Abstract

In January 2020, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) was discovered in Wuhan, China after pneumonia outbreak occurred. The World Health Organization (WHO) later defined as Corona Virus Disease 19 (COVID-19) and officially declared COVID-19 a pandemic in March 2020. Since then, over 470 million cases have been confirmed and over 6 million people worldwide have passed away due to COVID-19. As a response to the pandemic, Pfizer has developed a covid vaccine and is marketing their novel anti-SARS-Cov-2 main protease inhibitor (PI) in 2022. Paxlovid achieves its antiviral effect by inhibiting an essential protease in the viral replication process. The 3CL protease digests polyprotein to produce a set of proteins that are vital for the virus replication and transcription. By inhibition of the SARS-Cov-2 3CL protease, the virus is unable to proliferate, and the infection is halted. This research aims to describe the COVID-19 pandemic from multiple perspectives, to illustrate the journey covid patients follow from symptoms development to treatment and recovery, to identify questions healthcare professionals have surrounding novel antivirals, assess where and who supervises the prescription of Paxlovid, and what role Paxlovid can play in the future of this pandemic.

This research includes historical comparison to the HIV epidemic, an overview of the novel SARS-Cov-2 pathogen, a summary of the current treatment protocols for COVID-19 patients, the effects of the vaccines on the progression on the pandemic, the Paxlovid product profile, and the opinion of healthcare professionals in covid care. A new patient journey will be illustrated to show which parties are involved in the implementation and prescription of Paxlovid. In addition, the unmet need and the role of Paxlovid will be assessed based on the current pandemic climate and the view of healthcare professionals (HCPs) in the field.

At present, treatment initiation happens only when patients are hospitalized, which rarely happens within five days since symptoms onset. In order to introduce Paxlovid in the patient journey, the initiation of treatment has to move to primary care, overseen by the general physician. However, the general physicians do not possess the expertise that pulmonologists and infectious disease specialists do. These experts should transition their role from overseeing the treatment to advising the general physicians in assessment of eligibility for the therapy and its prescription, based on guidelines provided by SWAB and other medical professional organizations. The role Paxlovid could play for covid patients largely depends on the danger the pathogen poses at present times, which is relatively low. HCPs indicated that there is a small patient population at the moment and thus unmet need that antivirals could fulfill is small as well. However, the unmet need those individuals with a high risk of severe disease progression experience might differ from the estimation that HCPs.

Healthcare should be accessible and inclusive, therefore highlighting the importance of Paxlovid to the high-risk patient community. To ensure adequate administration of this antiviral therapy within the first five days since symptom onset, the general physician takes on a bigger role than just the prescribing party and will be the central point of oversight in the patient journey. The medical experts, pulmonologists and IDSs, will take on an informative and supportive role for the general physician. Furthermore, policy makers, healthcare organizations and regulatory bodies need to provide HCPs with clear and concise information and guidelines on the antivirals. When these measures are in place, Paxlovid can help protect high-risk patients from severe covid symptoms and hospitalization.

Layman's summary

In January 2020, a novel coronavirus was discovered in Wuhan, China after pneumonia outbreak occurred. The World Health Organization (WHO) later defined as Corona Virus Disease 19 (COVID-19) and officially declared COVID-19 a pandemic in March 2020. Since then, over 470 million cases have been confirmed and over 6 million people worldwide have passed away due to COVID-19. In The Netherlands, over 7.5 million cases have been confirmed between the 3rd of January 2020 and mid-March 2022, with over 21 000 registered covid deaths. Over the two-year pandemic period society has endured a cycle of restrictions and mandates in an effort to first stop the spread of the virus and later on to mitigate the number of new infections to relieve the healthcare systems. Lockdowns, mandates, vaccines have all tried to resolve the pandemic and the next line of defense is ready to be introduced. New anti-covid drugs are scheduled to enter the market in 2022, one of which is Pfizer's Paxlovid.

This research focuses on the introduction of Paxlovid on the Dutch market, in which the potential role of Paxlovid and the best place in the healthcare system will be investigated. First, possible lessons that can be learned from similar experiences have been explored, such as the HIV epidemic and the effects of vaccines and current treatments for COVID-19. To gain a better understanding of the procedures involved in covid treatment, market research under medical doctors has been performed. Their views on what these new drugs such as Paxlovid could contribute to pandemic are the main focus, as well as where these drugs should be introduced and who they should be described by.

At the present time there are no mandates or restrictions in The Netherlands, since the last ones were lifted on the 23rd of March 2022. The need for new covid drug might therefore feel small or even not necessary at all. The majority of society is protected against infection or severe covid symptoms through the vaccines, but that does not include everyone. A small yet significant part of the population is not susceptible for the vaccines and do not produce any antibodies to protect them. These high-risk patients could still benefit greatly from new covid drugs that specifically target the virus instead of targeting the symptoms.

To provide Paxlovid as a therapy and offer it a chance to reach it 89% efficacy rate seen in the clinical studies, the start of the therapy should be started within five days since the first symptoms started. In the current covid treatment plan, medication is only given to hospitalized patients while the most patients will not be admitted to hospital in those first five days. Therefore, Paxlovid should be introduced in primary care and prescribed by the general physician. They will be the central point of contact for patients to reach out to after a positive test to receive the therapy. Since Paxlovid and COVID-19 as quite complicated on their own, a general physician might not have all the knowledge to decide whether a certain patient can start with Paxlovid. In those cases, experts such as pulmonologists and infectious disease specialists will act as an advisory party and support the general physician. in this revised set-up, Paxlovid can fulfill a key role in the protection of high-risk patients and offer them similar protection against severe COVID-19 as the rest of society.

Introduction

In January 2020, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) was discovered in Wuhan, China (1, 2). What was thought to be a pneumonia outbreak in Wuhan in December 2019, the World Health Organization (WHO) later defined as Corona Virus Disease 19 (COVID-19) after the novel pathogen was identified to be a SARS-Cov-2 (1, 3). Since then up to mid-March 2022, over 470 million cases have been confirmed and over 6 million people worldwide have passed away due to COVID-19 (4). In The Netherlands, over 7.5 million cases have been confirmed between the 3rd of January 2020 and mid-March 2022, with over 21 000 registered covid deaths (4). COVID-19 has developed to be the largest healthcare issue of the 21st century, as well as exposing many different underlying problems in mental health, economical and societal aspects.

Timeline COVID-19 origin, spread to The Netherlands and further developments

The first COVID-19 case that has been declared in Wuhan, China dates back to the 8th of December 2019, yet the exact origin of SARS-Cov-2 remains unclear (1, 6). In fact, serological retesting of randomized blood samples from the pre-pandemic period between October 2019 and December 2020 in Italy has confirmed the presence of SARS-Cov-2 antibodies (6). This suggests that the coronavirus was already circulating in Lombardy, Italy since October 2019 (6). Wuhan, China is seen origin of the pandemic in terms of the spread to the rest of the world, since many first declared cases in other countries are correlated to individuals traveling from Wuhan and developing covid-like symptoms after arriving in their destination country. Even though the city of Wuhan and its province of Hubei went in lockdown to prevent the spread of the virus, it managed to spread globally and the pandemic is still ongoing over two years later (**Figure 1**) (1, 4). In February 2020, The Netherlands facilitated the return of its citizens from China, like many other countries did, and trying to contain any further spread of the virus by imposing travel restrictions (7). Despite all containment efforts, the virus did manage to reach the rest of the world and mid-February 2020 several cluster outbreaks occurred in Italy, making it the corona epicenter of Europe (7). On the 27th of February 2020 the first case in The Netherlands was discovered, a man who recently returned from the Lombardy region in Italy was hospitalized with covid-like symptoms and lab tests confirmed that he suffered from COVID-19 (7). Due to the remaining uncertainty around the virus and the disease, the Dutch government started to take measures in March 2020, like closing schools and issuing the " intelligent lockdown", thus initiating the first lockdown lasting up to June 2020 (7). Over the spring and summer of 2020, various campaigns were set up to adapt to the "new normal". This includes the financial support of businesses affected by the pandemic restrictions, the infrastructure for testing facilities, and the social distancing and mask mandates (7, 8). While the summer months of 2020 were spent with few mandates such as social distancing, the fall brought back most restrictions and The Netherlands was forced into a second lockdown by the ever so dominant alpha-variant (7, 9). In the meantime, several vaccines were on their way, at a higher pace than predicted at the beginning of the pandemic (10). The vaccine rollout began in January of 2021, providing some light at the end of the tunnel for many, yet the effects of the vaccines were not seen until months later. Moreover, the new year started off with the controversial curfew, which lasted up to mid-April 2021 (7). Following a similar timeline as the previous year, the summer of 2021 offered fewer mandates and more freedom, primarily provided by the vaccination program (7). The third wave, fueled by the new dominant variant delta pushed the Dutch population back into a lockdown during the fall and winter months (8). In yet another effort to suppress the infections, a booster vaccine campaign was set up and took off in December 2021 and January 2022, bringing the total number of vaccine doses to over 33 million (4, 8). Right around this time, a third variant became the new dominant variant in The Netherlands, the omicron variant took over when the new year started and caused roughly all infections by mid-January 2022 (9). The omicron variant caused a milder disease progression compared to the delta variant, infecting on average a younger population, and resulted in a lower

mortality rate (11). Decreasing amounts of hospitalizations, most likely due to a milder omicron variant and the booster vaccine, offered more room to step by step let go of the lockdown and other restrictions (8). By the 23rd of March 2022, all mandates were lifted and only a short list of advisory guidelines remained (8, 9).

