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MSc One Health

Minor Research Project (Research Profile)

The impact of prophylactic and antiviral treatments for COVID-19: a modelling study

Inês da Silva Soleiro Nunes Marcelino

Student nr. 9983759

Daily supervisor: Dr. Epke Le Rutte, Swiss TPH

Examiner: Dr. Ganna Rozhnova, UMC Utrecht

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Table of Contents

Summary

Since early 2020, a pandemic is occurring due to Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 can range from an asymptomatic disease to mild, severe or critical respiratory disease, that can lead to death. Certain groups of people in the general population are more at risk of severe disease and death, such as the elderly (60 years and older), people with chronic diseases, and/or obesity, among others. Additionally, SARS-CoV-2 has the capacity of mutating, that is, the ability of altering its characteristics, which can increase its capability to infect people, the severity of the disease, and/or decrease the immune response. All these characteristics point to the importance of implementing transmission control measures, such as social distancing, face-masks, quarantine and isolation, and others. As some of the measures implemented are not sustainable in the long term, parallel to their implementation, vaccinations were also being developed, as well as, prophylactic (i.e., preventive) and antiviral treatments. These measures have the capacity of preventing severe disease, therefore hospitalisation and death, which is very important from a public health perspective. By preventing the need of hospital care, COVID-19 hospitalisation health care related costs could be averted, and the burden on hospital capacity is reduced as a consequence, as well. Thus, it is important to understand what impact prophylactic and antiviral treatments could have for settings with varying levels of vaccination coverage.

This project aims to identify through mathematical modelling, how pre-exposure prophylaxis (PrEP) and antiviral treatments can prevent COVID-19 hospitalisations, in settings with different vaccination and booster coverages. For this purpose, a mathematical model of SARS-CoV-2 transmission was used. Simulations in three main different vaccination coverage settings (high, moderate, and low) were conducted over a one-year period, and two different efficacies of oral antivirals, 30% and 89%, were modelled based on clinical trial results. For an antiviral with 89% efficacy given only to the high-risk group, results show that there were 29%, 32% and 36% less hospitalisations in high, moderate, and low vaccination settings, respectively, when compared to no treatment. If coverage is increased to the total population, there are less 56%, 60%, and 63% hospitalisations for each respective vaccination setting. Averted hospitalisations increase between 1 to 5% if PrEP is also implemented, across all vaccination settings. Costs of vaccination decrease, and costs of hospitalisation increase with decreased vaccination coverage. Across all three vaccination settings, increasing spending on antivirals with higher efficacy (89%) by around 80% to increase antiviral coverage from high-risk group to total population could avert an additional 40% of hospitalisations.

Overall, the projections of the model suggest that both prophylactic and antiviral treatments can be a useful additional public health measures to decrease hospitalisations, and consequently ICU cases and deaths. The preliminary economic analysis conducted, even with some limitations, highlighted the benefit of these treatments to reduce total costs. Additional modelling will be useful to further analyse the benefits and drawbacks of antiviral treatment. Therefore, informing policy makers on the most optimal public health and cost-effective outcome.

Abstract

As a control measure against SARS-CoV-2, vaccinations were developed, as well as, therapeutic and prophylactic treatments. Prophylactic and antiviral treatment has the capacity to prevent severe disease, to avert hospitalisations and possibly related costs. From a public health perspective, it is important to understand what impact prophylactic and antiviral treatments could have for settings with varying levels of vaccination and booster coverage, and different target populations.

A stochastic individual-based transmission model of SARS-CoV-2 infection and COVID-19 disease (OpenCOVID) was used to simulate the introduction of pre-exposure prophylaxis (PrEP) and antiviral treatments in three different vaccination and booster settings, and identify its impact on public health, through averted hospitalisations. Additionally, a preliminary economic analysis was conducted.

Results indicate that across all vaccination settings, the administration of PrEP and antiviral treatment does not greatly impact the incidence of SARS-CoV-2, but is extremely beneficial on a public health perspective, as it leads to an increase in averted hospitalisations. Further benefits are observed if antiviral coverage is increased from high-risk group only to total population. Vaccinations and PrEP costs remain constant. Health service costs increase as vaccination coverage decreases, and an increase in spending on antivirals, especially with higher efficacy, to cover the total population, could avert additional hospitalisations.

These findings suggest that both prophylactic and antiviral treatments can be a useful additional public health measure to decrease hospitalisations, and consequently ICU cases and deaths. However, further research is necessary to analyse at which efficacy antiviral treatment will result in the most cost-effective solution. Thus, informing policy makers on how to optimise the usage of antiviral treatment.

Key-words: SARS-CoV-2, COVID-19, mathematical modelling, economic analysis

1. Introduction

Coronaviruses (CoVs) are RNA viruses with a zoonotic origin that can infect both animals and humans, usually leading to mild respiratory and gastrointestinal disease in humans. In 2002, a novel highly pathogenic virus emerged in China, SARS-CoV-1, causing severe acute respiratory syndrome. Ten years later, in 2012, an outbreak of an additional newly emerged virus, Middle-East respiratory syndrome coronavirus (MERS-CoV), occurred in Saudi Arabia. Presently, the world is facing a pandemic, which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was first detected in Wuhan, China, in December 2019. This virus has its origin most likely due to a zoonotic event (1), and leads to Coronavirus disease 2019 (COVID-19) in humans. At the time of writing, August 2022, COVID-19 continues to pose a challenge to worldwide health (2). All three of these novel coronaviruses denote the importance of CoVs as a public health issue of the 21st century.

