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Clinical and Epidemiological Dynamics of COVID-19 Prevention and Treatment with special focus on Chronic Obstructive Pulmonary Disease Patients

PhD thesis

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List of Abbreviations

CCI	Charlson comorbidity index
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
EMA	European Medicines Agency
FDA	Food and Drug Administration
HR	Hazard ratio
HUN-VE	Hungarian Vaccine Effectiveness study
LMWH	Low-molecular-weight heparin
MODS	Multiple organ dysfunction syndrome
NEWS2	National early warning score 2
NSAID	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PSM	Propensity score matching
RCT	Randomized controlled trial
RDV	Remdesivir
RNA	Ribonucleic acid
RR	Relative risk
SARS-CoV2	Severe acute respiratory syndrome – coronavirus 2
SD	Standard Deviation
SOC	Standard of care
SRA	Stringent regulatory authority
VE	Vaccine effectiveness
VOC	Variant of concern
WHO	World Health Organization
WHOS	WHO ordinal scale for clinical improvement

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has profoundly impacted global healthcare systems, necessitating effective strategies for prevention and treatment globally. As the pandemic evolved, there was an ongoing urgent need to explore evidence-based approaches to fight the spreading of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reduce hospital admissions, and improve patient treatment related outcomes. In this context, real-world clinical epidemiological research plays a crucial role in understanding the dynamics of COVID-19 prevention and treatment.

1.1 The pandemic

1.1.1 The first year of the pandemic and early efforts fighting the virus

The COVID-19 pandemic, caused by the novel SARS-CoV-2, has had a profound impact on global health, economies, and the whole population of the world. The outbreak was first reported in December 2019 in Wuhan, Hubei Province, China. It was initially characterized by clusters of pneumonia cases of unknown origin. The virus quickly spread within Wuhan and then rapidly expanded to other regions of China and starting early January crossed international borders.(1) The transmission of the virus occurs through respiratory droplets when an infected person coughs, sneezes, or talks. As the pandemic evolved, it became evident that SARS-CoV-2 could also be transmitted by individuals who were asymptomatic or pre-symptomatic, adding to the challenges caused by the virus. In terms of the global timeline, the virus rapidly spread beyond China, with major outbreaks emerging in countries such as Italy, Spain, the United States. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020, reflecting the global scale and severity of the disease.(2)

In Hungary, the first confirmed case of COVID-19 was reported on March 4, 2020.(3) The impact of the pandemic on the country was significant, with increasing numbers of confirmed cases and a growing burden to the healthcare system. In the early phases the government faced challenges in managing the spread of the virus, implementing public health measures, and ensuring adequate healthcare resources. However, after the summer, a seemingly transitory period with low number of new daily cases the second wave -starting end of August- of the pandemic hit harder, with around 368 000 confirmed cases until the end of January, 2021.(4)

During the end of the second wave vaccinations started on the 26th of December 2020, with an intensive campaign focusing on healthcare professional, being the first in the EU.(5)

In the early stages of the pandemic, efforts were focused on understanding the virus, its clinical manifestations, and the development of quick diagnostic tests.(6) The race to develop effective treatments began with numerous clinical trials investigating various drugs and therapeutic approaches. Initial treatment trials included the use of corticosteroids, convalescent plasma, anticoagulants (however they were already used as part of standard care), antiviral drugs such as favipiravir, and later remdesivir (RDV), and repurposed drugs like hydroxychloroquine, colchicine, and immunomodulatory agents like tocilizumab, or baricitinib.(7,8) These initial trials aimed to find effective treatments and options to manage severe cases. One of the first international efforts was the Solidarity trial, which was launched by the WHO on the 18th of March, 2020.(9) Another one starting a bit later, during the end of March 2020, the Recovery trial launched by the Nuffield Departments of Population Health and of Medicine at the University of Oxford.(10) Among other trials, an especially important on in the light of later results is the Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy trial), which was started on the 22nd of March, 2020 collecting data from multiple EU countries, and 48 centers.(11)

As mentioned earlier vaccines against the virus became available relatively fast. SARS-CoV-2 vaccines began with several candidates entering the clinical trial phase in early 2020. Moderna was the first to start human testing of a vaccine for the novel coronavirus on March 16, 66 days after the genetic sequence of the virus was released.(12) Some developers, including Moderna, could enter phase 2 and 3 trials in an unprecedented speed by leveraging the novel mRNA technology to quickly develop and produce highly effective vaccines. Notably, the Pfizer-BioNTech vaccine was the other with fast-paced development. Both vaccines received emergency use authorization from the U.S. Food and Drug Administration (FDA) on December 11, 2020.(13) The European Medicines Agency (EMA) also granted conditional marketing authorization for these vaccines around the same time. For the vaccine developed by Pfizer a conditional marketing authorization on the 21st of December, 2020 and for the one by Moderna on 6 January 2021.(14,15) In Hungary additional vaccines became available later, namely three viral vectors: Sputnik V®, developed by the Russia's Gamaleya National Centre of Epidemiology and Microbiology, approved in Hungary on the 21st of January, 2021,(16) later Vaxzevria®, developed by AstraZeneca, approved by the EMA on the 29th of January, 2021,(17) and lastly Jcovden®, developed by Janssen Vaccines in Leiden, Netherlands, approved by the

EMA on the 11th of March, 2021; (18) and the inactivated whole virus vaccine Sinopharm, developed by the Beijing Bio-Institute of Biological Products, which was approved for use in Hungary on the 30th of January, 2021.(19)

1.1.2 Waves of the pandemic in Hungary

During a pandemic, a "wave" refers to a period of increased infection rates and disease activity within a specific population or geographic area, however there is no strict definition for what is or is not an epidemic wave or phase. During the COVID-19 pandemic in Hungary distinct waves were associated with new variants, but this is not a necessity. Simply, the concept of waves in a pandemic arises from the pattern of disease transmission and the dynamics of viral spread.(20) When a new infectious disease emerges, such as the initial outbreak of COVID-19, the population generally has little to no immunity, making it susceptible to widespread infection. As the virus spreads, case numbers increase rapidly, leading to more carriers, leading to higher chance of getting the virus. This positive automatic feedback is causing the mentioned peak of numbers and is uninterrupted until public health interventions (e.g., social distancing measures, lockdowns), and later natural immunity in recovered individuals, and changes in human behavior will influence the trajectory causing a drop in the number of active cases.(20) If the virus is not effectively controlled and preventive measures are relaxed, or other variants with different virulence emerge subsequent waves of infections can occur. Later characteristics of waves will be influenced by factors such as viral variants, healthcare capacity, vaccination rates, and public health responses.(21) This mentioned pattern and the waves are noticeable in Figure 1, which shows the 7-day average of daily new confirmed COVID-19 cases between the 15th of February, 2020 and 15th of May, 2023. There are no official date intervals for the waves in Hungary, however the most common view is that minimum of 5 waves were distinguished.(22)

The first wave occurred in early 2020, starting with the first case on March 4, 2020 and was characterized by an increase in the number of confirmed cases and the introduction of various public health measures to control the spread of the virus. Hungary implemented several measures to contain the transmission of the virus, including extended travel restrictions, border controls, public health measures, such as the mandatory use of face masks in public spaces, social distancing, limitations on public gatherings, and the closure of non-essential businesses and educational institutions.(23) The number of cases during this wave is hard to estimate since during this time only limited number of laboratories could perform polymerase chain reaction

(PCR) testing for the virus, and antibody based test were only approved by the WHO on the 7th of April, and became available for use later.(24)

In the end of August 2020, the second wave started, but this time with a bit more loose measures in place causing a significant surge in cases, with daily new infections reaching record highs. Starting only around with 6000 confirmed cases until the end of August, at the end of January this number reached more than 366 000, meaning around a third million confirmed cases during this wave. The healthcare system faced immense strain as hospitalizations increased, leading to challenges in providing adequate care and managing the influx of patients. Due to the commercially available testing methods, and in the meantime many folds increased capacity of PCR testing, contact tracing efforts were strengthened to track and monitor the close contacts of confirmed cases, aiming to break the chains of transmissions. During this wave the most impacted subgroup of the population was the elderly, with about every 3rd death happening in social institutions and nursing homes according to the data provided by the chief medical officer of Hungary, on the 10th of March, 2021.(25) With the start of vaccinations during the end of this wave, these and other healthcare facilities and hospitals became less of a hot spot for the spread of the virus. However, at this point, it became evident how significant a danger the COVID-19 pandemic posed to healthcare workers by the danger of infection opposed during daily visits and any activities within the room of a COVID-19 patient.(26) The majority of healthcare workers were infected during the second wave, and the mortality rate among Hungarian healthcare workers was highest during this period.(27) Fortunately, as soon as vaccinations became available, the disease burden of COVID-19 on healthcare workers improved significantly.

As seen in Figure 2, the third wave was the deadliest, leaving an especially great burden. Between the beginning of February and end of May 2021 around 440 thousand confirmed cases were registered in Hungary. Despite the extensive efforts of vaccinations, which could lead to more than half of the population receiving at least one dose until the end of this period,(28) the spread of the virus was much faster. This was the effect of the new Alpha variant of concern (VOC), with an estimated 40–80% higher transmissibility than the wild-type SARS-CoV-2. This variant was the dominant during this period, being the only VOC starting in March 2021.(29) The second and third waves saw varying levels of public health measures. Compared to the second wave some measures were relaxed to balance the need to mitigate the spread of the virus with the desire to maintain socioeconomic activities, although mask-wearing and social distancing requirements remained in place. Also, during the second wave, there was a

heightened sense of urgency and adherence to safety measures by the general public.(30) By the third wave, pandemic fatigue and varying levels of compliance may have influenced the effectiveness of preventive measures, especially with the narrative focusing on vaccinations. While the third wave saw a higher proportion of cases among younger individuals, due to the above-mentioned reasons, the vulnerable and elderly populations remained at an increased risk of severe illness and worse outcomes. The first study published by the Hungarian Vaccine Effectiveness study (HUN-VE) workgroup focusing on nationwide effectiveness investigated this wave.(31)

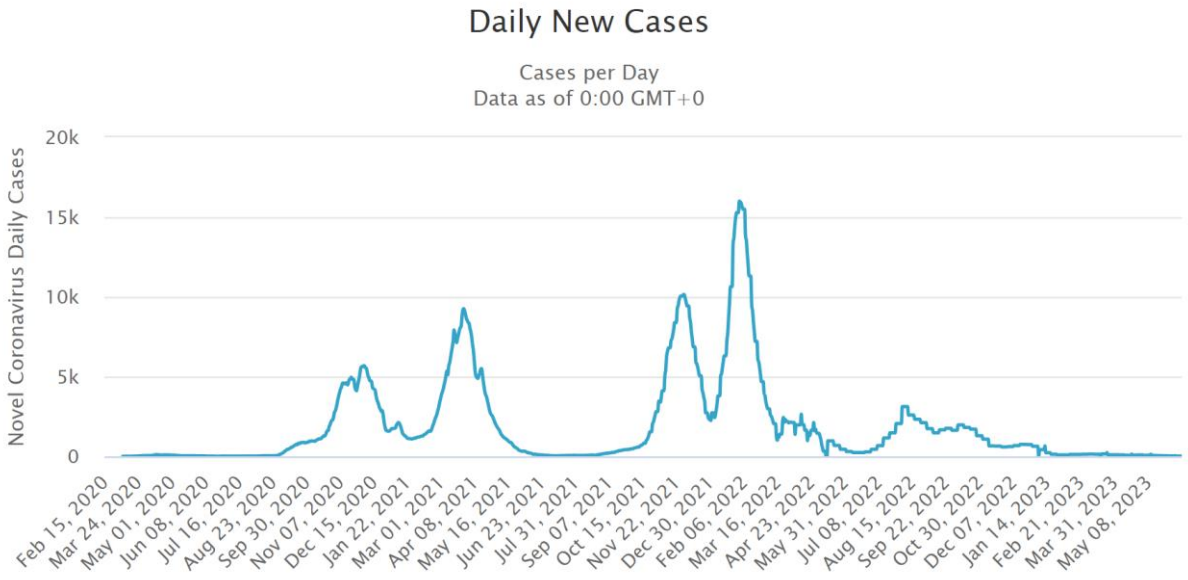
During the summer of 2021 all restrictions were lifted, but with the Delta VOC reaching Europe, and becoming the VOC in the surrounding area, case numbers started to rise again during August 2021. To this time in addition to SARS-CoV-2 testing, Hungary has fallen behind in vaccinations compared to the EU, falling back from being one of the countries with the highest vaccination rates just a few months before, to the middle of the pack with the population's 57% being fully inoculated (the EU average was 63% at the time).(32)