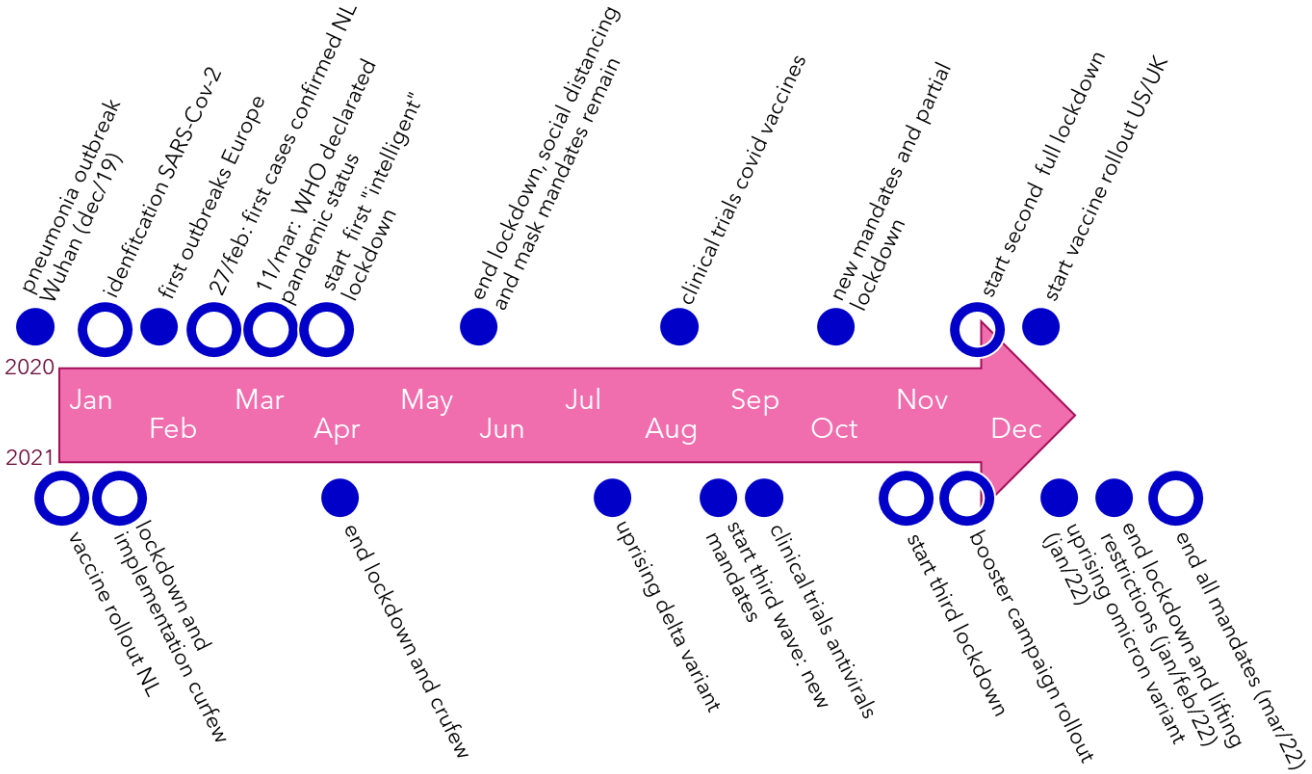

Figure 1: timeline COVID-19 pandemic with key events that happened since the outbreak in Wuhan in 2019. The major events, outbreaks, first infections, lockdowns, and vaccine rollout, are indicated with ⭘, other important events are indicated with ●. The timeline is up to date as of 31/03/22.

Efforts to end the pandemic

Over the two-year pandemic period governments have gone through a process of implementing restrictions in an effort to first stop the spread of the virus and later on to mitigate the number of new infections to relieve the healthcare systems (2). As a result of the limited understanding of the novel pathogen, the Dutch government, like many others, initiated *stay at home* mandates to reduce the amount of face to face interactions between people (9). Since these measures did not reduce hospitalization of covid patients sufficiently, the first lockdown in March 2020 was imposed (7). This lockdown proved to be effective up to a point that hospitals were able to manage, barely, after already postponing regular healthcare and putting most resources and personnel into covid care (8). Working and studying from home, no sports or entertainment leisure time and only staying at home did more than just affect the spread of SARS-Cov-2. Mental health issues became more prominent and prevalent, not being able to maintain social interactions pushed people to the brink of survival throughout each lockdown period (12). Social distancing, the spread of misinformation, quarantine and isolation caused many to experience and suffer from anxiety and depression (12, 13). In addition, business across nearly all work fields suffer financially due to lockdowns, travel restrictions and staying at home mandates. The first two that come to mind are the tourism and hospitality industries, which have been closed for a significant part of the last 24 months (7, 8). Society was waiting for a way out, a way to end quarantine and lockdowns, but safe enough to protect the high-risk (HR) groups and

spare the healthcare system. Vaccines were the promised solution, being developed at light speed and already in clinical trials by August 2020 (14, 15). With efficacies ranging from 70% to 95%, the vaccine rollout began in January 2021 and gave an additional pillar to build immunity against the novel coronavirus (15, 16). As discussed above and seen in the timeline (**Figure 1**) the Dutch population, alongside the majority of the world's population, faced a third wave despite having a >80% vaccination rate (9). The delta variant caused a higher mortality rate in-hospital and increased the pressure on the healthcare system once again (17). Mental health problems kept rising, patience and understanding started declining and the lockdowns became a topic of controversy. The people, schools, businesses, and countries were ready to return to the "old normal", more pillars to reopen safely were needed, and still *are* needed.

Antivirals specifically designed to inhibit the viral infection by SARS-Cov-2 could be the next and perhaps final component to end the pandemic. As of March 2022, many countries are lifting most, if not all, mandates, and restrictions, partly due to a dominant variant with lower hospitalization numbers in combination with largely vaccinated populations (11). Nonetheless, the pandemic is still ongoing with infection numbers on the rise once more (9). With this in mind, yet another mutation leading to a new dominant variant in the future is not inconceivable, potentially causing a fourth wave in the fall season again. It is therefore of great importance that novel therapies will become available to treat COVID-19, not symptomatically, but curatively. By targeting the pathogen, antivirals could potentially keep patients out of hospital through prevention of symptoms progression. Down the line, reducing the number of covid patient in hospital and intensive care units could prove to be the turning point in this pandemic. Even though these are just projections for the time to come, it is worth looking into the COVID-19 patient journey in The Netherlands and assess the contribution such antivirals could make. Besides, the individual covid patients and the general healthcare system treating these patients are not the only stakeholders in resolving the pandemic, as mentioned above, many socioeconomical issues that were lingering beneath the surface pre-pandemic suddenly became very serious problems in multiple aspects in life (12, 13, 18). From a mental health, social and financial perspective, antiviral therapies could be the final push society needs to overcome the pandemic.

Since drug development is usually a lengthy and complicated process, various companies and organizations have started working on COVID-19 specific antivirals at the start of the pandemic, in parallel to the research and development of covid vaccines (10, 19-21). As of March 2022, several antiviral therapies are in the pipeline, whereas a few others, like various monoclonal antibodies, are already used to treat covid patients [see methods & research section] (19, 20, 22). Planning to come to market in 2022 is Pfizer's protease inhibitor (PI) Paxlovid (co-packaged with Ritonavir), the main focus of this research. The progression of the pandemic has shown that uncertainty about the future development of SARS-Cov-2, possible new variants and the unpredictable strain on the healthcare system will remain for now.

