverage, such as the elderly and individuals with chronic conditions, resulting in a study population that deviates from these groups (196,197). Consequently, the results of matched cohort studies may not accurately reflect VE in these subpopulations (176). However, alternative analytical approaches may face similar challenges when attempting to mitigate confounding in subpopulations with low or high vaccination coverage. This difficulty arises from the potential lack of sufficient overlap between the exposed and unexposed groups, which could lead to extrapolation of estimates, potentially compromising the reliability of the results (191).

Propensity score matching has been extensively utilised; however, it has certain limitations. King and Nielsen (198) argued that it can increase model dependency and counterintuitively exacerbate imbalance between matched pairs in some scenarios. This imbalance occurs because propensity score matching might ignore crucial covariate data, leading to a situation in which pairs with similar propensity scores might have widely different distributions of covariates. Therefore, King and Nilsen recommend using exact matching instead of propensity score (198).

2.4.4 Negative controls for detecting residual confounding and biases

Observational studies conducted in the 1990s and the early 2000s suggested a high reduction in all-cause mortality by seasonal influenza vaccination among the elderly (199). However, these findings were not supported by immunological or ecological studies. For this reason, Jackson et al. conducted analyses to understand if the previous findings were influenced by bias (200). They estimated vaccine effectiveness against all-cause mortality outside the influenza season and against risk of injury or trauma and expected the vaccination had no impact for these outcomes. Because they observed vaccination being associated with lower risk for both findings, they argued that the finding was influenced by residual confounding.

The method of Jackson et al. (200) for detecting residual confounding and biases was later named negative control outcome analysis (187). For such an analysis to be effective, two criteria should be met

1) The confounders influencing the exposure–outcome and the exposure–negative control outcome association should be similar, and
2) The exposure must have no causal effect on the negative control outcome (187).

If an association between exposure and negative control outcome is observed, this indicates residual confounding or other bias (187).

In addition to injury-related outcomes, previous VE studies have used cardiovascular outcomes, cancer-related deaths, prostate biopsy, mammography, and non-melanoma skin cancer as negative control outcomes (201–203). Moreover, infection or related outcomes, such as hospitalisation due to infection caused by other microbes, can be used as negative control outcomes (204).

Some studies have also used non-COVID related hospitalisation and deaths as negative control outcomes (174,205). There are some concerns regarding the use of these outcomes as negative controls. Firstly, if misclassification of COVID-19 outcomes is present, some of the true COVID-19 outcomes are classified as non-COVID-19 outcomes. These misclassifications are dependent on vaccination (i.e. more misclassification among unvaccinated due to higher incidence of COVID-19 outcomes), and therefore violates the second criterion of negative control outcomes. Moreover, COVID-19 vaccinations could potentially reduce non-COVID outcomes. For example, influenza vaccinations reduce cardiovascular events (206); similarly, COVID-19 vaccinations are associated with a reduced risk of thromboembolic events (207). Furthermore, COVID-19 vaccinations may reduce the risk of exacerbation of chronic diseases, such as heart failure, although it should be noted that no high-quality studies have been conducted in this regard (208).

Similar to negative control outcomes, studies may have negative control exposures, although their use has not been as frequent as negative control outcomes. Here, the association between negative control exposure and the outcome of interest indicates a bias (187). For example, tetanus and hepatitis A vaccinations have been suggested as a negative controls for VE analysis (187,204). Alternatively, mammography, dental appointments, or

other routine examinations with similar health-seeking behaviours that influence vaccination uptake could be utilised.

2.4.4.1 Negative control period

Another negative control used extensively in COVID-19 VE estimation is the negative control period, which refers to the initial days after vaccination (196). During these initial days, vaccination should not protect from COVID-19 outcomes because the immunological response required for this protection takes a few days. Therefore, either increased or decreased risk of disease outcomes during these days indicates bias (196).

In COVID-19 VE analysis conducted in Israel using data from the Clalit Health Services, Dagan et al. (196), Barda et al. (209) and Magen et al. (210) utilized a negative control period for detecting bias in studies using target trial emulation with 1:1 matching. They focused on analysing the risk of SARS-CoV-2 infection over this period. They noted that the risk of SARS-CoV-2 infection was relatively similar during the negative control period, although some degree of residual confounding was detected. Moreover, for COVID-19 related hospitalisation the confounding effect seemed to be slightly higher (Table 4). Similar findings have been observed in other COVID-19 studies (174,211,211,212).

It has been postulated that the decreased risk of COVID-19 outcomes observed during the negative control period is caused by acute respiratory symptoms preceding SARS-CoV-2 infection (e.g. fever) (174,196). Such symptoms may prompt individuals to postpone vaccination. Symptom severity is also expected to play a role in this selection, with greater severity increasing the likelihood of postponement. This would explain the difference of VE estimates against mild and severe COVID-19 during the negative control period (Table 4). Alternatively, individuals who have been vaccinated might self-isolate to minimize the risk of SARS-CoV-2 infection before the vaccine becomes effective.

One approach to address bias observed during a negative control period is to model respiratory symptoms on the day of vaccination and in the days immediately following. An important aspect of this confounding is that it functions as a time-varying confounder influenced by the exposure. As discussed previously, using traditional methods, such as regression modelling, to address this time-varying confounding introduces bias (174,176).

Lastly, vaccination might induce a minor protection against infection even during the negative control period, throughout immunological response that is not yet well understood. For example, transient innate immune responses induced shortly after vaccination could, in theory, provide modest protection in the days immediately following vaccination (213). However, the effect should be so small that RCTs lacked the statistical power to detect it.

Table 4 Negative control period analyses in three studies conducted in Isreal.

	Study period	N of exposed/unexposed	Symptomatic SARS-CoV-2 infection		COVID-19 related hospitalization	
			N of events among exposed/unexposed	VE (95% CI)*	N of events among exposed/unexposed	VE (95% CI)*
Dagan et al. (196)	20.12.2020–1.2.2021	596 618/596 618	1 103/1 419	22% (16–28%)	31/58	47% (18–66%)
Barda et al. (209)	30.7.2020–23.9.2021	728 321/728 321	Not reported		31/91	66% (49–77%)
Magen et al. (210)	3.1.2022–18.2.2022	181 122/181 122	1 126/1 563	28% (22–33%)	38/53	28% (-9–53%)

* Estimation based on published data.

Negative control period (0–7 days since exposure) in three target trial emulation studies with 1:1 exact matching conducted in Israel. Here, VE is estimated based on these published studies as 1 – IRR between unexposed and exposed during 0 to 7 days. IRR is estimated as $IRR = \frac{Incidence\ rate\ for\ events\ among\ exposed}{Incidence\ rate\ for\ events\ among\ unexposed}$. The 95% CI for RR were estimated by Wald method $CI = exp\ (In(IRR) \pm 1.96\sqrt{\frac{1}{Events\ among\ exposed} + \frac{1}{Events\ among\ unexposed}}$. VE = Vaccine effectiveness, CI = Confidence interval.

3 Aims

The objective of this thesis was to evaluate the effectiveness of COVID-19 vaccines across different phases of the pandemic and various demographic groups to support evidence-based policy decisions in Finland. The objectives were:

1) To estimate VE against SARS-CoV-2 infection and COVID-19 related hospitalisation among the elderly, COVID-19 risk groups and healthcare workers and evaluate waning prior to the emergence of Omicron.
2) To estimate VE for homologous and heterologous primary schedules against COVID-19 related hospitalisation during Omicron period among adolescents.
3) To estimate long-term VE for primary and booster schedules against COVID-19 related hospitalisation caused by Omicron among the elderly.
4) To estimate the relative VE of bivalent BA.1 and BA.4-5 boosters against COVID-19 related hospitalisation and death among the elderly.

4 Methods

4.1 Study designs

This thesis compromises register-based studies conducted in Finland and across four Nordic countries. These studies utilized data from multiple registers linked by a unique personal identifier. An overview of these Studies is presented in Table 5. Two study designs were used:

1) A single-cohort design with time-varying exposure analysed using Cox regression (applied in Studies I–II and IV–V).
2) Target trial emulation using 1-to-1 propensity matching (applied in Study III).

Table 5 Summary of five Studies included in the thesis.

Study	I	II	III	IV	V
Study design	Single cohort with time-varying exposure	Single cohort with time-varying exposure	Target trial emulation	Single cohort with time-varying exposure	Single cohort with time-varying exposure
Model	Cox regression	Cox regression	1-to-1 propensity score matching	Cox regression	Cox regression
Study population	1) Elderly aged 70 years or more and 2) Chronically ill aged 16–69 years	Healthcare workers aged 16–69 years	Adolescents aged 12–17 years	Elderly aged 70 years or more	Elderly aged 65 years or more
Countries	Finland	Finland	Denmark, Finland, Norway, Sweden	Finland	Finland
Study period	27 Dec 2020 to 24 May 2021	27 Dec 2020 to 26 August or 26 Oct 2021*	28 May 2021 to 30 Apr 2023	27 Dec 2020 to 31 Mar 2022	1 Sep 2022 to 31 Aug 2023
SARS-CoV-2 variant(s)	Alpha	Alpha and Delta	Alpha, Delta and Omicron	Alpha, Delta and Omicron	Omicron (BA.5, BQ.1.X and XBB)
Comparison	One or two doses vs unvaccinated (no COVID-19 vaccination)	One or two doses vs unvaccinated	One or two doses vs unvaccinated	One, two or three doses vs unvaccinated	BA.1 or BA.4-5 bivalent booster vs ≥ 2 original monovalent doses
Outcomes	Laboratory-confirmed SARS-CoV-2 infection, COVID-19 related hospitalisation	Laboratory-confirmed SARS-CoV-2 infection, COVID-19 related hospitalisation	COVID-19 related hospitalisation, Laboratory-confirmed SARS-CoV-2 infection (secondary)	COVID-19 related hospitalisation and ICU admission	COVID-19 related hospitalisation, death due to COVID-19, death in which COVID-19 was a contributing factor

*Depending on outcome. If outcome was laboratory-confirmed SARS-CoV-2 infection, the study ended on 26 August when SARS-CoV-2 testing policy changed. The study ended on 26 October 2021 otherwise.

4.2 Data sources

The following Finnish registers were utilized in this thesis.