The fourth wave had similarities to the second in active case numbers, and surprisingly in fatalities, despite the ongoing vaccinations and the possibility of receiving a booster dosage from any vaccine available. This wave was dominated by a new VOC, called Delta, again contributing to quick spread and symptoms even in vaccinated population. However, the HUN-VE studies showed that unvaccinated people had a significantly higher chance for infection and especially in elderly worse outcomes.(33-35) Until the start of this wave the younger population have received less vaccinations, causing almost two times higher chance for infection in the age groups under 45 than above 55 years old.(35) This effect was strengthened with the reopening of schools and universities. The fourth wave posed particular pressure on healthcare systems, with increased hospitalizations and strain on medical resources.

From the first report of the new Omicron variant on 24 November 2021. it rapidly spread all around the world, due to the highest virulence of all the variants, and its ability to infect the vaccinated and recovered population, reaching Hungary at the end of the year and becoming the VOC in early January, 2022 causing the last listed wave.(36-38) The fifth wave was unique for its highest number of active cases, with roughly 600 000 confirmed new cases in 2022 until the end of March, and the lowest mortality rate.(34) On the 4th of March, 2022 government restrictions were lifted, and widespread testing became less frequent, finally the free testing for the general public was ended in one month.(39,40) With this final step the pandemic gradually

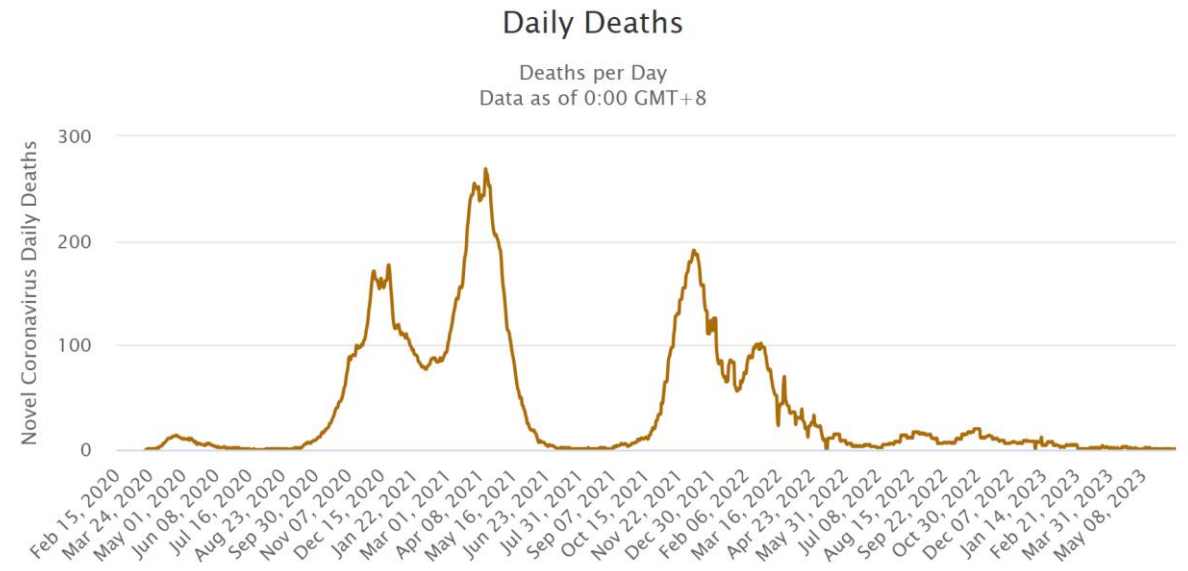
transitioned to a phase where the disease became part of daily life, and the population living with the ongoing presence of the virus.

Figure 1: 7-day moving average of daily new confirmed SARS-CoV-2 cases in Hungary between February 15, 2020, and May 15, 2023



source: Worldometer(4)

Figure 2: 7-day moving average of daily COVID-19 deaths in Hungary between February 15, 2020, and May 15, 2023



source: Worldometer(4)

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1.2 From Antivirals to Precautions: COVID-19 Treatment and Prevention

1.2.1 Treatment options for COVID-19

Throughout the first year of the pandemic numerous trials were started to find the best practices, drugs and therapies treating COVID-19 patients, as summarized in a paper published by Janiaud, P. et. al in the Canadian Journal of Cardiology.(41) Before discussing the most effective treatments for COVID-19, it is imperative to recognize and distinguish between the varying degrees of severity of the illness. COVID-19 manifests today (Q2 2024) as a mild infection in most cases, in the pre-omicron era the known infections escalated to be more serious.(42,43) This meant a spectrum of presentations had to be considered while talking about treatment, ranging from asymptomatic cases with positive virologic tests to critical cases characterized by respiratory failure, septic shock, and multiple organ dysfunction syndrome (MODS).(44) Understanding these gradations of severity is crucial as it informs the appropriate management strategies tailored to each patient's clinical condition. For instance, while mild cases may require minimal intervention and supportive care, severe and critical cases necessitate more intensive medical interventions such as oxygen therapy, mechanical ventilation, and targeted therapies to mitigate the risk of adverse outcomes. Therefore, accurate categorization of disease severity (Table 1) is fundamental while discussing treatment options.(45)

Table 1: Severity categories of COVID-19 based on the WHO guidance

	Clinical presentation
Asymptomatic COVID-19	Positive virologic test No symptoms
Mild COVID-19	Symptoms of COVID-19 without dyspnea, hypoxemia or pneumonia
Moderate COVID-19	Viral pneumonia No hypoxemia
Severe COVID-19	Pneumonia with dyspnea, hypoxemia with SpO2 < 90% Requires hospitalization and oxygen supplementation
Critical COVID-19	MODS, Acute respiratory distress syndrome Requires life sustaining treatment

Tabel 1. is adapted from the 2021 clinical management guideline of COVID-19 by the WHO(46)

For asymptomatic cases, no treatment is recommended, but it is imperative to underscore the significance of their role in the broader context of disease containment, as evidence suggests it

is important to isolate especially for those who are able to participate in the transmission of the virus to vulnerable populations.(47)

The treatment of mild to moderate COVID-19 is particularly important due to multiple available treatment options, including SARS-CoV-2 antiviral medication RDV. Also the treatment of mild disease has particular significance in those with higher risk for progression to severe disease.(48) Early interventions help mitigate disease progression and improve clinical outcomes. Treatment of mild disease consists of supportive care and early antiviral therapy.(49,50) The treatment considerations of patients with severe disease, on top of the before mentioned therapies, include anti-inflammatory agents and oxygen supplementation. These patients must be hospitalized. Usually, due to lung involvement, they are treated at pulmonary or general internal medicine wards. Nowadays critical COVID-19 cases are a rarity, but during the peaks of the pandemic, these cases required treatment at intensive care units. The complex therapeutics of these patients are not included in this dissertation.

1.2.2 Considerations of supportive care

Patients are advised to prioritize rest and ensure adequate hydration and nutrition to bolster their immune response and facilitate recovery.(51,52) Interestingly wearing masks help against the drying of airways, and could support talking about hydration with patients.(53) Additionally, symptomatic relief is achieved through the judicious use of antipyretics and analgesics such as acetaminophen, ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) to manage fever and discomfort.(54) For patients suffering from dry cough antitussive agents such as dextromethorphan and benzonatate may be prescribed, enhancing patient comfort and quality of life.(55,56) However, for hospitalized patients, and those experiencing productive cough accompanied, expectorants are recommended, because of the mucus accumulation caused by COVID-19 pneumonia.(57) The use of low molecular weight heparin (LMWH) was encouraged due to its role in preventing thromboembolic events, which are more common in COVID-19 patients.(58) Providing supplemental oxygen is vital for treating hypoxemic patients. Especially since the condition where patients may experience dangerously low blood oxygen levels without obvious symptoms, known as silent hypoxemia, could be part of the clinical picture of COVD-19 patients.(59) These supportive measures collectively help the care for individuals with COVID-19. Supportive care is recommended for all patients suffering from symptoms.(45)

1.2.3 Antivirals with the focus on remdesivir

Antiviral medications are a core component of the treatment, aiming to inhibit viral replication and attenuate disease severity. Ritonavir-boosted nirmatrelvir(60) and RDV(61) are among the preferred agents today,(45) effectively reducing viral load and help improving clinical outcomes. In instances where these preferred agents are unavailable, molnupiravir is a viable alternative for antiviral therapy.(62) RDV is particularly crucial in Hungary as it's the only antiviral medication accessible, supported by ample evidence, it's one of the most researched drugs for COVID-19 treatment. It can be used in an outpatient setting, while its primary significance lies in hospitalized patients.(63,64) Current guidelines stress the importance of starting RDV early, within the first week of infection, to optimize its effectiveness.(45)

Remdesivir was first recommended by the ACTT-1 trial results published by Beigel et al. in May, 2020. RDV is an inhibitor of RNA-dependent RNA polymerase thus disrupting viral reproduction and spread within the host.(65) Before 2020 it was not yet authorized for specific viral infections, however promising results were published for the use in Ebola cases.(66) In vitro the agent was found to be effective against multiple types of filoviruses, pneumoviruses, paramyxoviruses, and most importantly coronaviruses.(67) Based on the results of Beigel et al. and two other phase 3 trials RDV was the first drug approved by the FDA and later by the EMA. The first study incorporated in this dissertation was started during the time RDV became available for use in Hungary, making the results later shown in this work one of the several studies that reported effectiveness and showed use case of the drug in a real-life setting.

Some monoclonal antibodies, targeting different surface proteins of the virus, were developed within a few months and received authorization in late 2020 or early 2021, initially showing high protective efficacy against SARS-CoV-2.(68-70) These drugs have a combined effect. By attaching to the circulating viruses, they act as direct-neutralizators but could be considered immunomodulators as they facilitate antibody-dependent immunity. As new variants emerged, bamlanivimab and etesevimab were found to be less effective against the delta VOC, and later, casirivimab and imdevimab lost their activity against the omicron variants.(71,72) Before vaccinations became available, convalescent plasma was also used in Hungary to treat COVID-19, but it is now considered obsolete for wide clinical usage.(73) Meta-analyses have shown that convalescent plasma treatment was not statistically associated with prolonged survival or improved clinical outcomes.(74)

It is important to note that certain medications, such as chloroquine, hydroxychloroquine, azithromycin, and ivermectin are not recommended for the treatment of COVID-19 due to limited evidence supporting their efficacy and potential for adverse effects.