Research question

Over the last two years, governments, businesses, communities, and the individual were all forced to improvise and overcome never seen before problems on all fronts, be it financial, healthcare, social and even survival. Making decisions in these times has proven to be immensely difficult, in fact, deciding *who* should make certain decisions was and is an issue on its own. The implementation of a novel drug poses several additional unknowns and uncertainties, which is why it is beneficial to assess the current patient journey for COVID-19 and develop a proper introduction plan for Paxlovid. Two key questions in this process are; *what role can Paxlovid fulfill in the COVID-19 pandemic?* and *who should oversee the prescription and use of these antivirals?* To answer these two questions, this research will approach the pandemic historically to draw lessons from previous experiences with the HIV epidemic

in the 1980s and 1990s and the covid vaccine development. In addition, the current treatment pathways and patient journey will be considered, as well as the mode of action and administration of the novel antivirals. Furthermore, market research under healthcare professionals (HCPs) will be included to gauge the view of the medical field on this matter. Based on these topics, the hypothesis for this research entails the following: *novel antivirals will help further reduce the pressure on healthcare by preventing symptom progression and hospitalizations for high-risk patients. To obtain the best results possible, these antivirals should be overseen by infection disease specialists (IDS) and/or pulmonologists, prescribed by general physicians and fulfilled at all pharmacies.*

To summarize, in collaboration with the Hospital Business Unit (HBU) of Pfizer NL, the research aims to describe the COVID-19 pandemic from multiple perspectives, to illustrate the journey covid patients follow from symptoms development to treatment and recovery, to identify questions healthcare professionals have surrounding novel antivirals, assess where and who supervises the prescription of Paxlovid, and finally to offer recommendations to the HBU team on strategy development for introducing Paxlovid on the Dutch antiviral market.

Methods and research

The aim of this research project is to assess the current COVID-19 situation in The Netherlands, evaluate the patient journey and the needs herein, and propose recommendations for the optimal placement of the novel antiviral Paxlovid. The project covered the time period between September 2021 and March 2022. During this time period, the Delta variant rose and fell back to the background, the Omicron variant being the most prevalent variant in the first quarter of 2022. This is an important development, since the covid mandates have been mostly lifted, even though the incidence rate is at an all-time high due to the Omicron variant.

The aim of this report is to convey a multidisciplinary perspective on the pandemic, which includes a historical comparison to the HIV epidemic, an overview of the novel SARS-Cov-2 pathogen, a comprehensive summary of the current treatment protocols for COVID-19 patients, the effects of the vaccines on the progression on the pandemic, and the workings and predictions of the novel Paxlovid protease inhibitor.

Introduction and history on HIV

The HIV epidemic severely impacted society in the 1980s. The population grew fearful due to an unknown pathogen causing severe illness and death, without understanding the workings of the pathogen or how it transferred from one person to another. There are some parallels and some differences with the HIV epidemic and COVID-19 pandemic in terms of socioeconomic impact, drug development and key events in their respective timelines. The HIV pandemic offers an interesting case to describe the COVID-19 pandemic in a broader perspective. The comparisons will be explained in a historical, pharmaceutical, and societal aspects, with an expert opinion of Prof. Dr. David Burger (Radboud UMC, NL) shedding additional light on these matters.

Mid 1981, the Centers of Disease Control and Prevention (CDC) in the USA report cases of rare lung infections in young men in Los Angeles (23). Over a year later the CDC introduces the term 'AIDS' (Acquired Immune Deficiency Syndrome) for a disease caused by a 'defect in cell-mediated immunity' (23). A retrovirus responsible for AIDS was identified in 1984 and then labeled HTLV-III, later HIV. At this point in time, there were hopes of vaccine development within two years, in hindsight it proved to be much harder to find an effective vaccine. Over the years, specific HIV wards have been set up in hospitals to treat patients with HIV/AIDS and for six years no drug was available, until the introduction of zidovudine (AZT) in 1987 (23). AZT is characteristic for the first generation of anti-HIV-1 drugs, them all being reverse transcriptase inhibitors (RTIs), AZT specifically a nucleoside analog reverse transcriptase inhibitor (NRTI) (24). According to Prof. Dr. Burger, these drugs were mostly effective up to a point of prolonging the life of HIV patients by a few months, however, none of them offered a chance of an increased life expectancy by multiple years or decades. Moreover, long-term therapies with these NRTIs were troubled by drug resistance, therefore a new generation of antiretrovirals had to be developed (24). A second breakthrough in anti-HIV drug development was made in the mid-1990s when the HIV-1 protease inhibitors were introduced as well as the combination antiretroviral therapy (cART) (24). Currently, there are many different classes of antiretroviral drugs used worldwide, including the NRTIs, non-NRTIs, PIs and integrase inhibitors (INSTIs), which are used in various combinations for cART (23, 24). The HIV drug development is unfortunately characterized by the seemingly inevitable drug resistance issue when used long-term, driving ongoing research to produce novel antiretrovirals for resistant patients. The combination therapy is a key factor in effective treatment of HIV by making use of a "backbone" of NTRIs and a "key drug" such as PIs and INSTIs (24). Prof. Dr. Burger: "*The introduction of cART, the triple combination of the PIs with the already existing therapies were the turning point in the HIV epidemic."* This is when "*HIV patients went form terminally ill to chronically ill"*, meaning patients had a new outlook on the rest of their lives. cART reduced the

HIV-1 viral load in the blood plasma significantly, redeveloping the immune system and improving life expectancy back close to the mortality rate of the general population (24). The latest innovations include long-acting injections, perhaps the closest to a vaccine, long-acting nanomedicines, and implants, which are expected to be the next breakthrough in antiretroviral development (24). However, the actual key factor in the battle against HIV is likely providing medical care for all HIV patients around the world. As of today, cART has reached just under two-thirds of the global number of infected individuals, majority of them in developed countries (24). Due to ineffective treatment and lack of proper diagnostic tools in developing countries, the end of the HIV epidemic globally remains out of reach. When experts like Prof. Dr. Burger talk about the turning point in the HIV epidemic, and how that could look like for the covid pandemic, they are talking about the turning point in the western world. Besides investing in drug development and diagnosis of such diseases, an epidemic like HIV and a pandemic like covid can only be solved if equal investments are also made to ensure accessibility to such drugs globally.

New pathogen: SARS-Cov-2

For the third time in this millennium, a coronavirus has disease outburst, with a SARS (SARS-Cov) outbreak in 2002, a MERS outbreak in 2012, and currently SARS-Cov-2 (25). While MERS and SARS have shown to cause death at a much higher rate than COVID-19, the novel coronavirus disease turns out to be much more infectious, spreading globally and causing a pandemic (25). SARS-Cov-2 mainly affects the respiratory system, primarily nasal epithelial cells and pneumocytes, and the gastrointestinal system, enterocytes, similarly to other coronaviruses (5, 26). The clinical presentation of COVID-19 varies from asymptomatic tot severe respiratory disease, the most commonly presented symptoms being cough, fever, sore throat and a runny nose (5). In fact, compared to SARS-Cov, SARS-Cov-2 is responsible for a longer duration of illness in patients, moreover they develop reduced levels of neutralizing antibodies (27). In general, viruses that evade a human's immune surveillance like SARS-Cov-2 does, also evolve to be less infectious. For SARS-Cov-2 however, that is not the case, it is still highly infectious, possessing all the characteristics to cause a pandemic where previous SARS and MERS viruses did not (27). Key factors in the severity of infection in viruses are the cell entry receptors, which are also subject to a high mutation rate, making them also central to the ability of a virus to change and produce more variants (28). The main facilitator in the cell entry mechanism of the current coronavirus seems to be the angiotensin-converting enzyme 2 (ACE2) receptor (5, 28). By interacting directly with the S protein, the virus enters the host cell after which the viral genome is released (**Figure 2**) (5). The viral genome is translated into viral replicase polyproteins which are then cleaved by viral proteases to create functional proteins. RNA-dependent RNA polymerase (RdRp) in the viral replication complex mediate replication of the viral genomes, which are subsequently packaged and together with the translated viral structural proteins, form viral nucleocapsids that are released through exocytosis (5). The most dominant variant of the first two years of the pandemic, the alpha and delta variant, both contain mutation in the spike proteins, which host the receptor binding domain (RBD) for binding to the ACE2, thus facilitating cell entry and improving its infectivity (29, 30). Not just in terms of infectivity are novel variants a topic of concern, they could also be less affected by the covid vaccines and antivirals (3). Especially when it comes to high risk (HR) groups, such as immune-compromised individuals and patients with co-morbidities, the susceptibility of these variants to the covid vaccines largely determines their vulnerability to the disease, given they are vaccinated (3). All and all, the novel coronavirus SARS-Cov-2 brings a list of challenges, from is superior infectivity and stealth in the body to the multiple variants arising, posing new threats to manmade defenses such as vaccines.