- The *Population Information System*. Maintained by the *Digital and Population Data Services Agency*, this register contains individual-level data on names, addresses, dates of birth and death for all Finnish residents (214).
- The *National Infectious Diseases Register*. Maintained by *THL*, this register includes notifications of communicable diseases submitted by physicians and laboratories. For SARS-CoV-2, all laboratories in Finland were required to report PCR- and antigen-confirmed infections. The register operates in near real-time and is governed by the *Communicable Diseases Act and Decree* (215).
- The *Care Register for Health Care*. Established in 1994 as a successor to the *Hospital Discharge Register* (data available since 1969), this register contains information on inpatient treatment periods, day surgeries, polyclinic and emergency department visits. It includes primary and secondary diagnoses and is maintained by *THL*. Since 2020, the register has operated in near real time, following improvements implemented during the early stages of the pandemic (216).
- The *Register of Primary Health Care visits*. This register contains data on outpatient visits in primary health care, including diagnosis codes and visit dates. Established in 2008, it has provided nationwide public sector data since 2011, with occupational visits in private sector included in 2020. The register operates in near real-time and is maintained by *THL* (217).
- The *National Vaccination Register*. Maintained by *THL*, this register records vaccination data, including vaccine types, brands and administration dates. Introduced in 2012, it is based on data from the *Register for Primary Health Care Visits* (218,219).
- The *Care Register for Social Care*. This register contains data on residency or treatment periods in private or public nursing homes, institutional care for individuals with developmental or severe disabilities, mental health rehabilitation facilities, and substance abuse treatment facilities. It is updated annually and maintained by *THL* (220).
- The *Prescription Centre database*. This database includes outpatient drug prescriptions recorded with Anatomical Therapeutic Chemical codes. Public sector data have been available since 2010, and private sector data since 2017. It is maintained by the *Social Insurance Institution of Finland*. For this thesis, the database was copied on 30 November 2020, and this version was used in Studies I–V (221).
- The *Special Reimbursement Register for Medicine Expenses*. Maintained by the *Social Insurance Institution of Finland*, this register contains data on approved special reimbursements for selected prescription medications. Similar to the

Prescription Centre database, the database was copied on 30 November 2020, and this version was used in Studies I–V (222).

- The *Registers of Social Welfare and Healthcare Professionals*. These registers contain data on all registered social and healthcare professionals in Finland, including their professions (e.g. nurse, physician, physiotherapist). However, it does not include employment status or workplace information. It is maintained by *National Supervisory Authority for Welfare and Health* (*Valvira)* (223).
- The *Finnish Intensive Care Quality Register*. Maintained by *THL*, this register includes information on all ICU admissions in Finland, including admission dates and diagnoses (224).
- Death certificate data. In Finland, physicians complete death certificates, which are then reviewed by medico-legal specialists at THL. These certificates contain information on immediate and underlying causes of death, as well as contributing medical conditions. The data are recorded by *Statistics Finland* and typically have one year delay. However, during the COVID-19 pandemic, THL recorded all COVID-19 related deaths in near real-time for surveillance purposes, providing timely data for this thesis (225,226).

Study III was additionally based on corresponding registers from Denmark, Norway, and Sweden. Detailed descriptions of these registers are provided in the supplementary material of Study III. A summary of the use of Finnish register data is presented in Table 6.

Table 6 Use of Finnish register data in Studies I-V.

Register	Exposure	Outcomes	Covariates				
			Age, sex, residence	Healthcare worker status	Medical conditions	Medical treatments	Prior SARS-CoV-2 infections
Population Information System			I-V				
National Infectious Diseases Register		I–V					I–V
Care Register for Health Care		I–V			I–V		
Care Register of Primary Health Care visits					I–V		
National Vaccination Register	I-V					I-V	
Care Register for Social Care			I–V				
Prescription register*						I–V	
Special Reimbursement Register for Medicine Expenses*					I–V		
Registers of Social Welfare and Healthcare Professionals				II, III			
Finnish Intensive Care Quality Register†		IV					
Death certificates		V					

* For Study I, Special Reimbursement Register for Medicine Expenses register comprised data until 1 January 2020.
†Formerly referred to as Finnish Intensive Care Consortium's Quality Register for Intensive Care.

4.3 Study populations

For Studies I–II and IV–V, the study population included all individuals who met the eligibility criteria. The general eligibility criteria required permanent residency in Finland and belonging to a specific age group as presented in the Table 5. Additionally, there were study-specific inclusion criteria:

- Study I included only those 16–69 year-olds who belonged to the COVID-19 risk groups as outlined in Table 2 (38).
- Study II included only healthcare workers registered in the *Registers of Social Welfare and Healthcare Professionals*.
- Study V included only individuals who had received at least two doses of the original monovalent COVID-19 vaccine by 1 September 2022.

In Studies I–III, individuals with confirmed SARS-CoV-2 infection prior to the start of the study were excluded. However, Study V allowed the inclusion of individuals with prior SARS-CoV-2 infection, provided that at least three months had passed since the infection. Individuals could enter the cohort once this three-month period had elapsed.

For Study III, the study population was formed by extracting pairs of vaccinated and unvaccinated individuals from the source population of adolescents aged 12–17 years with permanent residency in Denmark, Finland, Norway, or Sweden and without history of COVID-19 related hospitalization.

4.4 Study periods

Table 5 presents the study periods. Studies I and II were limited to the pre-Omicron period, whereas Studies III and IV included the period of Omicron predominance. Study V was exclusively conducted during Omicron period. In Studies II–V the study periods were additionally stratified to evaluate the impact of different variants as follows:

- Study II: The study period was stratified into the pre-Delta (27 December 2020 to 20 June 2021) and the Delta period (21 June 2021 to 26 October 2021).
- Study III: The study period was stratified into the pre-Omicron and Omicron period, with specific dates varying across the four countries.
- Study IV: The study period was divided into quarterly intervals from Q1 2021 to Q1 2022, with Q1 2022 being predominantly Omicron.
- Study V: The study period was stratified into September 2022–February 2023 (dominated by BA.5 and BQ.1.X) and March–August 2023 (dominated by XBB).

In Study II, the outcome of laboratory-confirmed SARS-CoV-2 infection was analysed only for the period between 27 December 2020 and 26 August 2021. This restriction was

necessary due to a policy change that limited SARS-CoV-2 testing among vaccinated individuals with mild symptoms.

4.5 Outcomes of interest

The outcomes of interest varied across Studies and included laboratory-confirmed SARS-CoV-2 infection, COVID-19 related hospitalization, ICU admission due to COVID-19, death due to COVID-19, and death in which COVID-19 was a contributing factor. The detailed definitions and criteria for each outcome used in Finland are presented in Table 7. For Study III, country-specific definitions are presented in the supplementary material of Study III.

Table 7 Outcome definitions.

Outcome	Definition	Studies
Laboratory-confirmed SARS-CoV-2 infection	PCR- or antigen-confirmed SARS-CoV-2 case recorded in the *National Infectious Diseases Register*	I, II, III
COVID-19 related hospitalisation	Inpatient hospital admission registered in the *Care Register for Health Care* with: 1) Primary or secondary diagnosis of COVID-19 (ICD-10 codes: U07.1, U07.2), acute respiratory tract infections (J00–J22, J46), or severe complications of lower respiratory tract infections (J80–J84, J85.1, J86) 2) Positive SARS-CoV-2 sample registered in the *National Infectious Diseases Register* within 14 days before or 2–7 days after admission*	I-V
ICU admission due to COVID-19	ICU admission due to COVID-19, registered by the treating physician in the *Finnish Intensive Care Quality Register*. A positive SARS-CoV-2 sample during the ICU stay was also required.	IV
Death due to COVID-19	Death where COVID-19 recorded as the immediate or underlying cause on the death certificate, as recorded by the treating physician. Data derived exclusively from death certificates and did not require a laboratory-confirmed SARS-CoV-2 sample	V
Death in which COVID-19 was a contributing factor	Death where COVID-19 recorded as a contributing factor by the treating physician. Data were exclusively derived from death certificates and did not require a laboratory-confirmed SARS-CoV-2 sample.	V

* 2 days in Study V and 7 days in other Studies.
ICD-10 = International Classification of Diseases, Tenth revision

4.6 Exposure of interest

The COVID-19 vaccines evaluated in this thesis included:

- Comirnaty, Spikevax and Vaxzevria based on the original SARS-CoV-2
- Comirnaty and Spikevax BA.1 and BA.4–5 bivalent vaccines

Table 8 presents the exposure definitions of each study. In Studies I–II and IV–V, exposure status was time-varying, meaning it could change over the follow-up period (Figure 11). In Studies I–IV, the unexposed group was defined as individuals who had not received any COVID-19 vaccination. In Study V, the unexposed group consisted of individuals who had received at least two doses of an original monovalent COVID-19 vaccine, with the last dose received at least three months ago. This definition was chosen because:

1) At the start of the bivalent booster rollout, only individuals who had received at least the primary COVID-19 vaccination series were eligible for a booster.
2) By this stage of the pandemic, the unvaccinated population was highly selected. Defining the unexposed as those who had received at least two monovalent doses allowed for a more comparable reference group, reducing potential confounding (227).

Table 8 Exposure definitions.

Study	I	II	III	IV	V
Unexposed	Unvaccinated	Unvaccinated	Unvaccinated	Unvaccinated	Individuals with at least two original monovalent COVID-19 doses received at least three months ago
Exposure categories by vaccine product	COVID-19 vaccination, mRNA, Vaxzevria	mRNA, Vaxzevria, Comirnaty, Spikevax*	Comirnaty, Spikevax*	Comirnaty, Spikevax, Vaxzevria*	Bivalent booster, BA.1, BA.4–5 booster
Exposure categories by days since vaccination	1st dose: 0–6, 7–13, 14–20, 21–27, 28–34, 35–41, 42+ 2nd dose: 0–6, 7+	1st dose: 0–20, 21–41, 42+ 2nd dose: 0–13, 14–90, 91–180, 181+	1st dose: 14–194 2nd dose: 7–187, 7–372†	1st dose: 0–20, 21–83, 84+ 2nd dose: 0–13, 14–90, 91–180, 181+ 3rd dose: 0–13, 14–60, 61+	Day since booster dose: 0–2, 3–7, 8–13, 14–60, 61–120, 121–180, 181–240, 241–300, and 301–364

mRNA vaccine = Comirnaty and Spikevax, bivalent booster = Either BA.1 or BA.4–5 booster by Comirnaty or Spikevax
* Heterologous schedules were included (e.g. Comirnaty + Spikevax + Comirnaty)
† Follow-up began on the 14th day since first dose or 7th day since second dose and continued until 6 or 12 months had elapsed.

4.7 Covariates

Studies used different sets of covariates to address confounding. These are described in detail in each study. All Studies included age, sex, and region of residency, as recorded in the *Population Information System*.

All Studies also included target groups for COVID-19 vaccination due to presence of comorbidities and treatments predisposing to severe COVID-19 in Finland as confounders (Table 2), though the definitions varied slightly across Studies. These were identified using multiple registers, including the *Care Register for Health Care*, *Care Register for Primary Health Care Visits*, *Prescription Register*, and *Special Reimbursement Register for Medicine Expenses* (Table 6). Additionally, residency in a long-term care unit, as recorded in the *Care Register for Social Care*, was included as a confounder in Studies I and III–V.