1.2.4 Anti inflammatory treatments

As mentioned before, non-steroid anti-inflammatory agents are used as part of supportive care to reduce pain, inflammation of mucous membranes and to help bring down body temperature. In COVID-19 cases, due to the possibility of systemic inflammation, and its severe form called the “cytokine storm”, more anti-inflammatory drugs were used. In the pre-omicron era, the “cytokine storm” was confirmed to be one of the most important reasons for the worsening of COVID-19 cases. As of now, systemic glucocorticoids are not recommended for mild COVID-19 patients, however, evidence shows benefit for using dexamethasone or methylprednisolone in hospitalized cases, for those requiring conventional oxygen supplementation.(75-77) During the times of alpha and delta VOC immunomodulatory drugs were also recommended for severe cases to prevent further progression. These were mainly interfering with the activation pathways of leukocytes, interfering with signaling or directly with interleukins. In Hungary tocilizumab (an IL-6 inhibitor) was temporarily authorized and used for severe COVID-19 cases. As of today, the only immunomodulatory drug recommended is baricitinib, a Janus kinase inhibitor, which acts by suppressing the signaling of different cytokines and as an effect the activation of lymphocytes. It is only recommended in combination with dexamethasone, in hospitalized patients with pneumonia, requiring high-flow oxygen supplementation or non-invasive ventilation therapy.

Research is still ongoing to find even more effective therapies against COVID-19, albeit with reduced intensity following the emergence of the Omicron variant. Despite tremendous amount of progress, the need for more accessible treatment options remains important, given the current cost constraints, underscoring the importance of ongoing efforts to enhance therapeutic accessibility and affordability.(78) Much like influenza, where ongoing research is still active, trying to find new therapies in contrast to the fact that vaccinations are widely available and can be regarded as one of the most cost-effective healthcare interventions.(79) This also makes a good transition to the next segment on prevention strategies.

1.2.5 Preventive measures

In the battle against COVID-19, the simple practice of adopting cautious behavior can serve as a powerful weapon against the spread of the virus. Practices such as regular hand hygiene, cough etiquette, and avoiding touching the face can play a role in minimizing transmission.(80-82) Most importantly, the use of masks for individuals aged two and above, offers an added layer of protection.(83,84) It is crucial for masks to fit snugly over the nose and mouth, with N95 and K95 masks providing superior protection compared to surgical masks, while cloth masks offer the least protection.(85,86) The main goal should always be, adhering to local public health guidance. Finally in hospitals, or enclosed spaces with individuals more prone to developing serious disease (e.g. retirement homes), COVID-19 testing is recommended for individuals experiencing symptoms suggestive of COVID-19 and who have had close contact with known or suspected infected individuals. Even with consistent adherence to these cautious behaviors, their ability to fully protect against the virus is limited. Vaccinations remain the key to achieving widespread immunity and protecting society as a whole.(87)

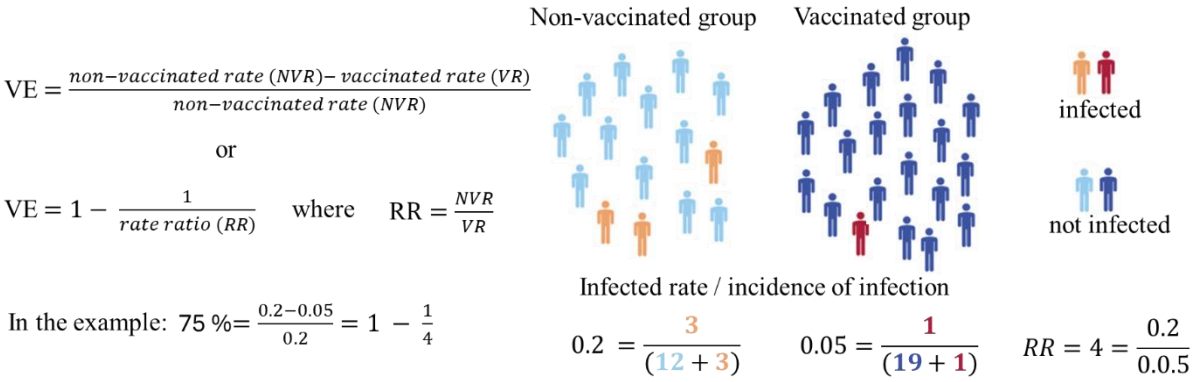
1.2.6 Vaccination and its effectiveness

Around the world 40 vaccines have been authorized against SARS-CoV-2 for full or emergency use by national regulatory authorities. Out of these, only 10 have been authorized by a regulator which is considered a stringent regulatory authority (SRA), and 7 others are still being investigated to be recognized.(88,89) In Table 2 the 13 most used vaccines are shown, in order of the number of authorizations they have with additional information. Some vaccines are administered in 2 doses (2-4 weeks apart) to provide the intended protection.

As also shown in Table 2 There are various types of vaccines, each induce immune response by introducing the body to a harmless form of the pathogen or its components. Viral vector vaccines use a harmless virus to deliver genetic material into cells. The newly developed mRNA vaccines contain it encapsulated in lipid nanoparticles, which are absorbed by the cells. In both types, the RNA will later be translated into proteins. These viral proteins will be presented on the cell surface but also secreted into the circulation, thus inducing both T and B cell mediated immune response and finally help creating T- and B-memory cells. Inactivated and subunit vaccines work on the principle that once introduced into the body, they will be taken up by antigen-presenting cells, and presented to mainly T-cells, which can form immunological

memory. However, memory B cells were also found in patients introduced to inactivated vaccines, showing that these types could induce other types of immunity too.(90) While the immune response differs with each vaccine, the complex immune reaction will finally result in protection against the virus. However, this protection can vary in effectiveness and duration based on different factors.(91) These influencing factors are characteristics of the person vaccinated (sex, age, comorbidities, nutrition, etc.), their environment and behavior (e.g. smoking) and finally the attributes of the vaccine itself. Due to these influencing factors and vaccinations being a preventative tool, usually the usefulness of vaccines is measured by epidemiological indicators. One of the most used measures is vaccine effectiveness (VE). The VE is always calculated from observational data, from a group of wide range of people (both sexes, broad age range, different comorbid conditions, etc.). The calculation of VE is simple and can be derived from the incidence or the rate of an undesirable outcome (infection, serious disease or even death) in the vaccinated and non-vaccinated. The calculation is shown with an easy example in Figure 3.

Figure 3: Calculation of vaccine effectiveness with an example



VE: Vaccine Effectiveness, NVR: non-vaccinated rate, VR: vaccinated rate, RR: rate ratio

It is important to mention that after COVID-19 vaccinations became available, VE of the commercially available products had to be measured in real time. Results of studies presented later in this work were among the first to publish results concerning this important indicator.

In Table 2 the last column is highlighting an interesting discrepancy, how in certain cases the latest robust report of VE is still from times of earlier VOC waves. As of August of 2024 there are no variants meeting the VOC criteria, however against the latest variant of interest (VOI),

the “Pirola” subvariant (omicron BA.2.86) there are only 3 providers (Pfizer-BioNTech, Novovax and Moderna), who published evidence of effectiveness.(92-96)

Table 2: Vaccines against SARS-CoV-2, during the first 4 waves of the pandemic, SRA approved and those under investigation by the WHO.

Manufacturer	Brand name	Type	Status	Doses	Latest evidence
Oxford-AstraZeneca	**Vaxzevria**	vector	SRA	2	delta
Pfizer-BioNTech	**Comirnaty**	mRNA	SRA	2	omicron
Janssen	**Janssen**	vector	SRA	1	delta
Moderna	**Spikevax**	mRNA	SRA	2	delta
Sinopharm	**BBIBP-CorV**	inactivated	SRA	2	alpha
Gamaleya Institute	**Szputnyik V**	vector	Investigated	2	delta
Sinovac	CoronoVac	inactivated	SRA	2	delta
Novavax	**Nuvaxovid**	subunit	SRA	2	alpha
Bharat Biotech	Covaxin	inactivated	SRA	1	delta
Valneva SE	**Valneva**	inactivated	SRA	1	omicron
Sanofi-GSK	VidPrevtyn B	subunit	SRA	1	omicron
CanSino	Convidecia	vector	SRA	1	omicron
Sinopharm	WIBP-CorV	inactivated	Investigated	2	delta

SRA: stringent regulatory authority, vaccines approved in Hungary are highlighted bold

1.3 The role of clinical science and epidemiology in the COVID-19 crisis

It is important to understand that at the beginning of the pandemic, the level of threat was not known. The first wave, coupled with rapid globalization, was sudden and unprecedented. In this high-pressure environment, the precise publication of experiences and retrospective data analysis became a necessity. The results presented in this dissertation are from investigations and studies conducted during this time. Due to the unusual circumstances of the pandemic an unusual approach had to be taken in the research process. Rather than focusing on a single topic, the studies presented encompass various fields and use diverse populations, and methodologies reflecting the past need to address real-time questions, which were pressing during each phase of the pandemic. Their retrospective nature and the use of mass amounts of electric health records unifies these works, but each study was designed to address specific clinical or public

health concerns. This approach allowed us to contribute meaningfully to the evolving body of knowledge during a time of great uncertainty.

2. Objectives

Before presenting the specific aims of this dissertation, it is important to provide context on my role within the broader scope of COVID-19 research efforts at Semmelweis University. My involvement in these studies evolved alongside the pandemic's challenges, as mentioned above. Initially, I conducted work as part of a research group evaluating clinical outcomes at the Pulmonology Department, Semmelweis University. One of the most urgent questions during at the hospital this time, the second and third waves, was the real-world efficacy of the emergency-approved, repurposed drug, remdesivir. This led to the formulation of the first two aims:

1. Evaluate the impact of a 5-day RDV treatment on 30- and 60-day all-cause mortality in hospitalized COVID-19 patients, focusing on those with more severe clinical conditions.

2. Identify patient subgroups benefiting most from RDV treatment. Determine which specific groups show the most significant benefits from RDV therapy in a hospital setting.

Later, I had the opportunity to join the HUN-VE workgroup, which operated on a larger, nationwide scale to assess the effectiveness and utility of the newly approved COVID-19 vaccines in Hungary. My involvement initially focused on analyzing booster vaccinations, and later on special patient groups. This broader focus resulted in the following second two aims:

3. Investigate if primary vaccination series and booster doses reduce the risk of hospital admission and 28-day all-cause mortality due to the SARS-CoV-2 delta VOC among the Hungarian elderly population.

4. Analyze VE against SARS-CoV-2 infection and hospitalization in COPD patients and in a matched non-COPD cohort and assess VE waning.

3. Methods

3.1 Study designs

The dissertation involves three separate retrospective investigations, each focusing on a specific aspect of the COVID-19 pandemic.