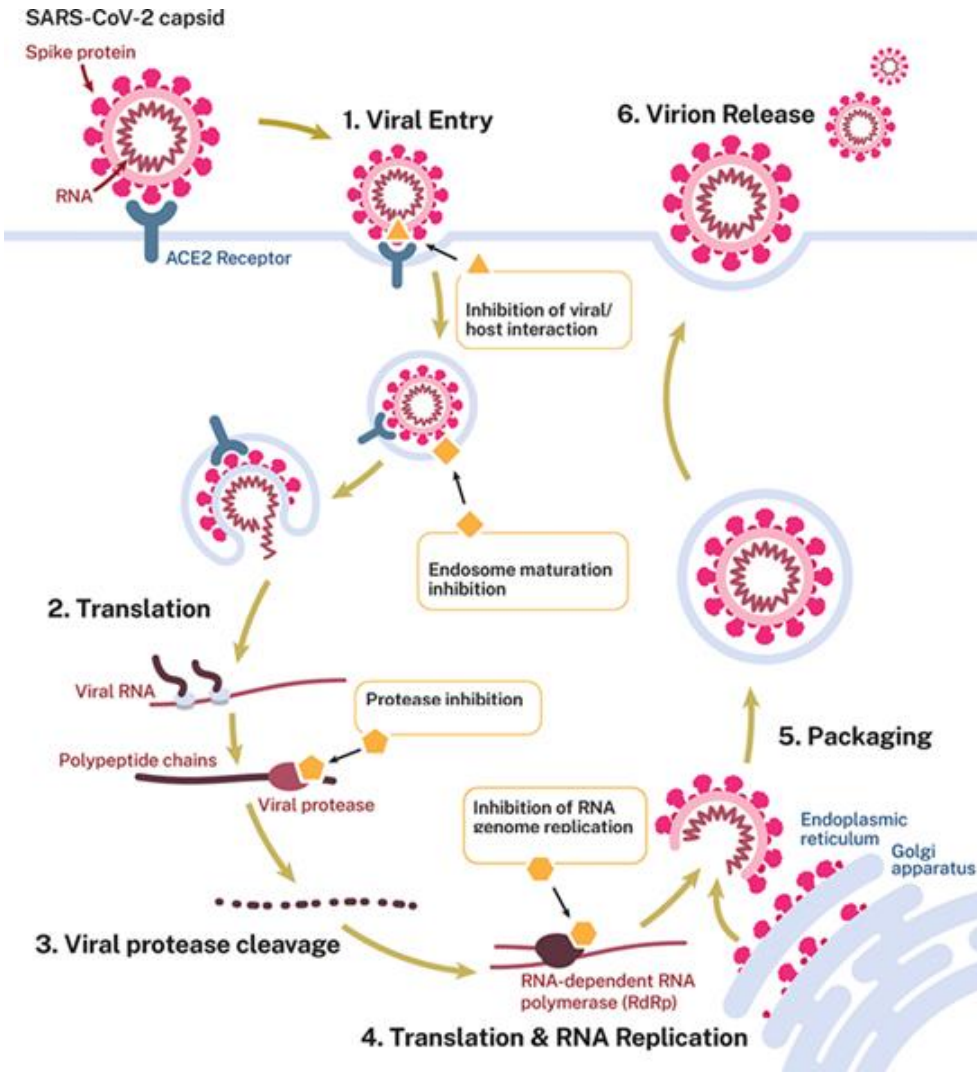

Figure 2: SARS-Cov-2 life cycle in human host cell (5). Cell entry mechanism is facilitated by the binding of the s protein to the ACE2 receptor [1]. After cell entry, the viral genome is released, translated into viral replicase polyproteins [2] and subsequently cleaved by viral protease to create proteins [3]. The viral genomes are replicated [4] and viral nucleocapsids are formed from the packaged viral genomes [5] and viral structural protein. These capsids are then released via exocytosis [6].

Covid vaccines

The development of anti-SARS-Cov-2 vaccines happened at a unprecedented pace, within a year after the declaration of the pandemic status of COVID-19, the first individuals got their first shot of a covid vaccine (16). Usually, the timeline of vaccine development follows the pattern of phases in which the next phase starts when the previous phase has been executed, analyzed, and deemed successful, the entire process spanning over 10 to 15 years (14, 16). In general, the pipeline starts with pre-clinical *in vitro* and *in vivo* studies, followed by phase 1, phase 2 and phase 3 of clinical trials, each phase including an increasing number of participants. After roughly eight to twelve years, the approval procedure of another one to two years initiates, where the medicine agencies must approve the actual drug to enter the market (14). Only after a completed pipeline, from preclinical data until a completed approval, will companies start upscaling manufacturing, and the novel vaccine will be introduced onto the market (14). Since the world was waiting for a long-term solution to the pandemic, the process of the vaccine development had to be accelerated, which was feasible due to the tremendous investments put

towards this goal, monetary as well as time and resources (16). In addition, the usual timeline procedure was replaced by "stacking" the phase roughly halfway on top of each other, meaning that the phases occurred parallel to each other instead of chronologically, enabling the development of various vaccines within 12 to 24 months (14, 16).

By looking at previous work done for the development of MERS and SARS vaccines, the industry already had an overview of the different types of vaccines, how they worked and what their advantages and disadvantages were (21). SARS-Cov-2 is the seventh coronavirus known to infect humans, all of them cause respiratory disease in different stages of severity, and they have become an increasingly bigger risk to healthcare (21). The earlier coronaviruses, in specific the MERS and SARS strains, have stimulated research into vaccine development at those times and provided a shortlist of suitable platforms when it comes to SARA-Cov-2 (21). These platforms include vaccines based on a whole inactivated virus, a live attenuated virus, viral vectors, protein subunits, viral-like particles, DNA and (m)RNA (21). The principal covid vaccines used worldwide use one of these platforms (see **Table 1**).

Table 1: overview most prevalent covid vaccines globally

Vaccine	Platform	Efficacy (16)
Comirnaty (BioNTech/Pfizer)	mRNA	87.5% - 95%
Moderna vaccine	mRNA	94% - 100%
COVISHIELD (AstraZeneca)	Adenovirus viral vector	70%
Janssen vaccine (Johnson & Johnson)	Adenovirus viral vector	57% - 72%
NOVAVAX (introduced at a later time)	Protein subunit / virus-like particle	60% - 89.7%
SINOVAC (China)	Inactivated virus	65% / 86-90%
SPUTNIK (Russia)	Adenovirus viral vectors	91.6%

Overall, the covid vaccine show an efficacy of >80% when it comes to the prevention of hospitalization (17). However, these numbers need a more in-depth analysis to fully assess the effect they had to the progression of the pandemic. When looking at the alpha and delta variant, these vaccines produce an effectivity 85% after two doses (17). Up to November 2021, these two variants have accounted for the overwhelming majority of covid cases, and the vaccine program was effective in reducing the number of novel cases and hospitalizations (3, 9, 17). Even though there was controversy and suspicions from some corners of society about the vaccines and their purpose, the vast majority of the Dutch population got the two jabs (9). However, two doses did not produce the same effectivity against the omicron variant, only about 65%, which pushed society back into lockdown over the holiday season when it became the dominant variant (9, 17, 31). Two vaccine doses taken by >85% of the population and yet again a lockdown and mandates were put in pace caused even more controversy among the *antivax* community. At this point, the need for effective covid measures to end the pandemic were only desired more, but anti-covid drugs were a long way from coming to market. By setting up a booster campaign, all eligible individuals were able get a third vaccine to boost their immune system once more (7, 9). Three doses ensure an 86% effectivity against the omicron variant (17). As of March 2022, the booster campaign and the decreased severity of the disease progression caused by the omicron variant led to the end of all mandates in The Netherlands. However, the virus remains highly infectious, and the rise of new variants is still a risk for the time to come. A diverse collection of vaccines and antivirals are essential to ensure protection against COVID-19 since the turning point in this pandemic has not been secured just yet.