To further control confounding, additional covariates were included:

- Studies III and V were adjusted for previous laboratory-confirmed SARS-CoV-2 infection, recorded in the *National Infectious Diseases Register*, to account for prior immunity.
- Study III included healthcare worker status, recorded in the *Registers of Social Welfare and Healthcare Professionals*. This was done as some 16–17-year-olds worked as healthcare workers (e.g. practical nurses) and were vaccinated earlier than others in their age group.
- Studies IV and V were adjusted for the number of nights hospitalized in recent years, recorded in the *Care Register for Health Care*, to account for health-seeking behaviour and frailty.
- Seasonal influenza vaccination was added as a covariate to Studies IV and V for adjusting health-seeking behaviour. Furthermore, Study V was adjusted for the number of monovalent original COVID-19 vaccine doses received prior to the study, recorded in the *National Vaccination Register*, to address for prior immunity to SARS-CoV-2.

4.8 Statistical analysis

4.8.1 A single cohort with time-varying exposure

In Studies I–II and IV–V, the individuals entered the cohort as unexposed and if they received exposure their exposure status changed (Figure 11). The exposure category defined as time since vaccination could also change over time. Individuals were followed until occurrence of a censoring event, which were study specific. For all Studies, the outcome of interest, death and end of study period were considered as a censoring event.

VE was estimated by comparing the hazard of the outcomes in vaccinated groups with the corresponding hazard in the reference group using covariate adjusted Cox regression with the calendar time as the underlying time scale. The VE was evaluated as 1–HR. In Study V, only HR was provided to highlight that the comparison group had received COVID-19 vaccination and therefore were not unvaccinated. Studies included also additional analyses – for example age and calendar time stratification – which are described in detail in each study.

4.8.2 Target trial emulation

The target trial method utilized in Study III is graphically presented in Figure 15. The propensity score, i.e. the conditional probability of receiving COVID-19 vaccination during the study period, was estimated with logistic regression utilizing covariate data at the baseline. Pairs were matched on age (in years) and the nearest propensity score. If the unvaccinated individual in a matched pair received a vaccination, the pair was censored, and the newly vaccinated individual became eligible for re-matching. The follow-up for each individual was started on day 14 from the matching day (i.e. index date) and continued until a censoring event.

The Kaplan-Meier estimator was used for evaluating the cumulative incidence at day 180 and day 365. Comparing the cumulative incidence of the vaccinated and unvaccinated the RR and RD were estimated. VE was defined as 1–RR. Each study site provided country-specific estimates, which were then combined by random effects meta-analyses.

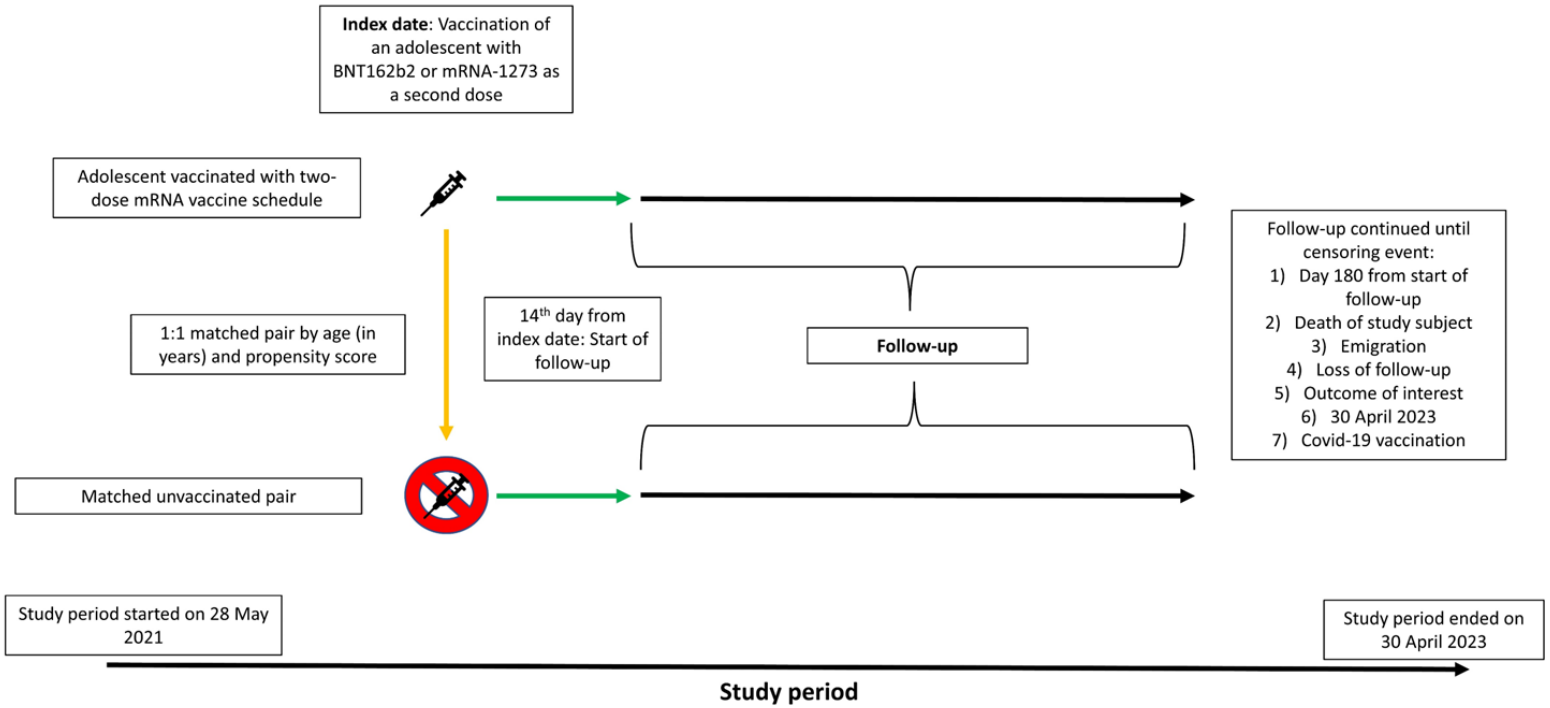


Figure 15 Study design and individual follow-up in Study III. From the supplementary material of Study III.

4.8.3 Negative control outcomes and negative control periods

Studies IV and V included each an analysis of a negative control outcome. This outcome was inpatient encounters due to injury, poisoning and certain other consequences of external causes (International Classification of Diseases, Tenth revision [ICD-10]: S00–T98) or emergency room visit due to injury (ICD-10 codes: S00–T14), respectively. The assumption was that COVID-19 vaccination would not affect these outcomes and, therefore, an association between the negative control outcome and exposure would indicate residual confounding.

For Studies I–II and IV–V, the HR of the COVID-19 outcomes was estimated during a negative control period, i.e. the first weeks after COVID-19 vaccination when vaccination is expected to have no effect on COVID-19 outcomes (Table 8). In Study V the negative control period was more closely examined by dividing the first 2 weeks since vaccination into smaller categories (Table 8).

4.9 Ethical considerations

Studies I–V were conducted at THL, the national expert agency for infectious diseases, as mandated by the Communicable Diseases Act (1227/2016) and the THL Act (668/2008). Under this mandate, THL has a legal obligation to evaluate the impact of widely used vaccines, such as COVID-19 vaccines. To fulfil this obligation, THL is legally authorized to link data from multiple national health and population registers, as outlined in the Communicable Diseases Act and the THL Act.

The studies were carried out in compliance with THL's data security regulations and were approved by a separate decision from the relevant department heads (decision number: THL/93/0.01.00/2017). All data were obtained from national registers and were pseudonymised prior to analysis.

Study III was conducted according to ethical regulations within each participating country as described in the Supplemental Table 9 in Study III.

5 Results

5.1 Study I – Vaccine effectiveness among the elderly and risk groups during Alpha period

5.1.1 Study population

Study I included 901,092 elderly individuals and 774,526 individuals aged 16 to 69 years in COVID-19 risk groups. The predominant vaccine type was mRNA, accounting for approximately 95% and 66% of the first doses in each group, respectively. A small proportion received a two-dose schedule (Figures 1 and 2, Study I). During the Study, 2,265 SARS-CoV-2 infections and 466 COVID-19 related hospitalisations were recorded.

5.1.2 Vaccine effectiveness

Among the elderly, one dose of mRNA vaccine lowered the risk of SARS-CoV-2 infection and COVID-19 related hospitalisation by approximately 50% and 60% after 28 days, respectively (Table 9). For a two-dose mRNA schedule, VE increased to 75% (95% confidence interval [CI]: 65–85%) and 93% (95% CI: 70–98%) against infection and hospitalisation after seven days from the second dose.

In risk groups, one-dose mRNA VE against infection ranged from 40% to 60% between 21 and 41 days post-vaccination, but declined thereafter (Table 2, Study I). VE estimates for COVID-19 hospitalisation had wide 95% CI, indicating low statistical power. For the two-dose mRNA schedule, VE was 77% (95% CI: 65–85%) against infection and 90% (95% CI: 29–99%) against hospitalisation after seven days from the second dose. One dose of Vaxzevria had approximately 50% effectiveness against infection after 28 days (Table 3, Study I).

5.1.3 Negative control period analysis

Among the elderly, adjusted HRs for SARS-CoV-2 infection ranged from 0.49 to 0.57 and for COVID-19 related hospitalisation from 0.43 to 0.73 within 0–20 days post-vaccination

(Table S4, Study I). In the risk groups similar trends were observed for SARS-CoV-2 infection, while HRs for hospitalisation ranged from 0.13 to 0.51 (Table S5, Study I).

Table 9 Vaccine effectiveness for one and two-dose mRNA vaccine schedule (Comirnaty or Spikevax) among elderly aged 70 years or more during a period from 27 Dec 2020 to 24 May 2021.

Dose	Days since vaccination	SARS-CoV-2 infection	COVID-19 related hospitalisation
1st dose	21-27	41% (95% CI 25-54%)	57% (95% CI 24-75%)
	28-34	47% (95% CI 30-59%)	59% (95% CI 26-77%)
	35-41	46% (95% CI 28-59%)	64% (95% CI 32-81%)
	42+	47% (95% CI 35-56%)	68% (95% CI 50-79%)
2nd dose	7+	75% (95% CI 65-82%)	93% (95% CI 70-98%)

5.2 Study II – Vaccine effectiveness among healthcare workers during pre-Omicron period

5.2.1 Study population

Study II included 427,905 healthcare workers, the majority being nurses (291,758; 68%). Between 27 December 2020, and 26 October 2021, approximately 90% received at least one COVID-19 vaccine dose. The most common primary schedule was a two-dose mRNA schedule, administered to 315,413 individuals (74%). A total of 5,631 SARS-CoV-2 infections and 555 COVID-19 related hospitalisations were recorded.

5.2.2 Vaccine effectiveness

For a two-dose mRNA schedule, VE against SARS-CoV-2 infection was 82% (95% CI: 79–85%) during 14–90 days post-second dose but declined thereafter (Figure 16). When 181 days or more had passed from the second dose, the VE was only 53% (95% CI: 43–62%). Similar results were observed for two-dose Vaxzevria and heterologous schedules. Effectiveness was comparable between the pre-Delta and Delta periods (Supplementary Tables 2–3, Study II).