The first study involved COVID-19 all patients admitted to the Semmelweis University's Department of Pulmonology between September 1, 2020, and April 30, 2021. The study cohort was divided into two groups based on the given treatment regiments. The control group included patients who received only standard of care (SOC) and the treatment group included patients who started RDV therapy on top of SOC. The analysis was based on the following baseline parameters: age at admission, sex, medical history of comorbidities, body mass index (BMI), Chest CT findings and laboratory parameters at admission, clinical severity during hospital stay and finally Charlson comorbidity index (CCI) was calculated. Comorbidities assessed included malignancies, hypertension, diabetes, coronary artery disease, heart failure, bronchial asthma, COPD, anemia, and dyslipidemia. Severity was assessed by using the highest daily National Early Warning Score 2 (NEWS2), which was recorded throughout the hospital stay.(97) Additionally, the peak level of oxygen dependency was recorded to assign a category for each case by the WHO Ordinal Scale for Clinical Improvement (WHOS). The NEWS2 is showing severity based on symptoms, and derived from six physiological parameters: respiratory rate, oxygen saturation and need for supplemental oxygen, systolic blood pressure, pulse rate, level of consciousness or new confusion, and body temperature. The WHOS is assessing severity of COVID-19 by clinical picture and oxygen dependency.(98) The calculated CCI is a prognostic tool used to predict ten-year mortality risk by assigning weighted values to their age and various comorbidities.(99) It can get a value of a whole number from 0 to 37 and originally the 10-year survival came out to be equal to $0.983^{\exp(CCI*0.9)}$, where CCI is the index of the person.

As the main outcome we chose 30-day and 60-day all-cause mortality, while we analyzed the orientation of discharge from our unit as a secondary outcome. These could either mean discharge from the hospital, transfer to a higher dependency unit (non-invasive ventilation or intensive care unit) or death. The baseline day was identified as the day of the first RDV dose given for patients in the RDV group or the day of admission for patients in the SOC group. We only included patients who started RDV treatment in the first 48 hours after admission.

As a secondary investigation of the first study cohort, we conducted a survival analysis using first univariate and finally multivariate models. Our main goal was to identify those patient groups that benefit the most from the use of RDV.

The second and third study of the dissertation utilized a nationwide observational database that was collected prospectively, the national COVID-19 Registry. This included all Hungarian residents with an active insurance (TAJ) number from the National Public Health Centre and the National Health Insurance Fund Manager databases. The database consisted reported comorbidities (since 2011), date of birth, sex, COVID-19 vaccination dates and types, date of hospitalizations and finally date of death. The data was analyzed retrospectively.

The second study focused on COVID-19 infection, associated hospitalization and 28-day all-cause mortality during the SARS-CoV-2 delta VOC in elderly people and assessed data from 65 years old and older cases. The analysis was done by group of vaccination status (unvaccinated, primary vaccinated and booster vaccinated). Due to the specially protected, anonymized database only limited aggregated data was available concerning baseline characteristics. This included age, sex, and some common comorbidities (heart failure, COPD, type 2 diabetes and any malignancies). The main outcome was 28-day all-cause mortality following SARS-CoV-2 delta VOC-related hospitalization. Secondary outcomes included hospitalization and infection frequency, and we calculated VE against all the three outcomes. Because daily and individual data was not accessible, and vaccination status could change during the observation period, the exact daily incidence of the outcomes were not calculated. Instead, we calculated an average incidence for the whole observation by counting the number of infections, associated hospitalizations and deaths by vaccination status during the whole period and divided these numbers by the average size of the population by vaccination status. We could use the mean of the populations calculated at the beginning and the end of observation as they were changing uniformly throughout the period. As an example, if the unvaccinated population was uniformly changing from 100 to 80 people from the beginning until the end of the observation period, we would use 90 people as the population average.

The third study population included Hungarian residents aged 18 to 100 years, with a comorbidity of COPD and a 1:1 exact matched cohort with same baseline characteristics without COPD. This study also focused on the incidence of infection and COVID-19 related hospitalizations by vaccination status. The primary outcomes were again infection and COVID-19 hospitalization during the observation period. In this study we could calculate risks and hazard ratios (HR) for the whole period, and additionally daily, and cumulated 15-day or 30-

day risks for both outcomes. From the daily, and accumulated risks we calculated VE. For visualization Kaplan-Mayer curves were used and we plotted VE over time since last vaccination with 95% confidence intervals (CI).

3.2 Statistical analysis

Data are presented as absolute (n) and relative (%) frequencies in case of categorical variables, while quantitative variables are presented as mean ± standard deviation (SD). In the first study the SAS 9.4 software package and in the later two studies SPSS software ver. 27.0.1.0 were used for statistical analyses in addition to calculations carried out in Excel 2016. For complex data processing and analysis, the Python programming language and the Pandas package were utilized.(100) The queries for the COVID-19 database were also written in Python.

The following sections outline the specific statistical methods applied in each of the three studies, highlighting how they helped to address the research questions.

Propensity score matching (PSM) was utilized in the first study to reduce bias between treatment groups by adjusting for baseline characteristics, including sex, age, baseline NEWS2 and CCI. We wanted to enable a balanced comparison of the RDV treatment's impact on mortality. For the comparison of the not matched variables Pearson’s Chi-square test and Student’s t-test were used to compare qualitative and quantitative variables respectively. Survival analysis was conducted using Kaplan-Mayer estimates and finally for the multivariate analysis Cox regression models to evaluate the effect of RDV therapy on survival outcomes. For the univariate analysis we tested grouping based on sex, VOC, CCI categories (0-3, 4-6, 7+) WHOS and all comorbidities. In this work we only show those results which came out significant. These were also the ones included in the multivariate models.

In the second study, the aim was to investigate VE. Here, relative risk reduction was calculated to assess the risk of infection, hospitalization, and 28-day all-cause mortality. Unvaccinated individuals without prior infection were chosen as the reference group. Incidence rates were derived from the absolute frequencies grouped by the vaccination status at the time of the outcome and mean population sizes as discussed above. This compensated for the dynamic nature of the populations at risk. The uniform change was tested by frequency test of the primary difference of vaccinated population at two time points compared to the time point exactly between them. The mid-p method and Chi-squared tests were used to compare populations based on the vaccination status.(101)

Finally, in the third study, VE against infection and hospitalization in COPD patients was determined by calculating incidence rates first for the whole period. In this calculation we distinguished between primary, and booster vaccinated populations just like in our previous study. After sorting only by the time (number of days) since the last shot given (not differentiating between primary or booster vaccination), we calculated daily risks for the outcomes during the observation period. Using this data and the daily risks of the unvaccinated population during the observation period we could retrieve VE for different time intervals. The weekly VE values were then presented in a graph with exact confidence intervals. The confidence intervals were added to represent the degree of uncertainty and not to estimate the exact populational value as this study used data from the whole Hungarian population. Additionally, as a post-hoc analysis we calculated hazard ratios for both outcomes using a multivariate model including COPD and type of vaccine (RNA based vs other) as grouping variables to serve as a reference for later studies which utilize HR in the calculation of VE.

3.3 Ethical approval

All the studies were approved by the appropriate ethical committees and complied with the standards set forth in those protocols. The first study was approved by the Regional, Institutional Scientific and Research Ethics Committee of Semmelweis University with the reference number of SE RKEB 271/2021. The two other studies were approved by the Central Ethical Committee of Hungary (OGYÉI/10296-1/2022 and IV/1722-1/2022/EKU) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

4. Results

The results of individual studies, while connected by the investigated disease and time period, stand as distinct investigations rather than a linear progression. Each study unfolds as a separate exploration, meticulously examining different facets of the intricate relationship between COVID-19 and its impact on pulmonary health. It is essential to approach these findings with the understanding that they are unique and independently derived, each contributing a different perspective to the broader discourse. The results of each study are presented individually.

4.1 Remdesivir treatment effect on mortality in hospitalized patients

In the observation period, 974 cases were admitted to COVID-19 wards at the Department of Pulmonology of Semmelweis University. 19 patients were discharged within 48 hours and in the remaining cases, 417 were treated with remdesivir. Using propensity score matching (with the covariates of sex, age, baseline NEWS2 and CCI two cohorts were created (group RDV and group SOC), each containing 370 cases. 47 patients could not be matched. The baseline characteristics with corresponding p values are presented in Table 3. Due to the nature of propensity score matching, the table shows p values even for the matching variables.

Table 3: Baseline patient characteristics of the remdesivir study

	Group RDV (n=370)	**Group SOC** (n=370)	**P**
Sex			
Female	151 (40.8%)	151 (40.8%)	1.000
Male	219 (59.2%)	219 (59.2%)	
VOC			
original	134 (36.2%)	237 (64.1%)	<0.001
alpha variant	236 (63.8%)	133 (35.9%)	
Age			
Mean (SD)	62.2 (14.63)	63.19 (15.92)	0.375
WHOS			
3 (Hospitalized)	0 (0.0%)	57 (15.4%)	<0.001
4 (Supplementary O2)	356 (96.2%)	306 (82.7%)	
5 (High-Flow O2)	14 (3.8%)	7 (1.9%)	

Continuation of Table 3

	Group RDV (n=370)	Group SOC (n=370)	P
Charlson index			
1-3	209 (56.5%)	204 (55.1%)	
4-6	111 (30.0%)	114 (30.8%)	0.933
7-	50 (13.5%)	52 (14.1%)	
Comorbidities			
Malignancy	31 (8.4%)	44 (11.9%)	0.113
Hypertension	220 (59.5%)	217 (58.6%)	0.823
Diabetes	115 (31.1%)	81 (21.9%)	0.005
Heart failure	44 (11.9%)	55 (14.9%)	0.235
Asthma	34 (9.2%)	22 (5.9%)	0.095
COPD	54 (14.6%)	67 (18.1%)	0.196
Anemia	20 (5.4%)	44 (11.9%)	0.002
Parenchymal involvement on the initial CT (%)			
<15	89 (24.1%)	189 (51.1%)	
15-50	183 (49.5%)	107 (28.9%)	<0.001
50<	84 (22.7%)	47 (12.7%)	
missing	14 (3.8%)	27 (7.3%)	
Baseline parameters mean (±SD)			
CRP (mg/L)	126.08 (±81.27)	91.04 (±88.07)	<0.001
PCT (uG/L)	0.41 (±1.63)	0.49 (±2.09)	0.601
Ferritin (ug/L)	1141 (±1114)	1027 (±1686)	0.290
IL-6 (pg/mL)	76.58 (±129.05)	77.65 (±220.29)	0.938
ProBNP (pg/mL)	1181 (±3509)	1938 (±4732)	0.017
eGFR (ml/min/1.73m^2)	72.83 (±19.69)	72.53 (±23.63)	0.853
Albumin (g/L)	32.56 (±4.21)	31.43 (±5.18)	0.001
TP (g/L)	63.56 (±6.45)	61.97 (±7.6)	0.003

COPD: chronic obstructive pulmonary disease, CRP: C-reactive protein, PCT: procalcitonin, IL-6: interleukin-6, ProBNP: pro b-type natriuretic peptide, eGFR: estimated glomerular filtration rate, TP: total protein

Significant differences were noted between the two groups in the suspected VOC, as more patients were receiving RDV treatment during the wave caused by the alpha VOC. The baseline WHOS difference suggests that the RDV group consisted of patients with more severe illness. This is a direct cause of the treatment protocol in our unit, as RDV was only available to those with need of supplementary oxygen therapy. For age, sex and CCI we achieved balance between the two groups, as they were identical or non-statistically significantly different. When

investigating single comorbid conditions, the RDV group incorporated more patients with type 2 diabetes, however in the SOC group more anemic patients were noted. The differences of lung involvement seen on baseline CT picture and the higher baseline CRP levels in the group RDV further strengthened the hypothesis that patients in the RDV group were suffering from more severe disease. However, in group SOC, the average ProBNP levels were significantly higher, suggesting a more severe average heart condition in this group

Table 4: Primary and secondary outcomes of the RDV study

	Group RDV (n=370)	**Group SOC** (n=370)	**P**
Primary outcomes			
30-day all-cause mortality	49 (13.2%)	74 (20.0%)	0.014
60-day all-cause mortality	58 (15.7%)	84 (22.7%)	0.015
Secondary outcome			
Orientation of discharge			
Death	36 (9.7%)	60 (16.2%)	
Higher intensity care unit	38 (10.3%)	33 (8.9%)	0.031
Discharge from the hospital	296 (80.0%)	277 (74.9%)	

The RDV group exhibited a significantly lower mortality rate compared to those receiving only SOC. The secondary outcome also shows that proportionally more cases were escalated to higher intensity care units from the RDV group. This observation is particularly important considering the baseline characteristics presented a more severe disease profile in this group, marked by significantly elevated CRP levels, larger pulmonary involvement on the CT scans and a higher proportion of patients requiring oxygen supplementation (WHOS 4 or 5).