Current patient journey and standard covid care

A small minority of individuals who tested positive for COVID-19 needs medical care in the form of hospitalization or intensive care (8). In The Netherlands the number of newly confirmed cases is roughly 200 times larger than the number of individuals who got hospitalized with COVID-19 (statistics of mid-March 2022) (8). To analyze the proper place for the introduction of antivirals on the Dutch market, the first step is to illustrate the journey that covid patients follow (**Figure 3**). The most common path usually starts at home when an individual gets a positive test result from the antigen self-test kits after they developed covid-like symptoms or due to routine testing after an international trip or when they were in close contact with another covid patient. In those cases, a PCR test is scheduled at the local GGD test center and the patient self-isolates until they receive their PCR test result. The isolation period gets prolonged when they test positive again and they stay home until they have recovered. These individuals, the vast majority of covid patients, are advised to take paracetamol to relieve any discomfort during their recovery and will not need any additional care. The GP will be notified of the test results of their patients, in case symptoms worsen, the patient will be able to contact their GP and receive medical advice and/or care from them.

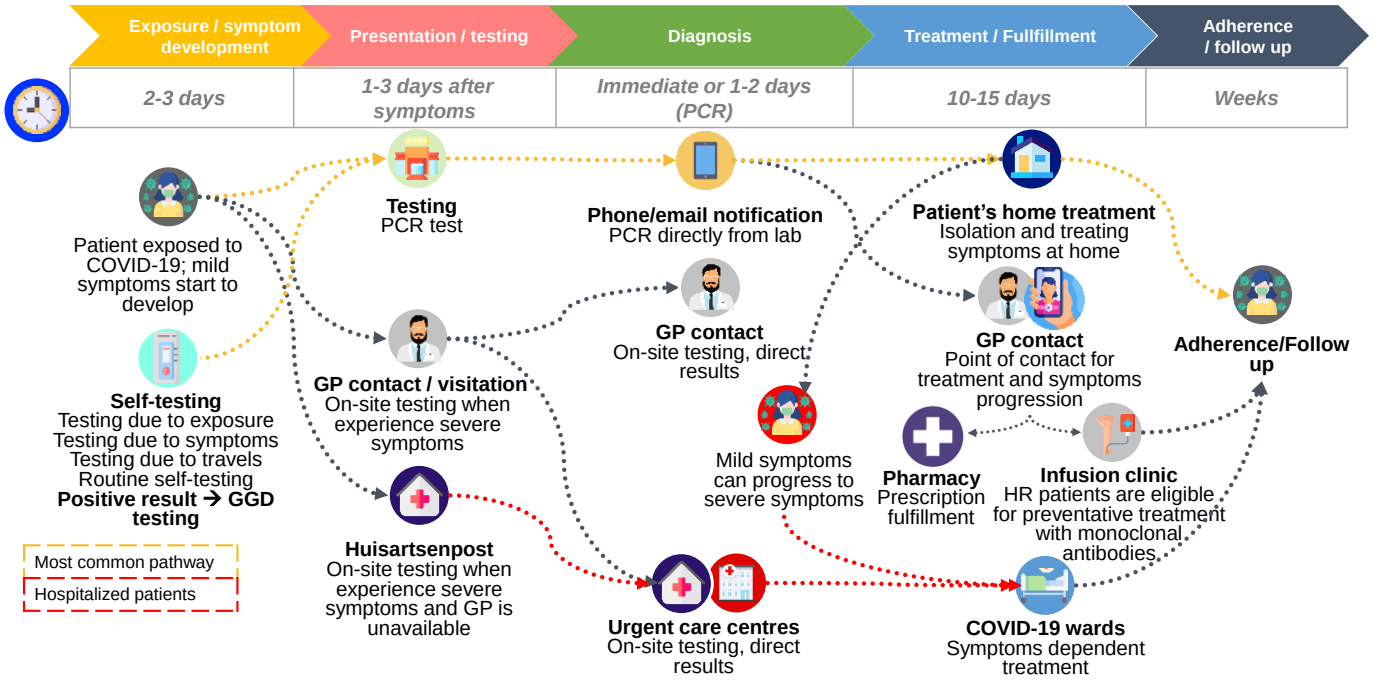

Figure 3: patient journey current state. Most covid patients start their journey at home after symptom development and/or a positive self-test. The majority of cases will remain home, get tested to confirm their diagnosis, and recover at home without medical intervention (indicated in the yellow dotted line). Moderate to severe symptoms will cause patients to either contact their GP or visit an urgent care center. From there on, patient might be hospitalized or transferred to an infusion clinic to receive monoclonal antibodies. A minority of patients do not fully recover and will suffer from long-covid, which can last weeks or months.

In The Netherlands, patients will not start any form of treatment until after hospitalization, except for HR patients who are at risk of fatal complications due to COVID-19. HR patients are able to receive monoclonal antibodies, however those decisions are based on the personal circumstances of the patient (32). The patient journey of when suffering from mildly severe to severe symptoms will lead to hospitalization on either covid wards or intensive care units. The Dutch Working Party on Antibiotic

Policy (SWAB) are the advisory agency in The Netherlands for covid therapies and write guidelines on the use of drugs for the treatment of COVID-19 (32). The SWAB recommends the use of Dexamethasone for hospitalized covid patients in need of oxygenation to diminish the immune system and thus relieve the immune reaction to SARS-Cov-2 (32, 33). In addition, the SWAB only recommends the use of monoclonal antibodies in cases of absence of antibodies, regardless if derived from vaccination, previous infection or inability to produce such antibodies (32). The central issue remains that any therapy currently used to treat severely ill covid patients focusses on treating the symptoms, not on targeting the responsible pathogen. This is the gap in the market that many are trying to fill.

New treatments: antivirals

Various antivirals are currently in the pipeline that do address the issue of curing the disease as well as relieve the symptoms. The European Commission has compiled a list of the 10 most promising treatments for COVID-19 (see **Table 2**) (34). 50% of these drugs are mono- or dual therapies of monoclonal antibodies, the other include a protease inhibitor, nucleoside prodrug, IL-1 receptor antagonist, JAK inhibitors, and a nucleoside inhibitor. The majority is already authorized for use in the European Union, while some are still awaiting approval.

Table 2: overview antivirals COVID-19 (34)

Antiviral	Company	Class	Status (28/03/22)
Paxlovid (PF-07321332)	Pfizer	Protease inhibitor	Authorized for use in the European Union
Lagevrio (molnupiravir)	MSD	Prodrug of synthetic nucleoside derivative N4-hydroxycytidine	Marketing authorization application submitted
Regkirona (regdanvimab)	Celltrion	Monoclonal antibodies	Authorized for use in the European Union
Ronapreve (casirivimab & imdevimab)	Regeneron Pharmaceuticals and Roche	Monoclonal antibodies	Authorized for use in the European Union
Xeduvy (sotrovimab)	Vir Biotechnology and GSK	Monoclonal antibodies	Authorized for use in the European Union
Evusheld (tixagevimab & cilgavimab)	AstraZeneca	Monoclonal antibodies	Marketing authorization application submitted
RoActemra (tocilzumab)	Roche Holding	Monoclonal antibodies	Authorized for use in the European Union
Kineret (anakinra)	Swedish Orphan Biovitrum	Interleukin 1 receptor antagonist	Authorized for use in the European Union
Olumiant (baricitinib)	Eli Lily	Janus kinase inhibitors	Marketing authorization application submitted
Veklury (remdesivir)	Gilead Sciences	Nucleoside analogue	Authorized for use in the European Union

Paxlovid

Pfizer's protease inhibitor Paxlovid, generic name nirmatrelvir, is the main focus of this research. The only protease inhibitor currently authorized by the European Medicines Agency for covid treatment is a five-day oral regimen best to be taken within three to five days within symptoms onset (35). The SARS outbreak in 2002 stimulated Pfizer to identify inhibitors for the SARS-Cov-1 main protease (SARS-Cov-1 M^{pro}), which produced the potent protease inhibitor PF-00835231 (36). When the SARS-Cov-2 outbreak began, PF-00835231 was tested to assess the potency of inhibition of the SARS-Cov-2 M^{pro} (or SARS-CoV-2-$3CL^{pro}$) (36). However, for oral administration, PF-00835231 was not suitable due to poor oral absorption and low passive absorptive permeability. Therefore, a phosphate pro-drug of PF-00835231 is now in the pipeline, PF-07304814, as a PI for intravenous administration (36). An oral formula would increase the accessibility of the drug, especially when it is meant to be taken to prevent hospitalization after infection and the patients still reside at home. Through five chemical synthesis steps, an increased orally available PI was produced, PF-07321332 or nirmatrelvir (36). Nirmatrelvir is co-packaged with a low dose of ritonavir, a different antiviral, however, not to act as an antiviral against COVID-19, but to boost the active pharmaceutical ingredient. CYP3A4 metabolized the active molecule, therefore, to increase the half-life of nirmatrelvir in the human body, ritonavir was added to act as a CYP3A4 inhibitor (36). Paxlovid now consists of a potent SARS-CoV-2 3CL PI and a booster, demonstrating a reduction in hospitalization or death by 89% (35).