5.2.3 Negative control period analysis

During the 0 to 20 days since the first dose, HR against infection for mRNA vaccines was 0.88 (95% CI: 0.69–0.89; Supplementary Table 2, Study II), while HR against

hospitalisation was 0.13 (95% CI: 0.04–0.42; Supplementary Table 3, Study II). For Vaxzevria, corresponding HRs were 0.64 (95% CI: 0.47–0.87) against infection and 0.31 (95% CI: 0.08–1.26) against COVID-19 related hospitalisation.

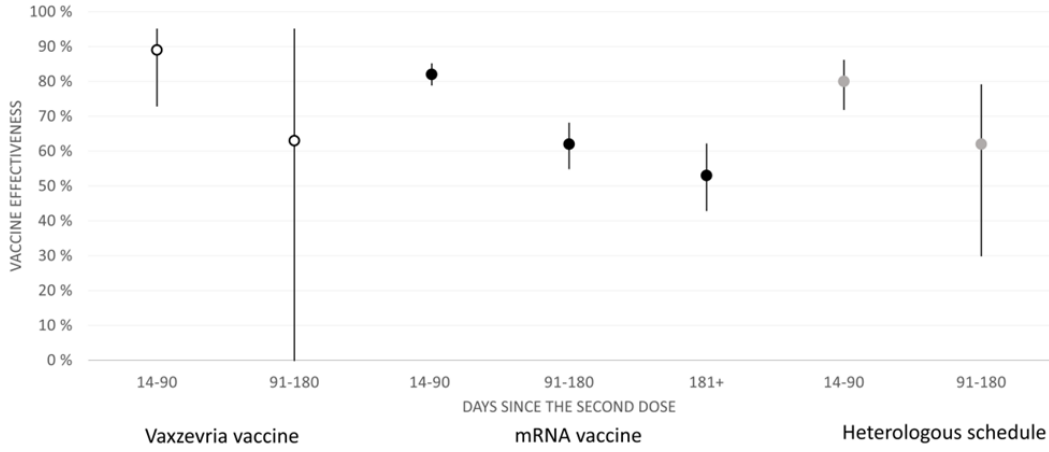


Figure 16 Vaccine effectiveness of primary schedule against SARS-CoV-2 infection among healthcare workers between 27 December 2020 and 26 August 2021. If an individual had received both Vaxzevria and mRNA dose, it was considered as heterologous schedule. From Study II.

5.3 Study III – Vaccine effectiveness among adolescents during pre- and Omicron period

5.3.1 Study population

Matched cohorts from Denmark, Finland, Norway, and Sweden included 526,966 two-dose vaccinated adolescents and an equal number of unvaccinated controls. The most common regimen was a two-dose Comirnaty schedule (N = 419,168, Table 1, Study III).

During the 12-month follow-up, 59 COVID-19 related hospitalisations occurred among two-dose Comirnaty-vaccinated individuals, compared to 182 in unvaccinated matched pairs. Due to the rarity of the other vaccine schedules, hospitalisation numbers in these groups were small (Table 10).

5.3.2 Risk difference and vaccine effectiveness

Cumulative country-specific incidence rates for COVID-19–related hospitalisation are presented in Figure 1, Study III. The RD for two-dose Comirnaty schedule against COVID-19 related hospitalisation was -2.8 (95% CI: -4.5– -1.0, Table 10) per 10,000 individuals for

six months of follow-up with the negative RD indicating lower risk among vaccinated. The corresponding VE was 73% (95% CI: 63–83%). When the follow-up was extended to 12 months, the RD and VE for two-dose Comirnaty schedule were -3.8 (95% CI: -5.4– -2.1) and 66% (95% CI: 55–76%). VE for Spikevax and heterologous schedule was 91% (95% CI: 73–100%) and 83% (95% CI: 64–100%) during 12 months of follow-up. Restricting the follow-up to Omicron period did not have a major effect on VE.

For the two-dose Comirnaty schedule RD and VE against laboratory-confirmed SARS-CoV-2 infection were -500 (95% CI: -960– -40) per 10,000 individuals and 20% (95% CI: 4–37%) during 12 months of follow-up. For Spikevax and heterologous schedules the corresponding VE was 3% (95% CI: -33–40%) and 27% (95% CI: 1–54%).

Table 10 Effectiveness of two-dose COVID-19 vaccine schedules among adolescents aged 12–17 years against COVID-19 related hospitalisation during 6- and 12-month follow-up in Denmark, Finland, and Sweden. From Study III.

	Vaccinated	Unvaccinated	Measures of association		Countries included
	Events/PYRS	Events/PYRS	RD (95% CI) per 10,000 individuals	VE (95% CI)	
Analysis of 6-month follow-up					
Comirnaty	37 / 151873.2	140 / 150774.0	-2.8 (-4.5– -1.0)	73% (63–83%)	DK, FI, SE
Spikevax	<5 / 15535.9	8 / 14527.6	-2.1 (-4.0– -0.2)	86% (57–100%)	FI
Heterologous	<5 / 20304.8	18 / 19012.0	-5.5 (-15.5–4.6)	81% (58–100%)	FI, SE
Restricted to period of omicron predominance (6-month follow-up)					
Comirnaty	35 / 94068.0	114 / 93273.4	-2.7 (-6.1– 0.7)	70% (46–95%)	DK, FI, SE
Spikevax	<5 / 9003.6	<5 / 8113.5	-1.4 (-3.6– 0.8)	80% (35–100%)	FI
Heterologous	<5 / 14005.3	14 / 12810.1	-9.8 (-21.3–1.7)	86% (65–100%)	FI, SE
Analysis of 12-month follow-up					
Comirnaty	59 / 276854.1	182 / 277969.0	-3.8 (-5.4– -2.1)	66% (55–76%)	DK, FI, SE
Spikevax	<5 / 27613.5	11 / 25610.8	-3.5 (-5.9– -1.1)	91% (73–100%)	FI
Heterologous	<5 / 37716.4	22 / 34680.8	-6.2 (-14.5–2.1)	83% (64–100%)	FI, SE

PYRS = Person years, RD = Risk difference, CI = Confidence interval, VE = Vaccine effectiveness, DK = Denmark, FI = Finland, SE = Sweden.

5.4 Study IV – Vaccine effectiveness against severe COVID-19 outcomes among the elderly during pre-Omicron- and Omicron-period

5.4.1 Study population

Study IV included 896,220 individuals aged 70 years or more, with 95% receiving at least one COVID-19 vaccine dose by the end of the study. Most person-time was contributed by individuals aged 70 to 79 years. A total of 2,234 COVID-19 related hospitalisations and 296 ICU admissions were recorded during the study.

5.4.2 Vaccine effectiveness

Between December 27, 2020, and March 31, 2022, two-dose Comirnaty VE against hospitalisation was 93% (95% CI: 89–95%) during 14–90 days since second dose, but VE waned over time (Figure 1, Study IV). Similar VE was observed for two doses of Spikevax, while two doses of Vaxzevria showed slightly lower effectiveness. VE against ICU admission was comparable or slightly higher compared to COVID-19 related hospitalisation across all vaccine schedules (Figure 1, Study IV).

VE increased after a booster dose, reaching 95% (95% CI: 94–96%) for a three-dose Comirnaty schedule during 14–60 days post-booster, but declined over time (Figure 17). VE was comparable for other mRNA and heterologous three-dose schedules. Additional analyses indicated lower VE among the oldest individuals and those in risk groups (Tables S10–S11, Study IV).

In a calendar time-stratified analysis, VE was similar between Q1/2021 and Q4/2021 (Figure 17). During Q4/2021, VE for three-dose Comirnaty was 96% (95% CI: 93–97%) within 14–60 days since a booster, and in Q1/2022, it was 94% (95% CI: 92–95%), suggesting similar short-term VE despite Omicron emergence. However, VE appeared to wane after 61+ days since a booster dose during Q1/2022, with the estimate at 87% (95% CI: 85–89%).

5.4.3 Negative control outcome and negative control period analyses

HR for the negative control outcome comparing vaccinated and unvaccinated individuals was 0.96 (95% CI: 0.93–1.00), indicating no association between the exposure and negative control outcome across all exposure categories. For Comirnaty schedules, HR ranged from 0.92 to 1.07 (Table S14, Study IV). Similar results were observed for heterologous and Vaxzevria schedules, though a slightly increased HR was noted for Spikevax. During the 0–20 days negative control period, Comirnaty, Spikevax, and Vaxzevria were associated with a

reduced risk of COVID-19 related hospitalisation, with HRs ranging from 0.28 to 0.68 (Supplementary Table S8, Study IV).