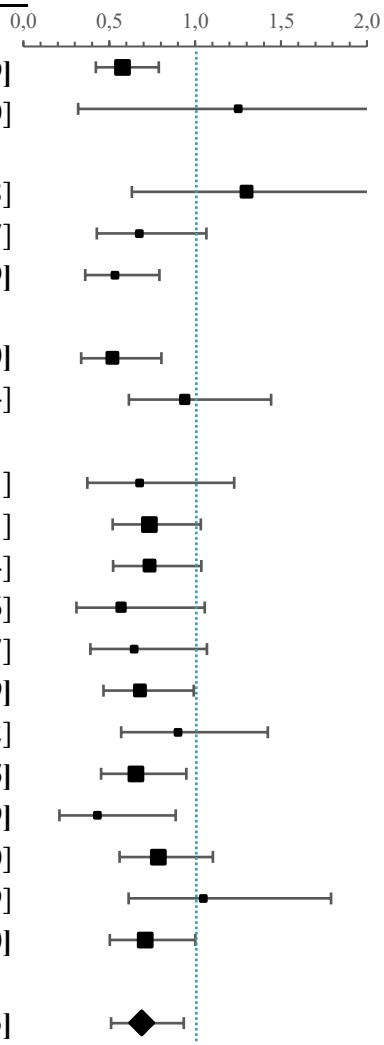
4.1.1 Secondary analysis: assessing subgroups

We planned our investigation to extend beyond the overarching question of general efficacy of RDV use. A second objective of this study was to discern specific subgroups within the patient population that might have pronounced benefits from this therapy. To achieve this, we conducted first an analysis employing a univariate method, assessing relative risk associated with RDV usage against in-hospital mortality. We stratified patients based on grouping variables: age group (<55, 55-64, 65-74, 75- years), sex (male or female), WHOS (4 or 5), CII (0-3, 4-6 or 7 and above), lung involvement in CT (above or under 30%) and by absence or

presence of investigated comorbidities. In Figure 4 we present only relevant subgroups, where statistically significant differences were detected. The lack of statistically significant benefit in the age stratified groups raises concern about the balancing of the groups, however this could also just be a sign of our test being underpowered for 4 groups.

Figure 4: Relative risks for in-hospital mortality by the subgroups

Subgroups by		Mortality (n/n) RDV		Mortality (n/n) SOC		Relative Risk
WHOS						
4		53 / 356		79 / 306		**0.58 [0.42-0.79]**
5		5 / 14		2 / 7		1.25 [0.32-4.90]
CCI						
0-3		16 / 209		12 / 204		1.30 [0.63-2.68]
4-6		23 / 111		35 / 114		0.67 [0.43-1.07]
7≤		19 / 50		37 / 52		**0.53 [0.36-0.79]**
Sex						
Male		26 / 219		50 / 219		**0.52 [0.34-0.80]**
Female		32 / 151		34 / 151		0.94 [0.61-1.44]
Comorbidities						
Malignancy	+	10 / 31		21 / 44		0.68 [0.37-1.23]
	-	48 / 339		63 / 326		0.73 [0.52-1.03]
Hypertension	+	44 / 220		59 / 217		0.74 [0.52-1.04]
	-	14 / 150		25 / 153		0.57 [0.31-1.06]
Diabetes	+	22 / 115		24 / 81		0.65 [0.39-1.07]
	-	36 / 255		60 / 289		**0.68 [0.47-0.99]**
Heart Failure	+	18 / 44		25 / 55		0.90 [0.57-1.42]
	-	40 / 326		59 / 315		**0.66 [0.45-0.95]**
COPD	+	8 / 54		23 / 67		**0.43 [0.21-0.89]**
	-	50 / 316		61 / 303		0.79 [0.56-1.10]
Anemia	+	10 / 20		21 / 44		1.05 [0.61-1.79]
	-	48 / 350		63 / 326		**0.71 [0.50-1.00]**
All cases		58 / 370		84 / 370		**0.69 [0.51-0.93]**



WHOS: WHO's ordinal scale for improvement, +: comorbid condition present, −:comorbid condition not present, COPD: chronic obstructive pulmonary disease. Figure adapted from Polivka, Lorinc, et al. "Long-term survival benefit of male and multimorbid COVID-19 patients with 5-day remdesivir treatment." Journal of Global Health 12 (2022).

The relative risk (RR) of in-hospital mortality showed significant benefit for the use of RDV in the subgroup requiring oxygen supplementation (WHOS 4), but not high-flow oxygen (WHOS 5). This benefit was seen for multimorbid (CCI ≥7), male, non-diabetic and COPD patients. The benefit observed in patients without the comorbidity of heart failure or anemia was likely because these subgroups included almost the entire cohort. The overall RR of in-hospital mortality was 0.69, which means the RDV group had around a third lower risk of in-hospital mortality compared to the SOC group.

Finally, using variables with significant differences between the RDV and SOC group, and those variables which had substantial distinctions in relative risks during the univariate analysis we created a multivariate logistic regression model. The final model included RDV therapy, sex, VOC and presence of comorbid conditions as binomial variables, while age and CCI as continuous variables. We could not include lung involvement on the CT scan due to the missing data. This model was used to calculate hazard ratios for mortality in the whole population and in previously identified relevant subgroups. The HR of RDV is presented in Figure 5 by subgroups and in the whole study population.

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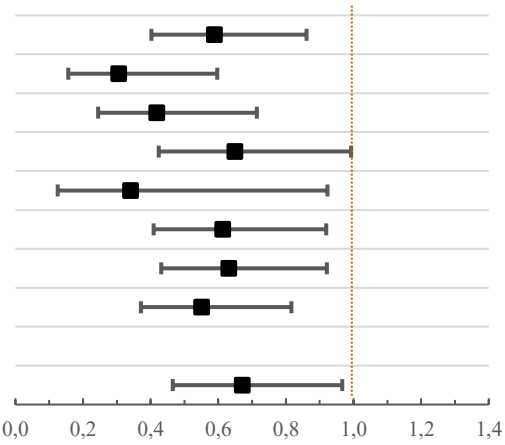
Figure 5: Hazard ratios of different characteristics for all-cause mortality in the hospitalized COVID-19 patients

Subgroups	HR	p
WHOS 4	0.59 [0.40-0.86]	0.006
Charlson index 7+	0.31 [0.16-0.60]	0.001
Male	0.42 [0.24-0.71]	0.001
No Heart Failure	0.65 [0.42-0.99]	0.046
COPD	0.34 [0.13-0.92]	0.034
No Anemia	0.61 [0.41-0.92]	0.018
No Dyslipidaemia	0.63 [0.43-0.92]	0.017
No Asthma	0.55 [0.37-0.82]	0.003
All cases	0.67 [0.47-0.97]	0.032



WHOS: WHO's ordinal scale for improvement, COPD: chronic obstructive pulmonary disease. Figure adapted from Polivka, Lorinc, et al. "Long-term survival benefit of male and multimorbid COVID-19 patients with 5-day remdesivir treatment." Journal of Global Health 12 (2022).

This analysis strengthened the results observed in the univariate analysis due to showing significant benefit in previously identified subgroups. Based on the multivariate analysis we found RDV therapy beneficial against in-hospital mortality. A HR of 0.67 could be interpreted as a 33% reduction in the hazard of in-hospital death among patients receiving RDV plus SOC compared to those who only received SOC, after adjusting for potential confounders.

4.2: Results of the nationwide retrospective study investigating vaccination efficacy in the elderly population during the 4th COVID wave (Delta VOC)

769 477 male and 1 214 699 female individuals were enrolled at the start of the observation (23 August 2021). During our observation period in this population there were 33 314 deaths recorded. Due to the assumed protective effect, patients with previous infections were excluded from the study population. The study population then was divided into three groups: unvaccinated, primary vaccinated and booster vaccinated. Who did not receive full regime (2 doses if required) were not included neither in the unvaccinated nor in the primary vaccinated group. At start 322 836 unvaccinated, 1 571 803 primary vaccinated and 36 567 booster vaccinated individuals were logged. Until the end of the observation (5 December 2021) 41 093 infections were registered, 13,006 in unvaccinated and 28,087 in vaccinated people. In association with these infections, hospitalization was required in 5087 unvaccinated and 6056 vaccinated cases. Hospitalization associated 28-day all-cause mortality were 0.420 in the unvaccinated and 0.307 in the vaccinated population. At the end of the observation period 281 422 unvaccinated, 684 164 primary vaccinated and 945 967 booster vaccinated individuals were logged. VE against infection, hospitalization and 28-day all-cause mortality after hospitalization is presented in Table 5. The aggregated patient characteristics of infected, hospitalized and died patients from the reference population (unvaccinated with no prior infection) and primary and booster vaccinated groups are shown in Table 6.

Table 5: Vaccine effectiveness against infection, hospitalization and 28-day all-cause mortality of primary and booster vaccinations compared to the unvaccinated without prior infections

	VE against Infection	VE against COVID-19 hospitalization	VE against 28-day all-cause mortality
Primary vaccinated	**48.88 [47.75 - 49.97]**	**71.55 [70.41 - 72.65]**	**79.87 [78.48 - 81.17]**
Booster vaccinated	**82.95 [82.35 - 83.54]**	**92.71 [92.12 - 93.27]**	**94.24 [93.42 - 94.98]**

Table adapted from Müller, Veronika, Polivka, Lorinc, et al. "Booster vaccination decreases 28-day all-cause mortality of the elderly hospitalized due to SARS-CoV-2 delta variant." Vaccines 10.7 (2022): 986.

Table 6: Baseline characteristics of infected, hospitalized and deceased patients by vaccination status

	Infected	Hospitalized	Died within 28 days after hospitalization
Unvaccinated[1]	12 843	5 064	2 133
Age (years ± SD)	74.8 (±7.8)	76.7 (±8.0)	78.4 (±8.3)
female-male ratio	65.6/34.4%	63.5/36.5%	60.8/39.2%
Primary vaccinated	22 757	4 993	1 488
Age (years ± SD)	74.2 (±7.1) *	76.7 (±7.4)	78.6 (±7.7)
female-male ratio	60.6/39.4% *	52.3/47.7% *	47.6/52.4% *
Booster vaccinated	4 296	724	241
Age (years ± SD)	76.0 (±7.4) *#	78.6 (±7.7) *#	80.5 (±8.1) *#
female-male ratio	56.0/44.0% *#	48.1/51.9% *#	44.8/55.2% *

[1]Those without prior infection (reference) * $p < 0.05$ vs. unvaccinated; # $p < 0.05$ vs. primary vaccinated.