The PI achieves its antiviral effect by inhibiting an essential protease in the viral replication process. The 3CL protease digests polyprotein to produce a set of proteins that are vital for the virus replication and transcription (36). The 3CL protease plays a key role in the proliferation of SARS-Cov-2, yet it has no close human analogues, avoiding any unwanted off target effects in the human body. The uniqueness of the protease to the coronavirus emphasizes the potential of 3CL protease inhibition (35, 36). In addition, whereas spike proteins on the surface of viral particles are prone to mutations, the 3CL protease has remained unchanged throughout all coronaviruses that broke through and caused human infections. Antiviral therapies highly mutative sections of the virus might turn out ineffective in novel variants that could pop up in the future, all the while the 3CL protease could be targeted regardless of spike protein mutations. Paxlovid has great potential to be a robust antiviral, the next challenge is discovering the optimal place for it to be implemented in the patient journey.

Market research

The aim of the market research is to understand the view of healthcare professionals (HCPs) on the potential role of Paxlovid in the Dutch patient journey. For this section of the research plan, Dutch medical professionals were interviewed and asked about their perspective on the COVID-19 patient journey, how they currently treat COVID-19 patients, what their opinion is on the new antivirals coming to market and what they think the effect of such antivirals could be on the patient journey.

The market research included eighteen medical doctors and two Municipal Health Service employees (GGD). A total of five general physicians (GPs), five pulmonologists, four infectious disease specialists (IDSs), four intensivists and two GGD employees participated in a one-on-one online interview. The inclusion of these specific groups of HCPs was based on their role in the patient journey of covid patients. GPs are usually the first person of contact for patient when they fall ill, and they are the point of oversight of the medical history and current drug prescriptions of their patients. Pulmonologists are the second line of healthcare providers when it comes to COVID-19, when symptoms progress to a mor severe state, patients will be referred to the hospital and pulmonologists will enter their patient journey. IDSs are another second line healthcare provider when it comes to COVID-19, usually involved in the severe cases. Only the covid patients in need of intensive care, experiencing oxygen deficits, will be treated by intensivists. The choice to include intensivists as well in the study, even though they most

likely will not see covid patients within five days since symptom onset, is due to the severe pressure the covid pandemic has put on the ICUs globally. Therefore, their view on what antivirals could contribute to relieving the strain on their units is of special interest. From a target list compiled for this research, participants were approached and interviewed based on questions and topics that came forth from the literature research and internal discussions for this project. The central questions include:

- How does the patient journey look like according to these HCPs?
- Which HCPs are involved in the treatment of COVID-19 in the first five days after symptoms development?
- Which decision making units are involved in the patient journey and treatment plan of a COVID-19 patient?
- What is the view of the HCPs on Paxlovid based on an anonymous product profile?
- What is the optimal place/position of Paxlovid in the patient journey?
- Who should be the supervising party when it comes to knowledge and prescription of Paxlovid?

The key focus of these questions is to gain insight into the way different stakeholders view the addition of Paxlovid to the treatment of COVID-19 in order to assess and implement the best possible market introduction of Paxlovid.

Results

The purpose of this research is to gather multivalent information to answer the key questions of this project: *what role can Paxlovid fulfill in the COVID-19 pandemic?* and *Who should oversee the prescription and use of these antivirals?* Literature and market research, as well as the current pandemic climate, form the base of information and insight to discuss the answers to these questions.

Comparison with HIV and the need of antivirals

There is much that sets these two health crises apart, yet they both tell a story about an unforeseen outbreak which resulted in mass fear of the pathogen and immense pressure on the healthcare systems. From the construction of separate covid and HIV wards in hospitals to the insecurity of the disease progression, these viruses impacted society on a large scale. By unpacking the similarities and differences of the HIV pandemic and the COVID-19 pandemic, the relevance of antiviral drugs can be assessed from a historic perspective. In addition, the experience of antiviral drug development, unforeseen immense pressure on healthcare, and societal anxiousness for an unknown pathogen provide take-aways that could also be applicable to the current pandemic.

The first major difference between the two viruses is the transmissibility, SARS-Cov-2 is more infectious than HIV due to the airborne transmission as opposed to the exchange bodily fluid like blood. Keeping this in mind, it is not surprising that the >470 million covid cases exceed the 37.7 million HIV cases by a ten-fold (4, 37). Prof. Dr. Burger: "*everyone in The Netherlands is at risk of contracting COVID-19, whereas only a small number of individuals are at risk of contracting HIV".* Nonetheless, the impact these viruses had on the healthcare system was and is debilitating in their own way. Concerning COVID-19, the disease profile varies between mild flu-like symptoms, to severe respiratory disease. The broad spectrum of symptoms, disease outlook and medical need within the COVID-19 patient population also illustrates the varying severity a COVID-19 diagnosis could mean to a patient. This could not be more different for HIV patients, especially in the first years of the uprising of the disease, when there was no medication available and being HIV positive meant a death sentence on the short term. After years of research and drug development, a HIV status is manageable up to a point of suppressing the viral load to undetectable levels and rendering the disease untransmissible (24). Another key difference is that HIV is a life-long condition, due to the insertion into the host DNA, and no cure has yet been developed either. Most COVID-19 patients recover within a few weeks after infection, often with little to no medication necessary. Up to 57.0% of COVID-19 patients do experience at least one long-covid symptoms for at least six months since symptoms onset (38-40). Time will tell whether long-covid will last years or a life-long time as well, yet HIV patients are certain of dealing with life-long medication in order to handle their diagnosis. The role antivirals can play in the progression of a disease also depends on the level of threat that the pathogen presents. Prof. Dr. Burger: "*HIV is as deadly now as it was 30 to 40 years ago, whereas the current dominant omicron variant causes milder symptom development than the delta variant. The impact of an antiviral therapy should reflect its potential danger".* HIV medication is therefore as important now for its patients as it was during the HIV epidemic, without it, HIV patients would face the same faith as in the early 1980s. The relevance of anti-SARS-Cov-2 therapies will vary overtime, from "*nice to have*" at present times to perhaps essential or redundant in the future, depending on the variant.

As discussed above, the introduction of effective antiretrovirals took years, partly due to the delayed identification and characterization of the pathogen. Prof. Dr. Burger: "*the discovery of the virus happened quite quickly, within a few years' time the pathogen was identified, which was quite fast for those times".* All the while the pressure of finding a cure for the disease kept growing. Eventually, six years since the identification of the first HIV cases, AZT was approved by the FDA in the United States (23, 24). However, the turning point, in the western world that is, was not reached until the

introduction of different classes of antivirals and combination therapies. Prof. Dr. Burger: *"the turning point in other parts of the world, such as countries in Africa, has not been reached yet. Antiretrovirals have already decreased the mortality rate significantly, hopefully the combination therapies will end the HIV epidemic globally as well".* Vaccines were the first hopeful remedy and potential turning point in the covid pandemic, many saw the vaccine development as *the way out* in 2020. However, that turning point has not been achieved yet, due to the omicron variant being less susceptible to the double dose vaccine strategy (31). Moreover, in mid-March 2022, there are still over 30.000 new cases being registered daily in The Netherlands and over 10 million globally, the pandemic is not over yet (4, 9). Perhaps the booster vaccine or the antivirals or another factor will be the turning point in the pandemic but that can only be determined in hindsight.