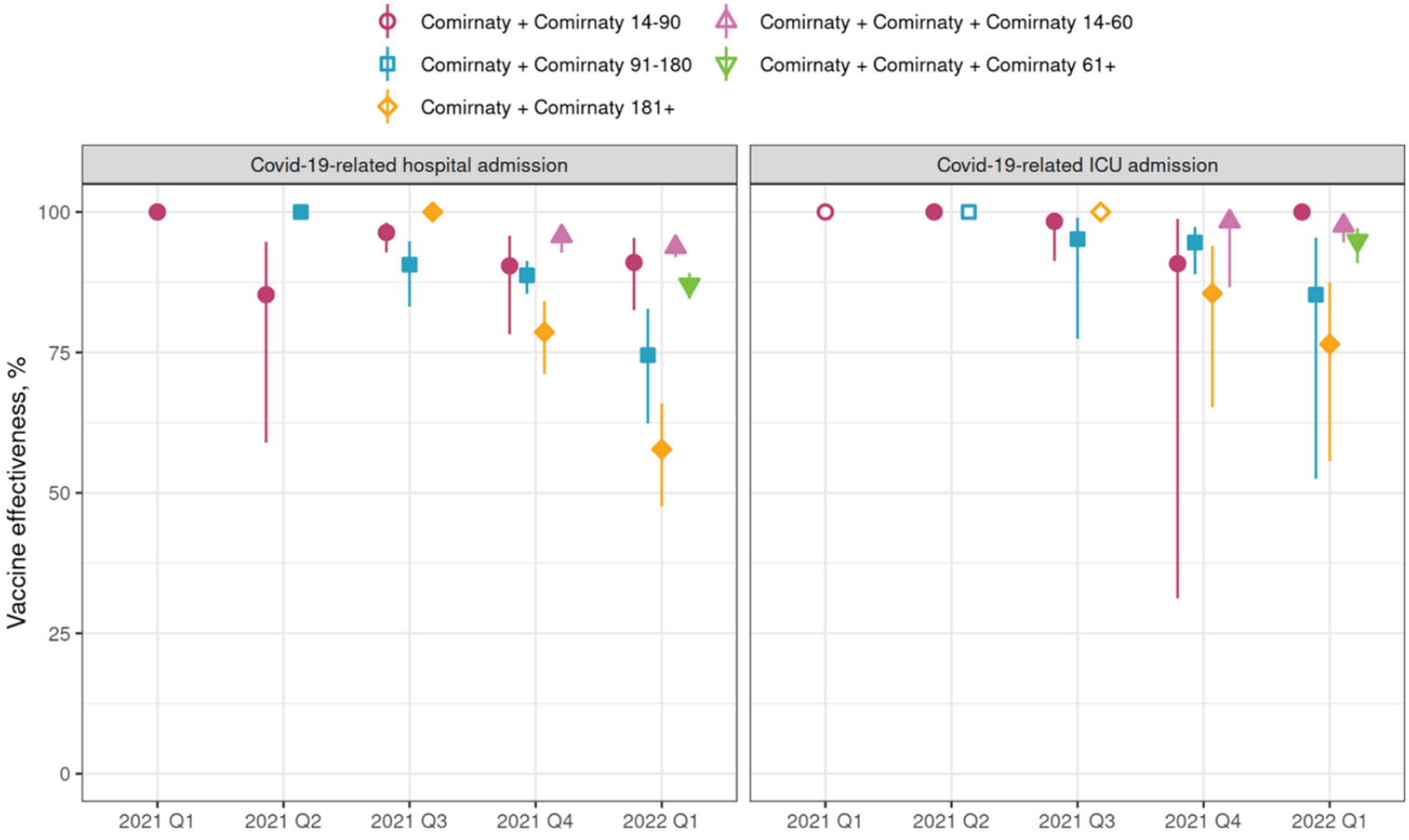


Figure 17 Vaccine effectiveness with 95% confidence intervals against COVID-19 related hospitalisation for homologous Comirnaty schedules quarterly from Q1/2021 to Q1/2022. The colour and point shapes distinguish the number of administered Comirnaty doses and the time since the last dose in days. A filled symbol indicates that the estimate is statistically significantly different from 0%, while an empty symbol indicates that the estimate is not statistically significantly different from 0%. Omicron was the predominant variant in Q1/2022. From Study IV.

5.5 Study V – Relative effectiveness of BA.1 and BA.4-5 bivalent boosters among the elderly during 2022–2023 season

5.5.1 Study population

Study V included 1,911,871 individuals aged 65 years or older, of whom 7% (N = 81,764) had a previously confirmed SARS-CoV-2 infection. During the study period, 652,746 individuals received either a BA.1 or BA.4-5 booster. The most common booster was Comirnaty BA.4-5 (N = 455,665), followed by Comirnaty BA.1 (N = 194,383). A total of 3,137 COVID-19 related hospitalisations, 1,624 deaths due to COVID-19, and 1,307 deaths where COVID-19 was a contributing factor were recorded.

5.5.2 Relative vaccine effectiveness

The bivalent boosters were associated with a reduced risk of severe COVID-19 outcomes during September 2022–February 2023 and March–August 2023 (Figure 18). During September 2022–February 2023, the 14–60 days post-booster HRs were 0.45 (95% CI 0.37–0.55) for COVID-19 related hospitalisation, 0.49 (95% CI: 0.38–0.62) for death due to COVID-19 and 0.40 (95% CI: 0.31–0.51) for death in which COVID-19 was a contributing factor. The 61–120 days post-booster HRs approached 1.0, suggesting waning protection.

During March–August 2023, 14–60 days post-booster HRs could not be precisely estimated due to the low number of events and limited person-time. However, the 61–120 days post-booster estimates were 0.53 (95% CI: 0.39–0.71) for COVID-19 related hospitalisation, 0.41 (95% CI: 0.24–0.70) for death due to COVID-19 and 0.38 (95% CI: 0.18–0.78) for death in which COVID-19 was a contributing factor.

In subsequent exposure time intervals, HRs approached 1.0, indicating further waning effectiveness. Additional analyses showed similar HRs across bivalent booster types (BA.1 vs. BA.4-5) and age groups (65–79 years vs. ≥80 years).

5.5.3 Negative control outcome and negative control period analyses

During September 2022–February 2023, the HR for the negative control outcome ranged from 0.92 to 1.08 after 14 days since a booster (Supplementary Table S5, Study V), with comparable results observed in March–August 2023. During the negative control period, HRs for COVID-19 related hospitalisation were lowest at 0–2 days since a booster (HR: 0.15; 95% CI: 0.06–0.36) but increased to 0.53 (95% CI: 0.36–0.77) and 0.54 (95% CI: 0.38–0.77) at 3–8 and 9–13 days since a booster, respectively. For the negative control outcome, 0–2 days post-booster HR was 0.59 (95% CI: 0.48–0.72), but subsequently approached 1.0.

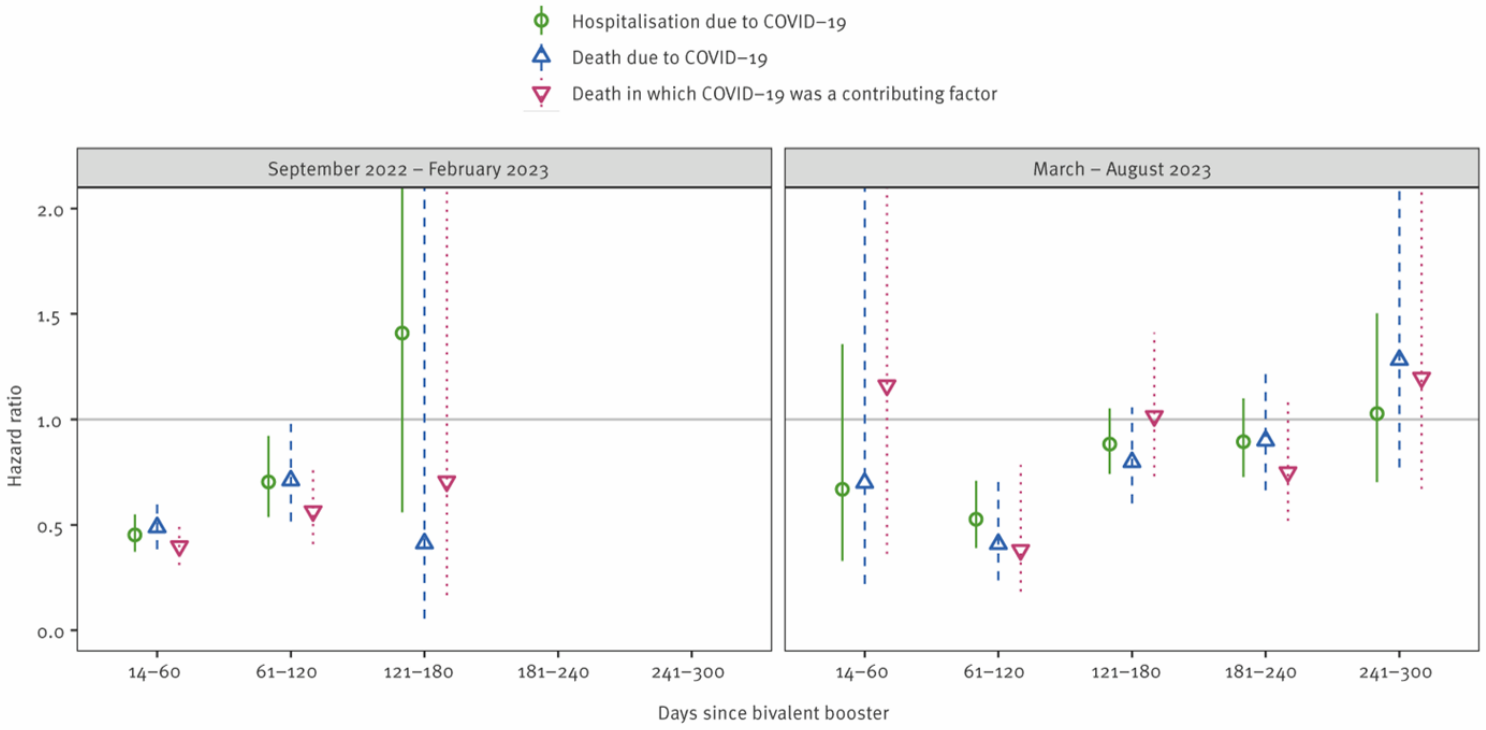


Figure 18 Hazard ratios (with 95% confidence intervals) for bivalent boosters against severe COVID-19 outcomes among individuals aged 65 years or more during September 2022–February 2023 (BA.5 and BQ.1.X predominating) and March–August 2023 (XBB predominating). From Study V.

6 Discussion

6.1 Motivation

In 2020, RCTs provided evidence on the efficacy of vaccines against symptomatic SARS-CoV-2 infection and severe COVID-19 among healthy participants (12–14). However, as the pandemic progressed and vaccines were rolled out, additional data on VE against different COVID-19 outcomes and subvariants in different subpopulations were needed to support policymaking. Therefore, real-time VE estimation was initiated in Finland immediately after the vaccine rollout. This effort built upon prior experience at THL in evaluating the efficacy and effectiveness of vaccines against pathogens such as influenza (227–229), pneumococcus (230–232), and rotavirus (233).

6.2 Main findings

In addition to Studies I–V, several other studies conducted elsewhere informed policymaking in Finland. These studies also utilized real-time data and were primarily conducted in Western countries where the pandemic and vaccine rollout were comparable to those in Finland. They are a central focus of the discussion. For a more comprehensive understanding of vaccine effectiveness, meta-analyses, such as those by Feikin et al. (228,229), Wu et al. (230), Xu et al. (231), and Zhou et al. (232), are recommended.

6.2.1 Vaccine protection in pre-Omicron period

6.2.1.1 VE against SARS-CoV-2 infection

In Studies I–II, two-dose COVID-19 vaccine schedules decreased the risk of SARS-CoV-2 infection by 70–80%, but VE waned over time. No meaningful difference in VE was observed across mRNA, Vaxzevria, and heterologous schedules. Therefore, COVID-19 vaccinations reduced the risk of SARS-CoV-2 infections among all adults in Finland and possibly contributed meaningfully to limiting the spread of SARS-CoV-2 prior to the emergence of Omicron (76). It is also likely that the COVID-19 vaccination rollout facilitated for the lifting of non-pharmaceutical interventions in summer 2021. The signs of waning in Study II also indicated the possible benefit of a booster dose in decreasing the risk of SARS-CoV-2

infection. These findings provided supporting evidence for the autumn 2021 booster campaign among the Finnish population.