Primary and booster vaccination were both significantly effective against all investigated outcomes, and booster vaccination was significantly superior against all outcomes. The most benefit was provided against infection based on the results, but it is important to note that infection data was the least rigorous, as testing was not mandatory for everyone during this period. However, the significant decrease in COVID-19 hospitalization and associated death due to booster vaccination is one of the key points of this work. The detailed analysis of the infected population revealed that the vaccinated population was significantly younger than the unvaccinated group, but hospitalized patients were older in the booster vaccinated and significantly not different in the primary vaccinated group. Interestingly the sex ratio changed more rapidly in the vaccinated groups, showing how men were in greater danger amongst the vaccinated. Amongst the infected, vaccinated populations had higher rates of all four investigated comorbidities (heart failure, COPD, Type 2 diabetes and any malignancies). This difference was even more pronounced between the hospitalized and deceased patients, but this is not presented in the table.

4.3 Results of the nationwide retrospective study focusing on vaccine effectiveness amongst COPD patients

In this study we included cases from the COVID registry aged 18 to 100 years, with the known comorbidity of COPD. According to definition, 189 998 patients with COPD fit the criteria, out of which 186 981 were matched with non-COPD control cases. These two groups together, counting 373 962 cases, constituted our study population. In both groups the female/male ratio was 52.2/47.8 with an average (±SD) age of 66.67 (±12.66) and 66.73 (±12.67) years in the COPD and non-COPD group respectively. The age difference was not statistically significant. The two groups were matched for the presence of known comorbidities too. The most common comorbidities were Type 2 diabetes (23.5%), any type of malignancy (15.1%), peripheral vascular disease (11.8%) and heart failure (9.9%) amongst the study subjects. The history of angina pectoris was also frequent with 14.7% of the population having medical records of such events. The groups were matched on immunization status too. At the start of the observation period 7.3% had already been infected. 20.3% of the study population was unvaccinated, 64.0% has already received primary and 8.4% boost vaccination at this time. For the calculation of VE, we excluded those with prior infection. Primary and booster VE for the two groups is shown in Table 7, with the average time elapsed until infection since the last vaccination dose.

Table 7: Mean VE against infection and COVID hospitalization during the delta VOC by vaccination status and group

	PRIMARY VACCINATED		BOOST VACCINATED	
	Matched	COPD	Matched	COPD
VE against Infection	46.8% [43.5% - 49.9%]	45.6% [42.3% - 48.7%]	86.1% [84.7% - 87.5%]	83.6% [82.0% - 85.1%]
VE against Hospitalization	72.1% [67.5% - 76.2%]	58.0% [52.6% - 63.0%]	92.6% [90.5% - 94.5%]	88.8% [86.3% - 91.1%]
Average time since last dose received (days)	240.67 ±57.82	239.06 ±59.79	69.3 ±45.16	69.89 ±45.74

VE: Vaccine Effectiveness, COPD: chronic obstructive pulmonary disease. Table adapted from Polivka, Lörinc, et al. "Waning of SARS-CoV-2 Vaccine Effectiveness in COPD Patients: Lessons from the Delta Variant." Vaccines 11.12

The VE projected over the observational period was only different significantly between the two groups only concerning hospitalization among primary vaccinated individuals.

To explore the change of VE after vaccinations, we first calculated the daily average risks for both outcomes in the unvaccinated cases, and then independently of prior vaccinations, we assessed the risks by day since the last vaccine dose for others. We assumed homogenous risk distribution for continuous periods in the unvaccinated cases, meaning that the risk of infection for a week was calculated as 7 times the daily average risk. This allowed us to calculate VE using the daily average risks for the outcomes for unvaccinated and the sum of daily risks for various time intervals (based on days since last vaccination dose) for the vaccinated cases. We created graphs based on VE calculated by 3-, 5-, 7-, 15- and 30-day intervals, but to compromise between resolution and statistical certainty we only utilized the results categorizing by 5-, 7- or 15-day. The 7-day-interval divided results, or in other words, the weekly change in VE is shown in Figure 6. In Figure 6/A VE against infection is illustrated, while Figure 6/B shows VE against hospitalization.

Initially, VE against infection is high, exceeding 80% within the first month post-vaccination in both the control group and the COPD cohort. VE against hospitalization starts at an even higher level compared to infection, exceeding 90% in both groups shortly after vaccination. This indicates a good protective effect after vaccination. Over time, a gradual decline in VE against infection is observed in both groups, with the control group maintaining slightly higher effectiveness compared to the COPD group. Similarly, a decline in VE against hospitalization is observed over time, though the rate of waning is slower. This suggests that vaccines provided longer-lasting protection against severe outcomes compared to mild or asymptomatic infections. By the end of the 25th week (approx. 6 months) after the last dose, the VE against infection drops significantly below 50% in both groups. Notably at the end of the 30th week (210 days or approx. 7 months) VE approaches 0%, meaning no significant benefit of vaccination against infection in either group. VE against hospitalization seemingly drops more rapidly than in the COPD group, reaching approximately 50% by 180–210 days post-vaccination. In contrast, the control group retains higher VE for a longer period. When we investigated this time period using a higher resolution model (5-day intervals) we found that liner trendlines drawn for both groups were statistically significantly different. The VE against hospitalization decreases by 3.5 percentage points in the control, and by 4.5 percentage points every 5 days in the COPD group. However, the clinical significance of this finding is questionable, as by 30 weeks VE approaches 0% in both groups and only remains significant for 2 weeks in the control group, after there is no more significant benefit in the COPD group.

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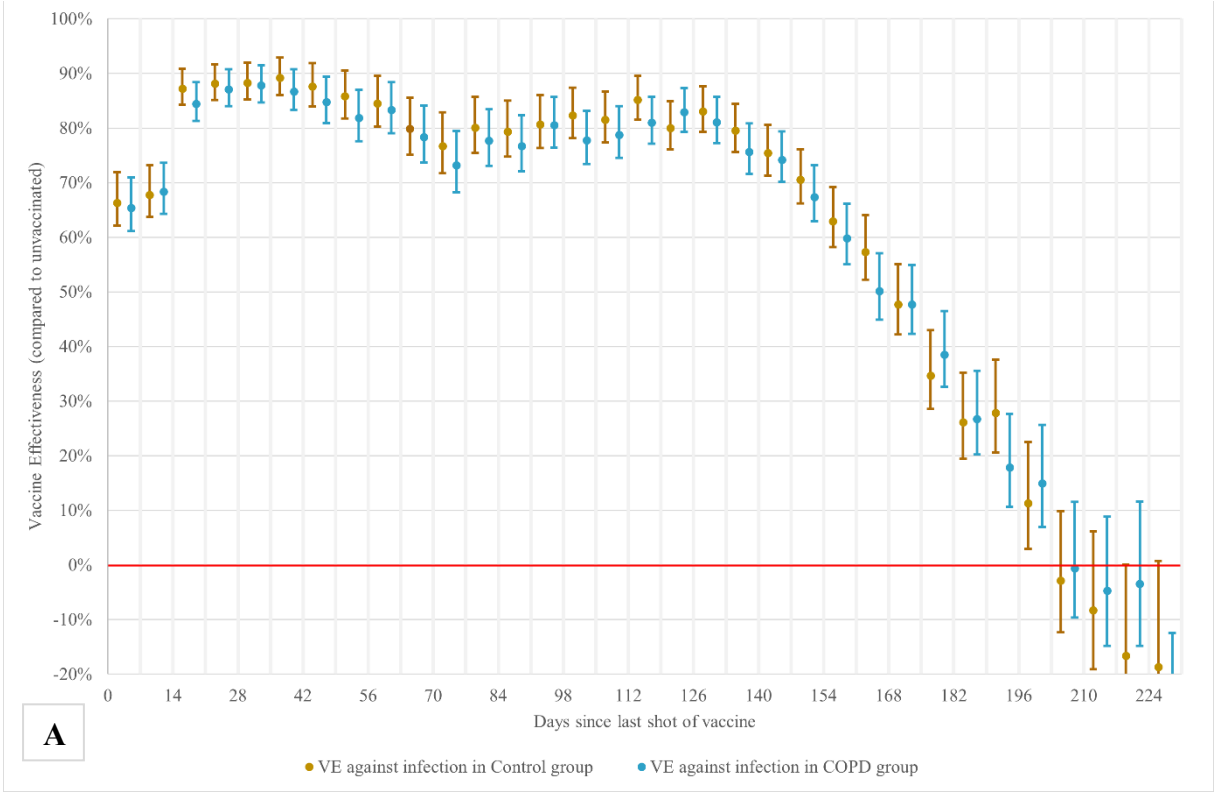
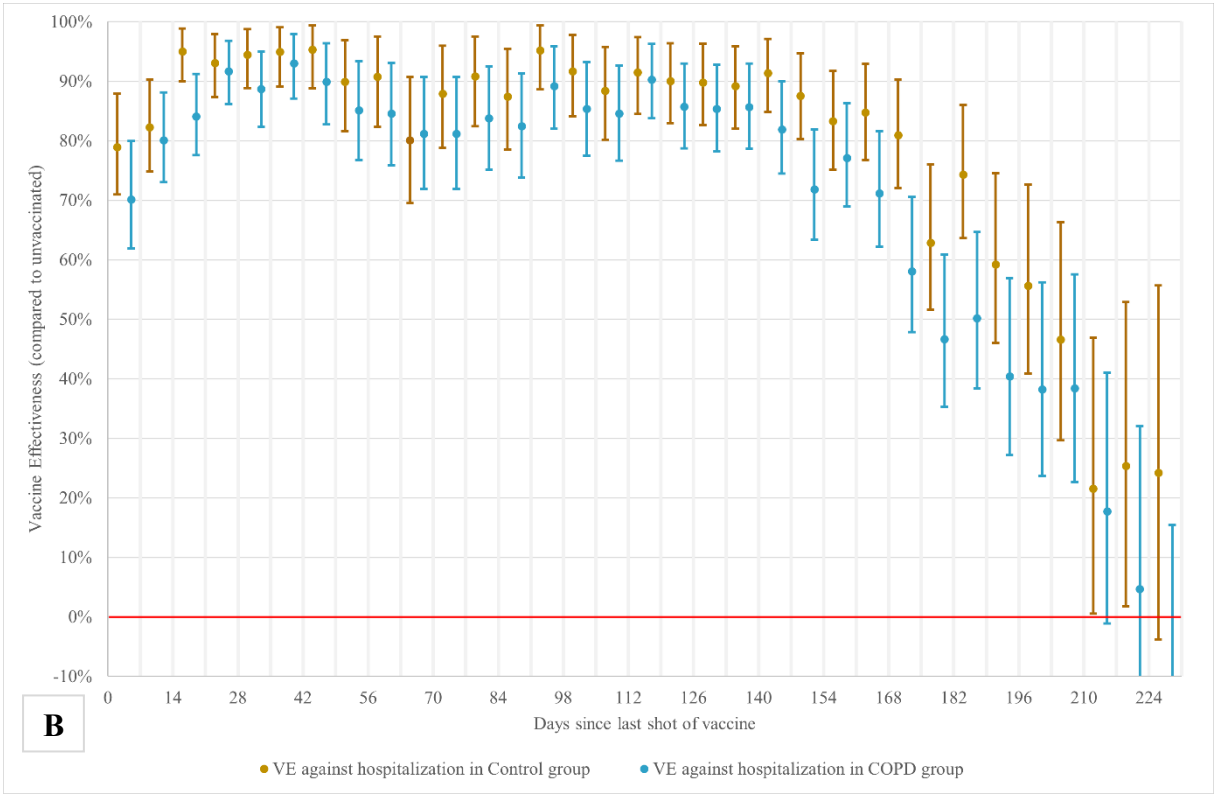
Figure 6: VE against infection (A) or hospitalization (B) by 7-day time intervals since last given vaccination dose





VE: Vaccine Effectiveness, presented with 95% exact confidence intervals

To further investigate the difference of the protective effect of vaccinations between the two groups, we employed a time-stratified multivariate Cox regression model investigating only the vaccinated population. In this model we included not only the group variable but also a variable for the type of vaccine dose (RNA-based vs. other) based on prior results of the HUN-VE workgroup.(35) The computed HRs are presented in Table 8. This grouping by the type of vaccine was not employed during the calculation of primary and booster VE as booster vaccination types were not strictly coherent with primary vaccine types. The vaccine types were also not used for the assessment of VE waning because daily data analysis required a robust population size and dividing by vaccine types underpowered our calculations.