Key lessons that can be learned from the HIV epidemic are the importance of a diverse spectrum of antiviral drugs to avoid drug resistance and a strategy to provide global access to antivirals. Various antiviral drugs could provide an effective therapy for different kinds of patients. A global approach to ensure access to antiviral for all covid patients worldwide is a way to prevent the development of novel potentially dangerous variants, besides it being the only ethical approach to solving a pandemic.

Market research

To understand the role and place of Paxlovid in clinical practice, the perspective of HCPs on covid treatments, the patient journey, decision making units (DMUs), antivirals, and Paxlovid itself has been investigated. Through ~60-minute interviews with GPs, pulmonologists, IDSs and intensivists, these topics have been explored and the opinion of HCPs will be summarized below.

Current covid care, patient journey and DMUs

During the first 18 months / two years, the alpha and delta variants caused shortages in drug provisions and medical equipment, up to a point that regular healthcare procedures had to be cancelled to make room for covid patients. Treatment plans were not fully developed yet and constantly changing due to the unprecedented nature of the pandemic and the different variants. The major stumbling blocks were treatment related, whereas the current struggles stem from organizational issues like staff shortages in hospitals due to illness. Treatment plans have been standardized by now and hospitalization numbers have decreased due to increased immunity, which shifts the workload from the second line, in hospital, to the first line, at home under GP care. The patient population has been reduced from a diverse group of patients to mainly unvaccinated and immunocompromised patients. The downsizing of the patient population leads to a downsize in the unmet need that could be fulfilled by antivirals drugs like Paxlovid. Looking at patients that could be considered for therapy with Paxlovid, the current system limits the pool of patient even more. Treatment initiation happens only when patients are hospitalized, which rarely happens within five days since symptoms onset, which is the window of administration for Paxlovid. This does not mean that hospitalization does not occur, symptoms tend to worsen at a later time point, after 5 days since the first symptoms have started.

Medical care for covid patients takes place almost exclusively in the second line, where pulmonologists and IDSs are the overseeing party, until patients are transferred to ICUs. To treat COVID-19 effectively with Paxlovid and prevent symptom progression and hospitalization, patients need to be able to obtain the treatment within the first five days of symptom development. However, the participants in the study proposed a few conditions to introduce antiviral treatments in the first line. Solid communication and agreement between the first and second line need to be in place, GPs should be able to get a second opinion from specialists quickly and directly. GPs want pulmonologists and IDSs to back up the treatment policy they will carry out, based on widely supported guidelines from the professional medical community. Another obstacle for HCPs to assess who is eligible for antiviral treatment in the first line is the heterogenous patient population. The target population is generally identified as HR

patients, however the definition of who is and is not high risk is changing regularly. At the start of the pandemic, criteria for HR included >60 years old, obesity, diabetes, cardiovascular disease, underlying illness and immunocompromised. HR groups identified as eligible for antivirals consists of mainly immunocompromised and unvaccinated individuals, although it remains ambiguous.

Introduction antivirals

Clear guidelines on the target population and prescription criteria are necessary for a smooth introduction of antivirals in the Dutch covid patient journey. Across all participants in the study, the GPs were informed the most on the novel anti-SARS-Cov-2 therapies, the specialists not so much. The GGD expressed willingness to fulfill an advisory roll towards patients concerning antivirals and expressed interest into the use of antivirals to prevent hospitalization. They could support the HR patient population and educate individuals to stimulate self-vigilance among this patient group. During the interviews in the study, the following conditions for prescription were indicated by the HCPs:

- Effective therapy, little to no adverse effects
- EMA approval
- Recommendations from National Health Care Institute (het Zorginstituut)
- Guidelines from SWAB
- Consensus from the HCP community
- Clear and concise guidelines
- Accessible and sufficient communication between HCPs
- Self-vigilance from HR patients about their health and healthcare needs

Product profile Paxlovid

When presented with unidentified product profiles, which included Paxlovid, Lagevrio, and monoclonal antibodies, the general first reaction showed prominent interest in Paxlovid because of its high efficacy and oral administration. A general consensus was observed about the timing of the introduction of such therapies since the unmet need has declined in the current pandemic climate. In terms of accessibility and efficacy, Paxlovid is the best candidate, however the HCPs mention contraindications due to the co-administration of ritonavir. To overcome doubt or hesitation the GPs have about potential adverse effects or contraindications, they would like to be backed-up by the specialists and be provided unambiguous information on prescription guidelines. Whether commencement of the treatment within three to five days after symptom onset is feasible, the HCPs were unsure. Some indicated that it would be complicated to start so soon in many cases, while others mentioned that self-test and self-awareness of the patients could overcome the time issue.

HPCs opinion on the role and place of antivirals

Anti-SARS-Cov-2 therapies are seen as a potential valuable contribution in the treatment of COVID-19, specifically for the HR patient population who are not protected through previous infections or vaccination and patients who are at higher risk of developing severe symptoms with a possible fatal consequence. However, the unmet need and the patient population are currently small in comparison to three to six months ago. A key contribution to the relevance of Paxlovid is its accessibility and high efficacy in prevention of hospitalization, which is never redundant in the treatment of COVID-19. To ensure that Paxlovid is able to reach its full potential, it should be introduced in the first line, with support and guidance from the second line. This pathway can provide access to the therapy within five days after symptom development. The participants in the study expressed confidence in this introduction plan, given that the conditions discussed above are met.

Future patient journey

In most cases, the GP is the first point of contact for covid patients when they experience mild to severe symptoms and want/need additional care. For some HR patients, they might contact their specialists who oversees their chronic illness, like immunocompromised patients. When predicting a patient journey to include Paxlovid, the GP will most likely fulfill a key role in connecting covid patients with pulmonologists and IDSs. During the market research study, the HCPs expressed their opinion on the place and role of Paxlovid in covid treatment. The GP will oversee a patient's medical dossier and the prescription of antivirals when they meet the HR population criteria. To facilitate access to these antivirals, the fulfillment should be the responsibility of all pharmacies. Pulmonologists and IDSs will support the GP and provide guidance based on the advice and guidelines provided by SWAB and other medical professional organizations. The future patient journey based on this description will center around the GP, with the patient driving the process by being aware of their condition and taking action when needed (**Figure 4**)

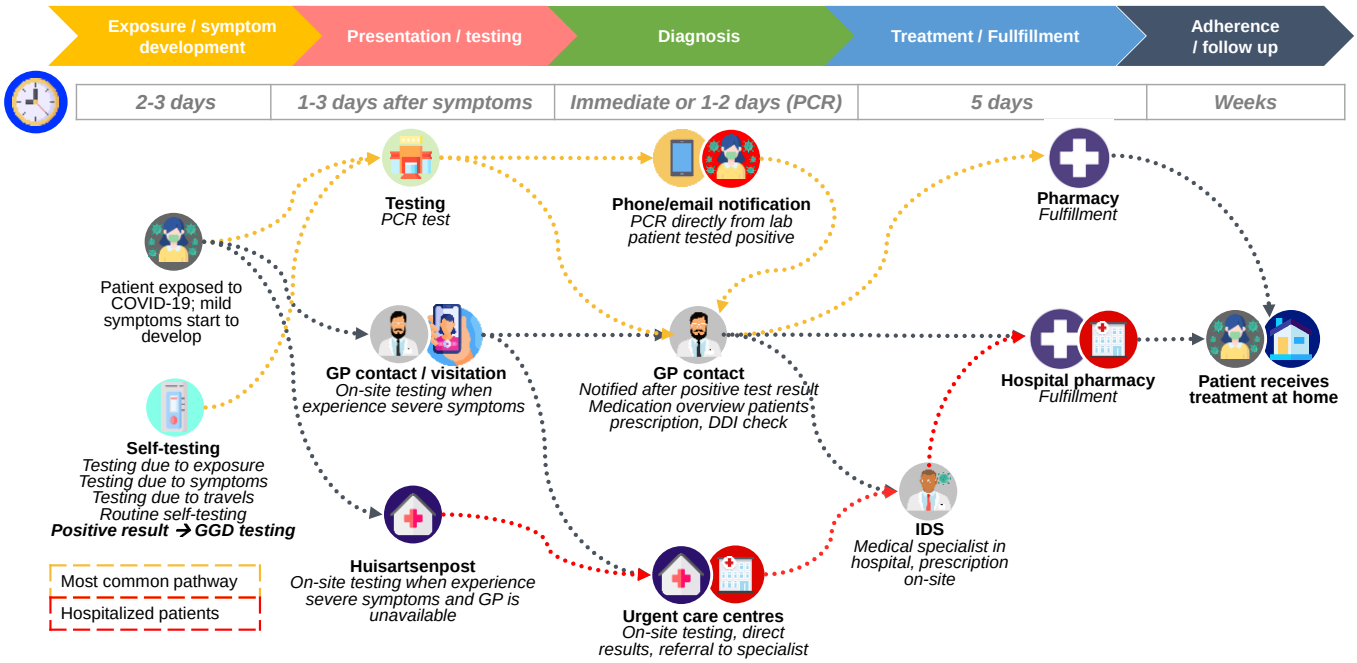

Figure 4: patient journey future state. With the introduction of Paxlovid in primary care, the GP will become the central point of oversight and prescription. They will need to be in close contact with the pulmonologists and IDSs for support when asked for. The HR patients could prevent hospitalization and transfer form the urgent care/hospital patient journey back to the most common pathway of testing, staying at home, confirming their diagnosis, receiving medical care at home, and recover at home (indicated in the yellow dotted line).