In RCTs of Comirnaty and Spikevax—including over 43,000 and 30,000 healthy participants aged 16 years or older—vaccine efficacy against COVID-19 (i.e. symptomatic SARS-CoV-2 infection) was higher than the VE observed in Studies I–II. In the RCTs over two months of follow-up, the efficacy of the primary series was 95% (95% CI: 90–98%) for Comirnaty and 94% (95% CI 89–97%) for Spikevax (13,16). However, consistent with the findings from Study II, efficacy declined over time (15). For the two-dose Vaxzevria schedule the efficacy was slightly lower, approximately 70–75%, in an RCT (14,233). In this RCT, an extended dosing interval was associated with superior protection (234). As an extended dosing interval was implemented in Finland, this may explain why VE for two-dose Vaxzevria schedule appeared slightly higher in Study II compared to RCTs in which dosing interval varied from 4 to 12 weeks. In RCTs, no clear differences in vaccine efficacy was observed across age groups or among participants with comorbidities for mRNA or Vaxzevria vaccines (15,16,233), suggesting that these vaccines provided high levels of protection even among vulnerable individuals.

In observational settings, VE for Comirnaty against documented SARS-CoV-2 infection was 90–95% during the first quarter of 2021 across different age groups in Israel indicating slightly higher VE compared to estimates observed in Studies I–II. In Israel, VE was estimated using both a target trial emulation approach (196) and a single-cohort design with time-varying exposure (235) and both approaches yielded similar VE estimates. In the UK (236), Sweden (237) and Denmark (259) VE against SARS-CoV-2 infection varied between 70–90% among the elderly corresponding to findings in Study I. The results also indicated slightly lower VE among the oldest old and individuals with comorbidities (237).

Overall, VE against laboratory-confirmed SARS-CoV-2 infection prior to the emergence of Omicron in Studies I–II appeared slightly lower compared to the RCTs and some observational studies. This might be related to several factors. Firstly, the population in Finland is skewed towards the oldest old (i.e. those aged 80 or 85 years or more) and it can be expected that VE is lower in these groups due to immunosenescence (239). This could also explain the slightly lower VE observed in the UK and Nordic countries compared to Israel. Secondly, outcome definitions and testing policies varied across different studies (e.g. laboratory-confirmed SARS-CoV-2 vs symptomatic SARS-CoV-2 infection). In Studies I–II, laboratory-confirmed SARS-CoV-2 infections likely included asymptomatic cases identified through, for example, SARS-CoV-2 screening in long-term care units. This likely resulted in slightly lower VE estimates, as VE against asymptomatic infection is generally lower than that against symptomatic infection (235). Thirdly, confounding by underlying health conditions might have been inadequately controlled, and meaningful residual confounding was probable especially in Study I, as indicated by the negative control period analysis.

6.2.1.2 VE against COVID-19-related hospitalisation

Studies I–II and IV evaluated VE against COVID-19 related hospitalisation during the pre-Omicron period. In Studies I and IV, among the elderly and those in risk groups, VE for the two-dose mRNA schedule was approximately 90–93%, with VE being lower among the oldest old. VE also appeared to wane over time, but a booster restored the high protection against COVID-19 related hospitalisation. Among the healthcare workers, vaccine protection against hospitalisation did not seem to wane over time.

Based on these findings, COVID-19 vaccinations significantly reduced the number of severe COVID-19 outcomes and, together with non-pharmaceutical interventions, likely prevented the exhaustion of hospital wards and ICU units in Finland during pre-Omicron period. Initially, individuals vaccinated with Vaxzevria had lower VE against COVID-19 related hospitalisation compared to those who received mRNA vaccines, but mRNA vaccine later in the schedule, as a second or booster dose, eliminated this difference. The booster rollout among the elderly and risk groups in late 2021—supported by the findings from Study IV—was also important in mitigating the impact of the Delta wave in November–December 2021, just prior to the emergence of Omicron.

In RCTs conducted among healthy adult participants, the vaccine efficacy of two-dose Comirnaty and Spikevax schedules was over 95% against severe COVID-19 during six- and five-month follow-ups, respectively, aligning with the findings in Study II (15,16). In observational settings, VE against COVID-19 related hospitalisation has generally ranged from 90% to 98% across various adult populations (198,234,238,246,248,250), corresponding to the estimates in Studies I–II and IV. Other studies have also shown that VE wanes slightly faster among the elderly and those in risk groups compared to the healthy adults (238,240–242).

In other observational studies Vaxzevria was also associated with lower VE compared to mRNA vaccines, as shown in a TND study conducted in the UK (240). Moreover, head-to-head comparisons in other observational studies have also indicated slightly higher protection with Spikevax compared to Comirnaty (243,244) although this difference between the vaccines was only marginal (245). In other observational studies Vaxzevria schedule was also associated with lower VE compared to mRNA schedules, as shown in a TND study conducted in the UK (240). Moreover, head-to-head comparisons in other observational studies have also indicated slightly higher protection with Spikevax vaccine schedule compared to Comirnaty (243,244) although this difference between the vaccines was only marginal (245).

6.2.2 Vaccine effectiveness during the Omicron period

6.2.2.1 Primary schedule VE among adolescents

In Study III, VE against COVID-19–related hospitalisation among adolescents for different mRNA vaccine schedules ranged between 70–85% during six months of follow-up and 65–90% during 12 months of follow-up. RDs over 6 and 12 months were 2 to 6 and 4 to 6 per 10,000 individuals corresponding to NNV estimates of 1,700–5,000 and 1,700–2,500. Similar to findings among adults (246), VE against SARS-CoV-2 infection was low, reflecting the immune-evasive properties of the Omicron variant.

Based on the findings in Study III, VE against severe COVID-19 varied from moderate to high among Nordic adolescents, but the absolute benefit of vaccination was only modest. For example, in an RCT of the 10-valent pneumococcal conjugate vaccine among children under 19 months of age, the NNV during a two-year follow-up was 671 to prevent one case of invasive pneumococcal disease and 185 to prevent one case of hospital-diagnosed pneumonia (247). Thus, the absolute benefits of pneumococcal vaccination in children appear several times greater than that of COVID-19 vaccination among adolescents during the pandemic.

Nevertheless, vaccine rollout among adolescents might have reduced the SARS-CoV-2 transmission in Finland prior to Omicron (76), which likely affected transmission in risk groups and might have limited the need for non-pharmaceutical interventions—such as school or hobby closures—among adolescents. This was also one of the objectives of the vaccine rollout among the adolescents (43). However, after the emergence of Omicron the impact of vaccines on SARS-CoV-2 transmission was likely small to negligible and therefore, additional boosters for adolescents were not recommended.

RCTs for the Comirnaty and Spikevax primary schedules among adolescents were conducted from October 2020 to March 2021 and from December 2020 to June 2021, respectively, prior to the Omicron period and demonstrated high VE against COVID-19. In an RCT involving 2,260 participants, VE for the Comirnaty primary schedule was 100% after seven days from the second dose, with a follow-up period of four months (153). Another RCT, which included 3,732 participants, showed VE for the Spikevax primary schedule of 93% (95% CI: 48–100%) with a median follow-up time of 53 days from the second dose (248). Due to the relatively small sample sizes, these RCTs did not provide efficacy estimates against severe COVID-19.

In Sweden, VE against COVID-19 related hospitalisation among adolescents was 76% (95% CI: 57–87%), consistent with the findings of Study III (249). In a U.S.-based TND study, VE for the Comirnaty primary schedule was approximately 90–95% against COVID-19 related hospitalisation during the Delta-dominant period (250,251), but declined to 40% (95% CI: 9–60%) during the Omicron period (251). In this study, no waning was observed during 44 weeks of follow-up. However, VE against critical COVID-19 (i.e. life support or death due to COVID-19) was 79% (95% CI: 51–91%), suggesting that some hospitalisations

classified as COVID-19 related may have included milder cases (i.e. hospitalisation with COVID-19), which could have led to an underestimation of VE against truly severe disease. In another U.S. study, VE against Omicron infection was 85% (95% CI: 84–87%), indicating high protection. In this study VE against moderate or severe COVID-19 caused by Omicron was comparable to the estimate for infection (252). Similarly, higher VE against symptomatic SARS-CoV-2 infection caused by Omicron was observed in a study conducted in the UK, although in this study VE appeared to decrease rapidly over time (253). The lower VE estimate for SARS-CoV-2 infection in Study III may be partly explained by differences in testing behaviour between vaccinated and unvaccinated individuals.

Another issue caused by the emergence of Omicron was the sharp increase in unregistered SARS-CoV-2 infections between December 2021 and March 2022. Therefore, many SARS-CoV-2 infections were likely missed in the study and interpretation of VE estimates especially against SARS-CoV-2 infection were likely biased due to difference in health-seeking behaviour between vaccinated and unvaccinated. Moreover, MIS-C cases were not included into the Study III. Notably, COVID-19 vaccinations might have prevented cases of MIS-C (254), which would lead to a slight—though not substantial—underestimation of the overall impact of vaccination among adolescents.

6.2.2.2 A first booster dose VE among the elderly

In Study IV, VE of the booster dose against COVID-19 related hospitalisation remained high – approximately 90–99% – during the first two months since vaccination across all booster schedules after emergence of Omicron. However, VE appeared to wane slightly over time decreasing to 85–90% two months after the booster dose. Still, the findings in Study IV were reassuring as they demonstrated that COVID-19 vaccinations continued to provide substantial protection against severe COVID-19 caused by Omicron. At the time of Study IV, it had already been known that VE against infection with Omicron was reduced (240), which – together with Omicron's higher transmissibility (Table 1) – led to a surge of infections between December 2021 and March 2022, while the level of protection against severe disease remained uncertain. Ultimately, in Finland, the booster campaign launched in late 2021 likely contributed substantially to reducing the number of COVID-19 hospitalisations during the initial Omicron waves. The waning observed in Study IV also suggested that additional boosters (i.e. fourth doses) could help maintaining protection against severe COVID-19 among the elderly. For this reason a second booster campaign was rolled out in spring 2022 for the elderly (255).

In a TND study conducted in the UK, VE for the booster dose against COVID-19 related hospitalisation among those aged 65 year or more was approximately 90% after 2–4 weeks since the booster but waned to 85% after 2–3 months – corresponding to the estimates in Study IV (256). In Denmark and Canada, VE against COVID-19 related hospitalisation

among individuals aged 60 years or more was slightly higher 96–98% during the first months after vaccination but also declined to 85–90% after 3–4 months (238,257).

In Study IV, VE against COVID-19 related hospitalisation appeared comparable across different booster schedules. This aligns also immunogenicity studies where Comirnaty booster dose produced comparable levels of neutralizing antibodies and T cell immunity after primary schedule of Comirnaty or Vaxzevria (258). Detailed analyses from Nordic countries suggested slightly higher protection with heterologous booster schedules compared to homologous ones (110). Similarly, an analysis from the U.S. indicated higher protection for the Spikevax booster compared to the Comirnaty booster (259) in accordance with immunogenicity data (258).

Although VE against severe COVID-19 remained high after the emergence of Omicron, there was a significant and clinically meaningful decline in VE against SARS-CoV-2 infection (246), coinciding with a substantial increase in infections. As a result, it became increasingly important to distinguish individuals hospitalised due to COVID-19 from those hospitalised with incidental SARS-CoV-2 infection. In Finland, this distinction was possible using the primary and secondary diagnosis codes available in the Care Register for Health Care. Without this differentiation it is likely that VE estimates would have been underestimated (260).