Table 8: HRs calculated for infection and COVID hospitalization calculated by a time stratified Cox regression model in the vaccinated cases

	Infection		Hospitalization	
	HR	p	HR	p
mRNA vaccine	0.660 [0.619 - 0.703]	<0.001	0.809 [0.68 - 0.962]	0.017
Group COPD	1.073 [1.008 - 1.142]	0.028	1.867 [1.592 - 2.19]	<0.001
interaction	1.034 [0.953 - 1.123]	0.420	0.889 [0.724 - 1.093]	0.266

HR: Hazard Ratio, COPD: chronic obstructive pulmonary disease. Table recreated from Polivka, Lörinc, et al. "Waning of SARS-CoV-2 Vaccine Effectiveness in COPD Patients: Lessons from the Delta Variant." Vaccines 11.12

Based on the results, mRNA-based vaccines were shown to significantly reduce the risks of both infection and hospitalization compared to other vaccine types, and the protective effect came out to be stronger against infection. Even in this analysis, where we only examined vaccinated individuals, COPD independently increased the risk of both infection and hospitalization, with a particularly large impact on the risk of hospitalization. This finding and the result presented above, where we have found lower VE against both outcomes in the COPD group are partially supporting each other. As the hazard associated with COPD was not examined specifically in unvaccinated individuals, a direct relationship cannot be conclusively established. Finally, the lack of a statistically significant interaction between the variables mRNA vaccine and group COPD suggests that the type of vaccines deployed was substantially not modified by COPD status.

5. Discussion

Our initial study focusing on assessing RDV's effectiveness in patients needing hospital care mainly due to pneumonia in the Delta and pre-delta VOC waves have valuable results which still hold up now. As real-world data are very important to underline clinical trial data on effectiveness, our large dataset on patients with lung involvement are still valuable in cases, when patients are not vaccinated, or do not have an immune response to the vaccine. One of the main strengths of our study is the matching algorithm we used, and that we only included patients surviving the first 48 hours in both groups, while not excluded those who could not finish full course remdesivir treatment. Numerous other retrospective studies compared patients who received a given number of days long remdesivir treatment to those receiving only SOC, introducing an immortal time bias in these studies.(102-105)

5.1. Current state of RDV therapy, and the context of our results

As mentioned earlier remdesivir emerged as one of the first antiviral treatments used during the initial wave of COVID-19 in Europe. Early trials, including the ACTT-1 study assessing RDV effect in the pre-delta era, demonstrated its efficacy in reducing the time to recovery in hospitalized patients, which positioned RDV as a baseline therapy against COVID-19.(106) Over time, it has remained one of the few antivirals recommended by health authorities worldwide, particularly for severe cases requiring hospitalization. Our study adds to the extensive body of scientific literature that supports the use of RDV. By demonstrating a significant reduction in mortality rates among patients hospitalized mainly in the pre-Delta and Delta VOC waves due to pneumonia and treated with RDV compared to those receiving standard care alone, our findings align with previous research, and with most recent publications, such as the work of Mozaffari et al., which still shows statistically and more importantly clinically significant benefit for hospitalized patients.(107) Additionally, even though the control group showed faster initial improvement in our study, the remdesivir group had more patients showing clinical improvement after 14 days, and better all-cause mortality underscoring its long-term benefits. This is particularly noteworthy given the baseline characteristics of our patient cohorts. Patients treated with RDV had more severe disease, evidenced by higher CRP levels and a greater need for oxygen supplementation. Despite these conditions, RDV therapy proved beneficial, reinforcing its role in COVID-19 treatment

protocols and the necessity of its inclusion in treatment guidelines and highlights the ongoing need for research to optimize its use.

Other publications showed the efficacy of RDV in COVID-19 treatment too. For example, several investigations were conducted as randomized controlled trials (RCT). These demonstrated a reduction in time to recovery among hospitalized patients. Among the first Sherief Abd-Elsalam et al. showed this effect with an RCT conducted in an Egyptian hospital involving 200 patients (remdesivir and control group 1:1).(108) An other investigation in Canada, with one of the largest number of participants in the literature, conducted during the same time as the timeframe of our retrospective study, focused on need for oxygen therapy or mechanical ventilation.(109) Karim Ali et al. showed that RDV significantly reduces 30- and 60-day mortality and promotes faster recovery Similarly, George A Diaz et al. in a Washington based hospital,(110) Quratulain Shaikh et al. in a single center study conducted in Pakistan,(111) Jerzy Jaroszewicz et. al in a Polish nationwide study focusing on patients with active malignancies only,(112) reported a significant decrease in mortality rates among patients receiving RDV compared to standard of care alone in the same time period. Furthermore, the earliest Hozaifa Khalil Elsawah et al.(113) conducted a meta-analysis of multiple RCTs concluding that RDV was associated with improved clinical outcomes in COVID-19 patients, however they could not show statistically significant mortality benefit. This was ultimately updated by a much later published meta-analysis by Alain Amstutz et al., thus including way more results of RCTs, which concluded a clear benefit on mortality from the use of RDV.(114) Anand P. Chokkalingam et al. showed the same results in a retrospective analysis using more than 24 000 electric health records of US patients. These studies collectively support the effectiveness of RDV as a treatment option for COVID-19. Current guidelines about COVID-19 treatment confirm the use of RDV in all patients who have the need for antiviral therapy.

The effect of remdesivir by sex has not been extensively investigated in the literature to my knowledge, and none of the meta-analyses or scientific reviews specifically address this aspect. The difference we observed between male and female patients in our study may be attributable to an unknown confounder associated with male sex. One possible confounder could be smoking habits, as there are numerous studies suggesting that patients with higher SARS-CoV-2 viral loads and low-grade systemic inflammation tend to benefit more from RDV.(115) Smoking is known to be associated with increased viral load and an impaired immune response, which could explain why men, who statistically smoke more, may show greater benefit.(116-118) This observed trend in our study may also apply to older and multimorbid patients, as these

groups are known to exhibit delayed and weakened immune responses to viral infections, often leading to higher viral loads.(119) Additionally, comorbidities are frequently associated with immunocompromised states, which could further enhance the benefit of RDV.

Mozaffari et al., in a poster presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases, demonstrated the benefit of RDV in hospitalized cancer patients. This conflicts with our results, which showed no significant all-cause mortality benefit in the population with malignancies.(120) This discrepancy may be due to unmeasured confounders or differences in the length of the observational periods but also could be a caused by the fact that their study was conducted during the delta VOC, while ours was earlier in the pandemic.

In outpatient settings, Brown et al. conducted a subgroup analysis of the PINTREE clinical trial, which found no significant difference in remdesivir's benefit across subgroups such as age (≥60 years), obesity, and certain coexisting medical conditions, including those assessed in our study.(121) These findings do not contradict our results but emphasize that our conclusions should be limited to hospitalized patients with more severe disease. It is important to note that our study only included patients who were given remdesivir alongside supplementary oxygen, and thus the results are not generalizable to milder cases or outpatients.

Finally, I would like to highlight that the increased benefit of RDV for patients receiving low-flow oxygen, which was demonstrated in the ACTT-1 trial, remains consistent.(65) This is especially important, as there were real-world studies which were not supporting the findings of the trial.(106) This finding was forming a basis for standard of procedures we implemented in our hospital, and has not been contradicted by later studies, further supporting the rationale for RDV use in more severely ill, hospitalized patients.

5.2 Results concerning COVID-19 Vaccine Effectiveness in the elderly and relevant reports from the scientific literature

The second study investigated the importance of booster vaccinations, particularly among the vulnerable population of elderly people. In our cohort investigating the elderly, infection, hospitalization, and mortality risks were significantly lower in primary vaccinated (48.88%) and especially in booster vaccinated (82.95%) populations compared to unvaccinated populations. These findings align with our previous results regarding the alpha VOC, and with numerous real-world observational studies, such as the work of Gomes et al. from Germany, or

the investigation by Baum et al. conducted in Finland.(122,123) These results are quite unique, as other epidemiological studies usually work with mathematical simulations based on sample populations, or focus on regions, administrative cohorts, or specific populations because population-wise retrospective data is usually not available.(124-128) Lot of studies focused on one type of vaccinations, or categorized their study populations by vaccine type. The above cited Bavarian study reported for the vaccine type BNT162b2, produced by Pfizer, a VE of 68.3% against infection, 73.2% against hospitalization and 85.1% against mortality in an older population (80 years or older), which is better than in our results.(122) However, a much larger Argentinean study by Analía Rearte et al. focusing on 60 years or older individual reported worse VE against infection for the ChAdOx1 nCoV-19 produced by AstraZeneca and the Sinopharm BBIBP-CorV vaccines.(129) They reported respectively a VE of 68.5% and 43.6% against infection, and 80.1% 73.4% against mortality. The VE against mortality was almost identical to our results in the case of the AstraZeneca vaccine and worse in the Sinopharm vaccinated individuals. This lower VE against infection and mortality in the older population (51 years or older) was also reported in a study focusing on only the VE of Sputnik V published by Matveeva et al.(130) In our population, if we focus on the distribution of different vaccines between those who were only administered one type (Pfizer ~48%, Sinopharm ~23%, Sputnik V ~11%, Astra ~10%) and the fact that we investigated a population of 65 years or older, the reported average effectiveness in our population is conclusive with the results presented above.