Discussion

At the start of this research, September 2021, the pandemic climate differed from the current one and has changed almost monthly in those seven months. Since then, The Netherlands has gone through time with little restrictions and mandates followed by a partial lockdown, a full lockdown, a novel variant quickly causing the majority of infections, subsequently back to letting go of the lockdown and lifting all restrictions and mandates (7-9). Even in these uncertain times, the two research questions central to this report remained relevant anyway. The answers to the questions *what role can Paxlovid fulfill in the COVID-19 pandemic?* and *who should oversee the prescription and use of these antivirals?* determine the strategy for the introduction of Paxlovid to the Dutch antiviral market. As of October/ November 2021, in the middle of retreating into restrictions, closing of entertainment spaces and eventually a full lockdown, the hypothesis for these research questions were: *novel antivirals will help further reduce the pressure on healthcare by preventing symptom progression and hospitalizations for high-risk patients. To obtain the best results possible, these antivirals should be overseen by infection disease specialists (IDS) and/or pulmonologists, prescribed by general physicians and fulfilled at all pharmacies.* As of mid-March 2022, the pandemic is still in effect, yet in a state that does not decimate the healthcare system, therefore all restriction and mandates have lifted. A different zeitgeist results in a different perspective on the threat the pandemic poses and the unmet need of antivirals.

Covid vaccines, current treatment options and the extend in which covid affects the healthcare system are indications of what antivirals could contribute to the current pandemic climate. In general, the need for antivirals depends on the severity of the crisis at hand and the measures already in place to handle the crisis. The HCPs expressed a low unmet need and a small patient population for antivirals such as Paxlovid, due to the effects of the booster campaign on the omicron variant and a milder disease profile with omicron in general (3, 11, 17, 31). In addition, the number of hospitalizations has been lower in February and March 2022 compared to the first, second and third wave, although they are on the rise again (9). In a crisis like a pandemic, the severity of the disease at a specific time point will be assessed in relativity to the rest of the pandemic, and it therefore subject to biases. Since these HCPs see and refer less patients nowadays than earlier in the pandemic, they deem the introduction of novel antivirals less important as well. However, a subset of the population, individuals without any protective effect from antibodies, could benefit greatly from these antivirals (41). These groups included immunocompromised patients due to illness or otherwise, and individuals who did not get vaccine, due to fear, mistrust or refusal. Currently, these individuals are all defined as “high-risk”, however the exact composition of the HR population is unclear and vague. Most patients admitted to hospital are labeled HR, which makes the population in actual numbers for which the antivirals do fulfill an unmet need larger than perhaps evaluated relatively by HCPs. Through market research, a better insight into the needs of these HR patients can be obtained. To gain a wider understanding, a follow-up study should include individual patients within the HR population, as well as the patient organizations that represent them. For now, the HCPs tend to dismiss the unmet need for these patients, while the opinion of them has not yet been asked for or even considered. Even though the general population would probably manage without the addition of antivirals to the treatment plan, the benefits of such novel therapies for a more vulnerable portion of society should not be overlooked.

Through comparison of COVID-19 to HIV, the importance of diverse antiviral therapies is stressed once more. One of main issues of the first antiretroviral drugs was drug resistance, often caused by the long-term use of these drugs. The same issue is seen with some monoclonal antibodies used for covid treatment, up to a point that some of these therapies are no longer suitable due to variant becoming resistant (42, 43). Although the S protein on the surface of the virus provides an easy access drug target, this protein is susceptible to mutations, rendering S-protein specific antibodies ineffective after

too many mutations (44). This is where Paxlovid could prove to be a more robust antiviral therapy, since it targets the SARS-Cov-2 M^{pro}, which is less prone to mutate (36, 44). In addition, the five-day oral administration of Paxlovid, further reduces the risk of drug resistance and increases accessibility over intravenous administrative drugs.

For Paxlovid to reach its potential, the short delay between in symptoms onset and initiation of the therapy is ideally not over five days. To achieve such quick action between receiving a positive test result, the prescription and the fulfillment of the medication, the treatment plan and policy need to be adapted. The medical professional community needs to prepare for the introduction of antivirals but is not able to do so without guidance and support for the use of such therapies. Policy making from institutions as the Ministry of Health, Welfare and Sport (VWS) should stimulate and help organizations for medical professionals to form put out guidelines and protocols on antivirals. Only then will the HCPs involved in covid care feel confident to implement antivirals such as Paxlovid in their patient journey, based on the interviews conducted. In fact, the administration of Paxlovid within the first five days can only be achieved through the introduction of the therapy in primary care. However, the medical experts on antiviral therapies for COVID-19 reside in the second line of care, so their role shifts from involved in treatment to advisory to support the GP. Although some HCPs indicated that the healthcare system has learned to be highly adaptable during the pandemic, structural changes as explained here might take longer and more effort to integrate than desirable. A proactive stance from all parties involved could offer a solution.

Conclusion and recommendations

Circling back to the research questions, the hypotheses made in the fall of 2021 do not fully hold up in the spring of 2022. Often, the contribution a novel therapy could make is based on the danger a pathogen poses the general population, while in the case of COVID-19, the unmet needs should be based on the absolute number of individuals it could help. Whereas the vaccines have provided protection for the majority of people and allowed the return to “normal”, many individuals are left in a vulnerable position. Paxlovid can still provide a reduction in risk of hospitalization, specifically for a smaller patient population. Nevertheless, healthcare should be accessible and inclusive, therefore highlighting the importance of Paxlovid to the HR patient community. To ensure adequate administration of this antiviral therapy, the GP takes on a bigger role than just the prescribing party. The GP will be the central point of oversight in the patient journey, assessing the eligibility of a patient for the therapy, as well as the prescription and follow-up part. The medical experts, pulmonologists and IDSs, will take a step back and take on an informative and supportive role for the GP. Furthermore, policy makers, healthcare organizations and regulatory bodies need to provide HCPs with clear and concise information and guidelines on the mechanism of action, the intended use, and the target patient population. The individuals included in the patient population can play a vital role in the acquisition of antiviral therapy as well. Through self-awareness and vigilance, these patients can proactively reach out to their healthcare providers when they are diagnosed with COVID-19 and receive medical care that reduce the risk of being hospitalized a later stage of the disease.

Pfizer NL wants to introduce Paxlovid onto the Dutch antiviral market, but the current treatment protocols and patient journey are not ready yet. Pfizer NL could help drive along this process and support HCPs involved in covid care, by providing the information and guidance that HCPs are asking for. Firstly, Pfizer NL could compile an accurate patient profile, for example by assessing who is eligible for therapy with Paxlovid. A clear definition of “high-risk” patient would help tremendously, as the current definition of HR includes many different patients but remains quite vague as different HR groups are meant for different assessment (eligibility for treatment, severe disease progression, and more). Secondly, Pfizer could help the manufacturing of the highly desired guideline and protocols by offering to support to the approving and advisory organizations such as EMA, RIVM, NAG, and SWAB. Even though Pfizer NL it not inherently responsible for these actions, it would benefit them and the patients to stimulate and cooperate with these organizations anyway. Lastly, through collaboration with patient organizations and the GGD, Pfizer could help create more awareness amongst the HR patient community and encourage a proactive mindset when it comes to their healthcare.

All and all, Paxlovid could fulfill a medical unmet need for a specific patient population, which is unequivocally the most important contribution drug development can provide.

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