Similar to Study III, a large portion of SARS-CoV-2 infections were not registered during Study IV due to the surge of Omicron infections which had an impact on the results. The rapid increase in Omicron cases led to a rise in infection-derived and hybrid immunity, which could not be fully accounted for in the VE analyses. This introduced a significant source of confounding, as individuals with recent mild infections were less likely to seek COVID-19 vaccination than others, thereby biasing VE estimates. For this reason, no VE analysis for the fourth booster dose was published in Finland in spring 2022.

6.2.2.3 Bivalent booster VE among the elderly

In Study V, the relative VE for BA.1 and BA.4-5 bivalent boosters was approximately 50% against severe COVID-19 outcomes among those aged 65 years or more. However, the protection appeared to decrease after 120 days possibly due to waning immunity or emergence of XBB-variants. VE was comparable for BA.1 and BA.4-5 booster and in both age groups of individuals aged 80 years or more and those aged 65 to 79 years.

In Finland, the rollout of bivalent boosters among elderly successfully reduced number of hospitalisations and deaths due to COVID-19. Although variant-adapted vaccines presented higher titres of neutralizing antibodies against Omicron variants compared to the original formula (261), the benefit of the adaptation for limiting severe COVID-19 cases was yet unknown. Because VE for BA.1 and BA.4-5 bivalent was comparable, at least small differences in vaccine formula did not appear to result in meaningful benefit for limiting severe COVID-19 cases. In retrospect, this is not surprising –the immunological studies had

shown only modest differences in immunological responses to Omicron variants between various COVID-19 vaccine formulations (103,262,263).

In Israel, relative VE for bivalent boosters was approximately 70% against COVID-19 related hospitalisation among those aged 65 years or more during a four-month follow-up period (264) and therefore slightly higher compared to the estimates in Study V. In the UK, relative VE for BA.1 boosters was approximately 30–50% against COVID-19 related hospitalisation during the two months since the booster among those aged 50 years or more (265). In that study, VE appeared slightly lower against COVID-19 related hospitalisation caused by C.H.1.1 and XBB.1.5 compared to hospitalisation caused by BQ.1, although the low statistical power limited the strength of this conclusion.

In Norway among the elderly, relative VE against COVID-19 related hospitalisation was initially approximately 60%, and similarly to findings in Study V, the protection waned (266,267). However, in the Norwegian studies the relative VE for bivalent boosters against COVID-19 related mortality was higher – estimated at 70–90% (266,267). In Italy using both a target trial emulation and a single cohort design approach, VE for bivalent boosters was 50% among those aged 60 years or more, with results indicating waning over time (268). VE against hospitalisation caused by the XBB variant appeared also slightly lower compared to other Omicron variants in another Italian study (269).

In the subsequent 2023–2024 season, relative VE for XBB variant-adapted boosters against COVID-19 related hospitalisation was approximately 60% in the Nordic setting over 24 weeks of follow-up (186) indicating similar VE as the bivalent boosters. Therefore, variant-adapted COVID-19 vaccines in the 2022–2023 and 2023–2024 seasons appeared to provide similar or slightly higher effectiveness than typical seasonal influenza vaccines against hospitalisation (270–272).

Because the frequency of severe COVID-19 among healthy working-age adults remained low during the 2023–2024 and 2024–2025 seasons, and COVID-19 vaccinations had only a minor impact on transmission at the population level, mass vaccination campaigns were no longer as beneficial as they had been during the pandemic years of 2021–2023. Moreover, mass vaccination would have required a substantial amount of healthcare resources, which could have been allocated to interventions with a higher public health impact. Therefore, targeting vaccinations to selected groups for the 2024/25 and 2025/26 seasons was a rational approach (273).

It also appears that during the 2024/25 season, the overall COVID-19 burden has continued to decline compared to previous years (274). It remains to be seen whether this downward trend will persist in the coming years. If so, COVID-19 vaccinations may eventually be recommended only for very small, high-risk groups—or potentially discontinued altogether. However, if larger waves occur in the future, broader rollouts might once again become necessary.

6.3 COVID-19 vaccination rollout in Finland

Overall, the COVID-19 vaccination rollout was a success in Finland and vaccine uptake was high (275). For example, between December 2020 and March 2023 COVID-19 vaccination rollout has been estimated to have averted over 20,000 deaths in Finland (276). Nevertheless, Finland experienced excess mortality during the pandemic, similar to other countries (277). Age-standardized excess mortality in Finland was comparable to that in other Western European countries, such as Germany, Italy, and Denmark, although few countries—such as Sweden—appeared to have had lower excess mortality. In Eastern European countries, however, excess mortality was noticeably higher (277). This may have been related to low vaccination coverage in these countries (278), but other factors—such as socioeconomic conditions, health-related factors (e.g. smoking), and the implementation of non-pharmaceutical interventions—likely influenced the figures as well.

In Finland, decision-making during the pandemic was dynamic and the register-based analyses provided timely evidence to support policymaking. For example, the introduction of first boosters for healthcare workers was implemented rapidly after waning VE was observed following the primary schedules in Study II and other studies (15,152). Similarly, second boosters were introduced immediately for the elderly when VE was observed to wane after the first booster against COVID-19 related hospitalisation caused by Omicron. The low impact of COVID-19 vaccinations among adolescents observed in Study III also contributed to the decision to recommend COVID-19 vaccination only for selected groups among 5–11-year-olds , although all children in this age group had the opportunity to receive the vaccine (279–281), and not to initiate the vaccination rollout for those under 5 years of age.

Some policy decisions—when viewed retrospectively—appear to have been suboptimal. For example, COVID-19 boosters in autumn 2023 were likely administered too late for the elderly, contributing to elevated mortality between October and December 2023 (Figure 5). At that time, it was already well understood that VE wanes over time and that booster doses can restore protection among elderly and risk groups. Therefore, based on the available evidence, an earlier rollout of the booster could have been decided, possibly averting deaths in winter 2023–2024. On the other hand, earlier administration would also have resulted in lower VE during the later stages of winter 2024 due to waning, as observed in Study V.

The impact of some policy decisions made during the COVID-19 pandemic remains uncertain. For example, the effect of the extended interval between doses for the primary schedule is still unclear. Addressing this question would require more detailed analyses, for which the findings from Studies I–II and IV could be valuable.

6.4 Strengths and limitations

The register-based VE estimation had several strengths. It could be conducted in real-time, enabling assessment of waning immunity and the impact of newly emerged SARS-CoV-2 variants in real-time. The pandemic also led to notable improvements in register data. Most

importantly, the timeliness of the Care Register for Health Care was enhanced early in the pandemic, allowing for real-time monitoring of the COVID-19 hospital burden. These improvements were crucial for this thesis. Moreover, because this VE estimation approach built on existing infrastructure, it can be continued at low cost in the future. The lessons learned during the pandemic may also be applied to the evaluation of other vaccines, such as those for influenza and RSV.

In addition, the register data were easily adaptable for Nordic collaborations, supporting studies on vaccine safety (136) and effectiveness (110,186,282), including Study III. The register data also enabled the identification of chronic conditions and medications that predispose individuals to severe COVID-19, which was essential for addressing confounding in VE analyses (38). Furthermore, the definitions for both exposure and outcomes were accurate. As noted previously, the ability to distinguish between hospitalisations due to COVID-19 and hospitalisations with incidental SARS-CoV-2 infection was particularly valuable in VE estimation against COVID-19 related hospitalisation.

Studies I–V had some limitations. Most notably, negative control period analyses indicated residual confounding. Similar findings have also been observed in other observational studies (196,209–212), although in some studies the bias seemed to be more limited (196,210,212). As discussed in Section 2.4.4.1, the hypothesis is that this bias is related to the absence of respiratory symptoms at the time of vaccination and self-isolation immediately after vaccination, which are not accounted for. The fact that VE studies conducted during the period of active SARS-CoV-2 testing prior the Omicron—when nearly all symptomatic infections were registered on the same day as symptom onset—appeared to address this bias better (196,210,212) than studies in later periods (211) also supports this hypothesis. Moreover, among vaccinated individuals, the number of SARS-CoV-2 tests taken decreases on the day of vaccination and in the following days, but thereafter returns to a level comparable to that of the unvaccinated (210).

Currently, controlling bias during the negative control period is one of the major challenges in real-world VE studies. The concern is that if this bias cannot be controlled, it may persist beyond the negative control period, complicating the interpretation of VE estimates. One suggested strategy is to model acute respiratory symptoms during the initial post-vaccination days (174), but these symptoms might be difficult to measure accurately without active surveillance of the study subjects.

Another way to address concerns about confounding detected during negative control period is through negative control outcome analysis, as performed in Studies III and V. These analyses indicated no residual confounding, thereby increasing confidence in the findings. Moreover, since Studies I–V were conducted during the pandemic, it was noted that bias observed during the negative control period highlighted the need for further methodological development of VE estimation, which could be pursued after the pandemic.

As an additional limitation, some data sources—such as the Care Register for Social Care and the Prescription Centre Database—were not updated regularly. Moreover, data on symptoms of the subjects were unavailable. Furthermore, after the emergence of Omicron,

methods to account for individual-level infection-derived or hybrid immunity would have been beneficial for VE analyses.

Lastly, the Studies would have benefitted from additional follow-up time. For example, the follow-up after the second dose in Study I was too short for estimating the VE of the two-dose Vaxzevria schedule. Similarly Study IV would have benefitted from an extended follow-up during the Omicron period potentially enabling more precise VE estimation. However, due to pandemic situation it was necessary to produce and publish the results as soon as possible.

6.5 Future prospects

In Finland, VE estimation could be improved in several ways. One priority is enhancing the identification of infection related outcomes, such as death due to infections. Currently Statistics Finland publishes cause-of-death data with a 1–2 year delay (283). However, during the pandemic, deaths related to COVID-19 were manually collected from death certificates by THL's forensic department. This enabled VE estimation against both COVID-19 related deaths and deaths in which COVID-19 was a contributing factor in Study V. Real-time access to cause-of-death data would enable timely VE monitoring against severe outcomes for variant-adapted COVID-19 and seasonal influenza vaccines which could help guide vaccine strain selection for upcoming seasons and inform the timing of vaccine rollouts.

In the future, a major objective is to try to limit the confounding and other biases in register-based VE estimation. For instance, certain important confounders, such as overweight or unhealthy lifestyles, were not identifiable in national register data and developing methods to detect these conditions from the register could improve VE estimation. Moreover, the best approaches to address confounding (e.g. propensity score vs exact matching) could be investigated.