Some studies reported VE in populations where more types of vaccines were used also. A retrospective, population-based study conducted in Columbia by Arregocés-Castillo et al. focusing on 60 years or older adults reported a VE of 61.6% against COVID hospitalization and 79.8% against death following hospitalization in a population where 5 different types of vaccines were used (including single-dose and two-dose, mRNA based, vector and whole inactivated virus vaccines, like in Hungary).(131) The latter result is almost identical with our results which concluded a 79.87% against mortality in the primary vaccinated elderly population. The hospitalization rates might differ due to the different admission criteria and availability in hospitals of the two countries. A highly cited paper by Andrews et al. focusing on booster vaccinations showed also similar results to ours concerning 50 years or older individuals, who received BNT162b2 (Pfizer) as a booster vaccination.(132) They measured an effective VE between 84.7% and 93% against infection, and between 98.7% and 97.6% against hospitalization independent of the primary vaccine. Our only bit worse VE results of 82.9% against infection and 92.7% against hospitalization could be an effect of their investigated

population being younger, however strongly support our main conclusion, that booster doses should be administered to the elderly for better protection against the disease. Another highlight of our results is that booster vaccinations were particularly effective in reducing 28-day all-cause mortality in hospitalized patients. This is in line with the results of multiple real-world studies, which most of are presented in the meta-analysis published by Rahmani et al.(133) The pooled VE against hospitalization for all vaccine types together in a population of 14 years and older was about 85% which is better than what we found in the elderly for primary vaccinations (79%).

5.3 Vaccine Effectiveness waning and the special case of COPD patients

With much of the population vaccinated at the year of 2024, we face questions about the future trajectory of COVID-19. Our last study focused on the waning of protection from vaccinations, providing insights into the need for revaccinations. While this study focused on the specific group of patients of COPD, it is useful in the considerations and guidelines of COVID-19 prevention and control as we reported the observed waning in the control group too. The scientific literature to date has much less coverage on the waning of VE in real world populations, especially with those using multiple types of vaccines. In this topic, one of the most cited paper is a retrospective study investigating 12 years or older individuals from one of the healthcare providers in the United States by Tartof et al. focusing on only the VE waning of Pfizer vaccine in the first 6 months after administration.(134) They reported a peak VE of 97% against infection, which waned to 50% after 6 months, and an average of 93% against hospitalization which significantly did not differ throughout the 6 months. These are better results than a peak of 89% waning to 27% against infection, and the peak of 95% waning to 65% against hospitalization, what we measured in our control group (non-COPD patients), which could be an effect of our population being exposed to other types of vaccines, which has been shown to have lover VE against all outcomes. An Italian study published by Fabiani et al. showed however contradicting results for mRNA based vaccines, which are more in line with our results.(135) They reported a much higher rate drop of VE after 6 months with a 82% waning to 33% against infection and a slight drop with 96% waning to 80% against hospitalization or death. They also concluded that those aged 60 years or older lose significant VE against infection after this time period. Finally, a US based study published by Ferdinands et al. with one of the largest investigated populations in this topic, concluded a VE waning from

89% to 66% against hospitalization in 5 months.(136) This result is painting a picture of an even faster declining protection and highlights the importance of setting of these studies. The only investigation on the Hungarian population was conducted by the HUN-VE workgroup, and as part, our results concerning this population is a unique and valuable resource.

We showed that COPD is associated with lower vaccine effectiveness (VE) against both SARS-CoV-2 infection and hospitalization. COPD patients have always been at higher risk for severe outcomes of COVID-19, as shown in a meta-analysis by Firoozeh et al. published in The Lancet.(137) Our finding of increased hazards in the Cox regression models further highlights their vulnerability. This does not translate to a lower VE automatically as VE shows the relative risk reduction compared to the unvaccinated COPD patients. However, the detected difference could be due to other COPD-associated characteristics not investigated in this study, such as smoking habits, which are known to affect immunization by vaccines. Compared to a robust retrospective study by Nordström et al., we observed a more extended period of protection against severe disease and estimated a similar timeframe for the decline in VE (around four months). Our study provides additional insight, confirming a statistically significant but clinically negligible difference in the decline of VE between the COPD and non-COPD populations, partially corroborating the results of Southworth et al.

Results concerning the COPD patient group were usually from single center studies, or populational studies, which reported comorbidity specific vaccine effectiveness.(138,139) None of these were powered for a detailed insight of VE and waning in this patient group. The only comparable studies, inlcude a Hong Kong based retrospective analysis focusing on the VE of Pfizer and SinoVac vaccines against hospitalization in COPD patients by Kwok et al.(140) and a smaller Chinese study investigating Asthma and COPD patients vaccinated by the same vaccines.(141) Both of these studies concluded that vaccination in this group has the same benefit as in non-COPD patients, which is in line with our results. The report of VE and especially waning in this group was first presented in our results in scientific literature.

5.4 International improvements in the therapeutical guidelines since the publications, and the current place of antivirals

Since our studies, antiviral treatment for COVID-19 became primarily reserved for vulnerable individuals, such as the elderly or immunocompromised, similarly to those hospitalized for severe flu infections, emphasizing its targeted use in specific patient populations.(142) When used, antivirals are strictly recommended early in the disease course.(142) Remdesivir, the

nirmatrelvir-ritonavir combination, and molnupiravir (not used in Hungary) are now the only recommended antivirals. RDV remains the top choice for hospitalized patients, emphasizing its continued importance, while other antivirals can be used is the first line for non-hospitalized patients.(143) The emphasis on anti-inflammatory therapies has diminished with the widespread use of vaccines, however in rare cases of severe disease the use of iv dexamethasone is still encouraged. It is important to note that drug-drug interactions need further considerations when applying antiviral therapies, which might limit the use of available oral antiviral treatment.

5.5 Vaccines in use and revaccination efforts, similarities to the Flu vaccine

In response to the COVID-19 pandemic, multiple vaccines have been authorized for use in the USA, and EU. Currently authorized vaccines (as of April 2024) are shown in Table 9. While bivalent vaccines (containing two different VOC antigens) were temporarily used, current authorization focuses on monovalent vaccines specifically designed to target the Omicron variant, showcasing the adaptability of vaccine development in addressing evolving strains. In a recommendation for the 2023/2024 respiratory season published by the Hungarian National Public Health Centre online the two main goals are to prevent severe complications and protect healthcare staff.(144)

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Table 9: COVID vaccines authorized by the CDC and EMA. April, 2024

Manufacturer	Brand name (formula)	Type	CDC	EMA
Moderna	SPIKEVAX (2023-2024)	mRNA	Approved	Approved
Pfizer-BioNTech	Comirnaty (2023-2024)	mRNA	Approved	Approved
Novavax	Nuvaxovid XBB.1.5 (2023)	subunit	Approved	Approved
Janssen-Cilag	Jcovden (2023)	mRNA	Not approved	Approved
HIPRA	Bimervax (2023)	recombinant	Not approved	Approved

Since May 5th, 2023 the WHO declared COVID-19 no longer a pandemic but a continuously present health issue. Vaccination remains crucial, especially against the highly infectious Omicron variant. The recommended target groups for COVID-19 vaccination mirror those for influenza, including individuals over the age of 60 years, the chronically ill, immunocompromised individuals, and long-term care residents. Vaccination decisions should be based on the individual's health status, with the available vaccine providing protection against the Omicron variant, recommended regardless of previous vaccinations. This recommendation is in line with the international guidelines, but only includes one authorized vaccine in Hungary, the Spikevax XBB 1.5 manufactured by Moderna.

Current guidelines recommend periodic revaccination based on factors such as age, underlying health conditions, and the specific vaccine received.(142, 145, 146) The new COPD document, Global Initiative for Chronic Obstructive Lung Disease included COVID-19 vaccination into the recommended preventive measures.(147) Ongoing research and real-world data, including our study, continue to inform decision makers about the efficacy of revaccination strategies for long-term immunity against COVID-19.

5.6 Future research directions

With the end of the pandemic, COVID-19 research has almost halted, however, longitudinal studies are still needed to assess long-term efficacy and safety of existing vaccines, including the further investigation of revaccination doses and the process to conserve immunity over time. The future research of VE of COVID-19 vaccinations will probably focus on special groups, such as the immunocompromised or those with malignancies. There is vaccine surveillance ongoing already in almost all western countries, so the follow-up of new vaccines should not require substantially more resources. As an example, the US Center for Disease Control and Prevention lists on its website some of the biggest ongoing COVID-19 monitoring studies.(148) Complementary efforts still must focus on the dynamics of disease to inform in time if a new, more dangerous variant is on the rise. In this case, targeted public health interventions and control strategies will be needed again, which will be able to build upon the most recent studies concerning the disease. Another large focus is on the long-term studies aimed at understanding post-acute and long-term health effects, including potential complications and sequelae.(149) In the Pulmonology Department of Semmelweis University, multiple ongoing and published studies are investigating Post-COVID syndrome. One result showed less Post-COVID associated symptoms in RDV treated patients, connecting partial results of this paper to the long lasting effects.(150) Other published result from the hospital showed, how sleep related Post-COVID symptoms might be related to the different variants of SARS-Cov-2, and finally another investigated interstitial lung disease in Post-COVID patients.(151,152)

6. Conclusion

This dissertation addresses key aspects of in hospital COVID-19 treatment and vaccine effectiveness, focusing on outcomes in specific patient groups.

1) In hospitalized COVID-19 patients needing supplemental oxygen 5-day RDV treatment reduced 30- and 60-day all-cause mortality compared to those, only receiving SOC.
2) Particular benefit of the RDV treatment was observed in male, non-diabetic or elderly patients and those with multiple comorbidities.
3) Booster vaccinations among the Hungarian elderly population during the delta variant confirmed that booster doses significantly reduce the risk of hospitalization and 28-day all-cause mortality.
4) VE in a cohort of COPD patients to a matched non-COPD cohort no significant difference in the rate of VE decline between the two groups was identified. However, the length of meaningful protection in the COPD and the non-COPD group lasted for around 120-130 days, and significant effectiveness against hospitalization was lost roughly after 210 days in both groups.

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7. Summary

This work summarizes investigations of the COVID-19 prevention and treatment dynamics through a clinical epidemiological lens, focusing on key aspects such as treatment of hospitalized patients, prevention and booster vaccinations effect on hospital admissions. The studies conducted within the framework were carried out in Hungary, with a particular emphasis on patients connected to the field of pulmonology. The results of three published datasets are summarized for a more global view representing data from Hungary and from the Department of Pulmonology at Semmelweis University.

The first paper presents a retrospective observational cohort study that evaluates the long-term outcomes of RDV treatment in hospitalized COVID-19 patients at the clinic.(153) By analyzing real-world data, the study assesses the effect of treatment on all-cause mortality, particularly among patients with more severe clinical conditions. This study provides insights into the effectiveness of RDV and its potential benefits for specific patient groups.

The second paper focuses on the impact of booster vaccinations with a specific emphasis on the vulnerable elderly population.(33) The study investigates the effectiveness of booster vaccinations in reducing the risk of hospital admission and mortality. These findings show the importance of vaccination strategies needed for high-risk individuals.

The third paper explores another group with increased susceptibility to respiratory infections: COPD patients. This study investigates vaccine effectiveness (VE) and the associated risk of infection and hospitalization.(154)

The clinical epidemiological approaches used in these studies may offer valuable insights into the beneficial use of clinical registries and databases. Furthermore, as these studies were conducted in Hungary, they provide context-specific findings that can contribute to the development of targeted strategies for managing COVID-19 in the local healthcare setting. Overall, this dissertation seeks to contribute to the growing body of knowledge on COVID-19 prevention and treatment by highlighting the importance of clinical epidemiology and providing evidence-based insights as its main conclusions.

Overall, our research was used as direct feedback from clinical practice, and the above discussed results highlight the importance of timely antiviral therapy and booster vaccinations to improve COVID-19 outcomes, particularly in high-risk groups.

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