Target trial emulation is a relatively new approach in VE research. One promising approach would be to use other vaccines as a comparator group. During the pandemic, head-to-head comparisons for different COVID-19 vaccine schedules have already been conducted (110,244,259), yielding relative VE estimates. In these studies, confounding was likely smaller compared to studies that compared vaccinated and unvaccinated assessing absolute VE. However, comparisons of vaccinated and unvaccinated groups might be improved by selecting an 'active control' group—such as individuals vaccinated with another vaccine. For example, in a target trial emulation, VE against COVID-19 could be estimated by comparing individuals who received a COVID-19 vaccine (i.e. the active arm in the hypothetical RCT) with those who received a tetanus or hepatitis A vaccine (i.e. the control arm). In this observational setting, confounding might be better addressed than in a comparison between vaccinated and unvaccinated individuals. This design could also address the confounding observed during the negative control period.

In Finland, residual confounding due to health-seeking behaviour could be addressed in TND studies based on register data but this would require identifying the test-negative results from the registers. A TND approach would be especially useful for evaluating VE against mild disease. For instance, in Study II, VE against SARS-CoV-2 infection could have been estimated more reliably using a TND based on symptomatic healthcare workers with both positive and negative test results. The same design would also benefit studies of other vaccine-preventable diseases —such as pertussis— where health-seeking behaviour is a major confounder. In addition, home test results could be valuable for assessing VE against mild illness. Although these data are currently unregistered, they could be collected through a participatory cohort in which individuals self-report test results, enabling VE estimation.

Despite advances in observational methods, the benefits of randomisation should not be overlooked (284). Randomisation should be considered as one option in future vaccine rollouts. For example, during the initial COVID-19 vaccine and bivalent booster rollouts, supply shortages led to stepwise vaccination where there were limited number of vaccines for different prioritization groups. In these cases, vaccines were administered on a "first-come, first-vaccinated" basis, meaning socially disadvantaged individuals–such as those with mental disorders or low educational level–may have been less likely to receive the vaccine. In such cases, randomising the order of vaccination—similar to a stepped-wedge design—could have been a fairer and more informative approach (285) (Figure 19). In this design, clusters receive the intervention at different time points, with all eventually receiving it. As Hemming et al. note (285) this design may be useful in situations—such as a pandemic—where researchers require more data on an intervention, even though key stakeholders (e.g. politicians) are already pushing to implement it. The randomisation could be automatized, and each individual could have been informed via electronical message.

Finally, artificial intelligence (AI) holds promise for improving VE estimation and public health decision-making. Kraemer et al. recently highlighted the potential of AI in infectious disease modelling (286). AI could improve epidemic forecasting for COVID-19 and influenza which would help optimise the timing of vaccination campaigns. It might also enable the prediction of future variant mutations, allowing for earlier development of variant-adapted vaccines. AI tools could also identify symptoms related to infections from patient records, providing important data for use in a TND study based on register-data. Furthermore, AI could identify risk and priority groups at the individual level. For example, in densely populated urban areas, superspreaders might be prioritised, while in rural regions, elderly or clinically vulnerable individuals may be the focus. Different vaccination strategies could also be randomised between regions to evaluate which approach is more effective, allowing an AI-driven vaccination system to continuously "learn" and adapt rollout decisions in real time. Personalised messaging—for instance, through electronic alerts—could also be used to improve vaccine uptake (287).

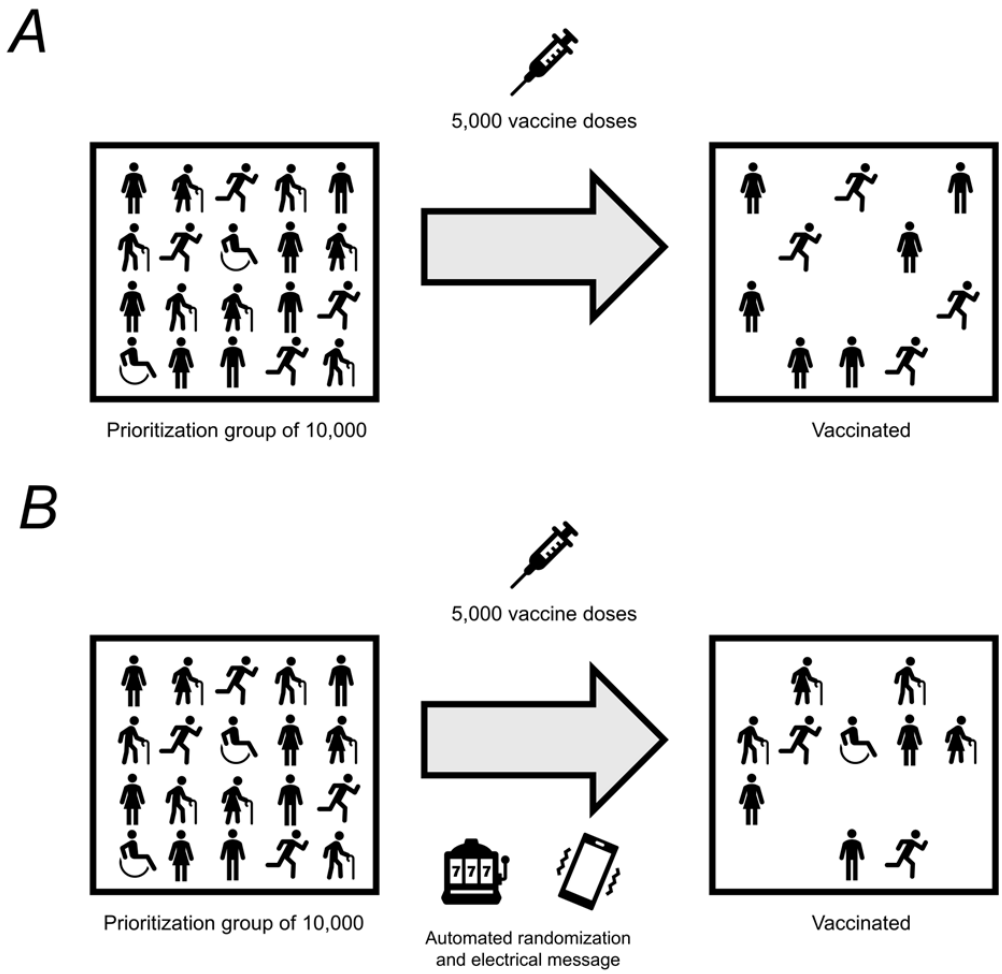


Figure 19 First-come, first-vaccinated vs. randomisation in vaccine roll-out. When vaccine deliveries (e.g.,5,000 doses) arrive, vaccines are administered using a "first-come, first-vaccinated" approach within different prioritization groups (A). For example, such a group might include individuals aged 70 years or older. In these groups, it is likely that those who are more socially engaged receive the vaccine first. However, vaccine roll-out could also be randomised within the groups (B). This might be a fairer approach, as everyone would have an equal chance. Moreover, it would allow more precise VE estimation. Ideally, both the randomisation and messaging would be automated.

7 Conclusions

The objective of this thesis was to estimate COVID-19 VE during 2021–2023, and the findings were used to support policymaking in Finland. The following conclusions can be drawn:

1) Two-dose COVID-19 vaccine schedules significantly reduced the number of SARS-CoV-2 infections and COVID-19 related hospitalisations in 2021.
2) Prior to the emergence of Omicron, vaccine protection against SARS-CoV-2 infection waned notably within 4–6 months, while the protection against severe COVID-19 was better sustained.
3) Although after the emergence of Omicron vaccine protection against SARS-CoV-2 infection was low, protection against severe COVID-19 remained high across all age groups, and vaccinations prevented a substantial number of COVID-19 related hospitalisations in 2022–2023.
4) The rollout of the boosters and variant-adapted bivalent vaccines enhanced protection against severe COVID-19 among the elderly.
5) The benefit of booster doses after autumn 2022 was smaller than that of the 2021–2022 primary schedule rollout; bivalent boosters provided additional protection against COVID-19 related hospitalisation comparable to that of seasonal influenza vaccines.
6) Register-based analyses provided timely evidence to inform policymaking during the COVID-19 pandemic.
7) The adoption of new approaches, such as target trial emulation, enhances the ability to analyse vaccine effectiveness using register data, unlocking more robust and nuanced insights into VE.

8 Statement regarding the use of artificial intelligence

Language editing support was provided using ChatGPT and Paperpal. All content and any remaining errors are solely my responsibility.

Acknowledgements

First and foremost, I would like to express my deepest gratitude to Professor Tuija Leino and Dr. Ulrike Baum for supervising my thesis. They have been inspiring role models who taught me the foundations of epidemiology, statistics, and research. I especially admire Tuija's sharp mind and the clarity with which she approaches every problem. Ulrike has been not only a brilliant colleague but also a true friend, and I am forever grateful for the opportunity to work with her over these years.

I am sincerely thankful to the pre-examiners, Professor Mika Rämet and Professor Merryn Voysey, for reviewing my thesis and for their valuable comments. I also wish to warmly thank Professor Preben Aavitsland for kindly agreeing to serve as the opponent in the public examination.

My gratitude extends to Professor Hanna Nohynek for her warm support and inspiring enthusiasm for vaccinology and public health. I also wish to thank Dr. Heini Salo, Dr. Terhi Kilpi, Dr. Arto Palmu, and Professor Kari Auranen for their support and guidance over the years. I am indebted to Dr. Sirkka Goebeler, MSc Jori Perälä, and MSc Toni Lehtonen for their valuable contributions to the studies included in this thesis.

I wish to acknowledge Professor Anders Hviid, Dr Niklas Worm Andersson, and MSc Emilia Myrup Thiesson from the Statens Serum Institute, whose contributions were essential to the conceptualisation of Study III. I am equally thankful to my Nordic colleagues MSc Nicklas Pihlström, Dr. Anja Bråthen Kristoffersen, Dr. Hinta Meijerink, Dr. Jostein Starrfelt, and Professor Rickard Ljung for their collaborative spirit and valuable contributions to Study III and beyond. It has been a privilege to work with such talented colleagues.

My sincere thanks also go to Dr. Erika Lindh, MSc Aapo Juutinen, MSc Oskari Luomala, MSc Jukka Ollgren, and my colleagues in the COVID-19 Situation Reporting Team, as well as many others at the Finnish Institute for Health and Welfare, for their assistance and for creating such a supportive working environment.

I am especially grateful to Professor Benjamin Cowling at the University of Hong Kong for the opportunity to collaborate with him in the spring of 2024. I also owe special thanks to Dr. Sheena Sullivan, who, together with Professor Cowling, introduced me to the fundamentals of the test-negative study design.

I gratefully acknowledge the University of Helsinki, the Finnish Medical Foundation, and the Finnish Institute for Health and Welfare for funding my doctoral research. Without their generous support, this thesis would not have been possible. I also wish to thank the European Medicines Agency for supporting Study III.

Finally, my deepest gratitude goes to my dear Anna, for her love, understanding, and all the happiness she has brought to my life; to my parents for their unconditional support; and to my sisters Maija and Mari, the best sisters one could hope for. I also wish to thank Jani, Heili, Albert and Tuomas for being my closest family, and Timo, Timo, and Aleksi for being true friends.

Helsinki, 20 October 2025
Eero Poukka

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