COVID-19 is characterised by a development of severe acute respiratory syndrome in humans, with a range of symptoms, which include fever, cough, as well as severe dyspnoea in severe infections. The disease can be asymptomatic or symptomatic, culminating in mild, severe or critical disease, and possibly death (3). It has been reported that certain risk factors, such as, cardiovascular disease, diabetes mellitus, obesity, older age (60 years and older), among others, contribute to the development of severe disease, and increased mortality (3,4).

Additionally, SARS-CoV-2 has mutated several times since the beginning of the pandemic, and new viral variants have emerged and become the dominant strain. All variants have different characteristics regarding their disease severity, infectivity, and immune evading capabilities. The World Health Organization (WHO) and other international institutions have been monitoring SARS-CoV-2 variants since January 2020 (5). The WHO defines Variants of Interest (VOI) as SARS-CoV-2 variants that are recognised as the cause of increase in community transmission or increase in several clusters in multiple countries. These increases are caused by genetic modifications that have altered virus characteristics such as transmissibility, disease severity, and immune, diagnostic or therapeutic escapes. When VOIs further exhibit characteristics of increased transmissibility, virulence, as well as decreased efficacy regarding control measures or available diagnostics, vaccines, and therapeutics, the WHO identifies them as Variants of Concern (VOC). Currently, during the summer months of 2022, there are no circulating VOI, and the only VOC circulating is Omicron (5).

Due to the characteristics of the virus and severity of COVID-19 disease, it became of utmost importance to implement measures to control the high transmission rate occurring at the beginning of the pandemic. As seen in several countries, when an extremely high transmission rate was occurring, a high number of severe and critical patients were being hospitalised,

creating serious disruptions in essential health care services (6). This created a global scale public health concern. Soon after, and before the development of vaccines and treatments, non-pharmaceutical interventions (NPIs) were put in place, and countries adopted several different measures. Generally, these measures included social distancing, hand hygiene, face-masks, curfews, contact tracing, isolation, quarantine of contacts, travel bans, school and business closures, among others. These measures were enforced by entities such as the European Centre for Disease Control (ECDC), country governments, as well as the WHO (7,8). However, these types of measures also created social and economic repercussions that were not sustainable to be maintained for a long period of time (9,10).

Parallel to the adoption of NPIs, vaccination development started. By December 2020, the first vaccine, developed by Pfizer, was authorised by the European Medicines Agency (EMA) (11), as well as the Food and Drug Administration (FDA) of the United States (US) (12). At the time of writing, August 2022, the WHO Emergency Use Listing contains eleven different vaccines (13). Vaccinations have been shown to reduce the risk of infection, severe disease, and consequently hospitalisation. However, it has also been reported that vaccine-induced immunity wanes over time (14,15). Vaccine rollout started at different levels in different countries. At the start of vaccine administration, low-income countries reported a vaccination coverage of around 16% of the first dose, whereas high-income countries reported first-dose coverages of around 80%. In richer countries, healthy adults and younger people have been receiving second doses and subsequent booster doses, while in lower-income countries some high-risk groups have yet to receive the first dose, despite the creation of the COVAX initiative, which was designed to lead to equitable COVID-19 vaccination access (16). Therefore, attaining a much-needed global coverage remains a current issue.

Furthermore, treatments for COVID-19 have also been developed continuously throughout the pandemic. The first available were the symptomatic, therapeutic treatments. These are given in hospital (inpatient treatments) to severely ill patients to relieve symptoms, prevent worsening of the disease, and ultimately prevent death. Examples are corticosteroids, interleukin-6 (IL-6) receptor blockers, and Janus kinase (JAK) inhibitors, as recommended by the WHO (Figure 1) (17). Additionally, antivirals were developed as outpatient treatment for cases of mild symptomatic disease, and to halt and further prevent development of severe disease. Moreover, prophylaxis as also been developed, in particular pre-exposure prophylaxis (PrEP) (Figure 1). PrEP is used to prevent infection and disease when exposure to the pathogen has not yet occurred. Both PrEP and other therapeutic treatments were identified as research priorities by the WHO early in the pandemic (18).

The EMA, FDA, and the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) have authorised one pre-exposure prophylactic treatment called

Evusheld (19–21). Evusheld is a combination of two monoclonal antibodies, tixagevimab and cilgavimab, administered as one dose given under 2 separate intramuscular injections. Under a clinical trial, a primary analysis indicated a relative risk reduction of 77% in RT-PCR positive cases in the treatment group versus the placebo group, and at a 6-month follow-up the reduction was 82.8% (22). Furthermore, the EMA, FDA, and MHRA have similarly authorised three antiviral treatments (Supplementary Table 1). These antiviral medications have shown efficacy in preventing the development of severe disease in people who got infected with COVID-19 and are showing no signs or mild symptoms of disease. These are two treatments in tablet form, called Paxlovid (Nirmatrelvir and ritonavir), and Lagrevio (Molnupiravir), and one intravenous infusion, called Veklury (Remdesivir), with an 89%, 30%, and 87% efficacy, respectively (23–25).

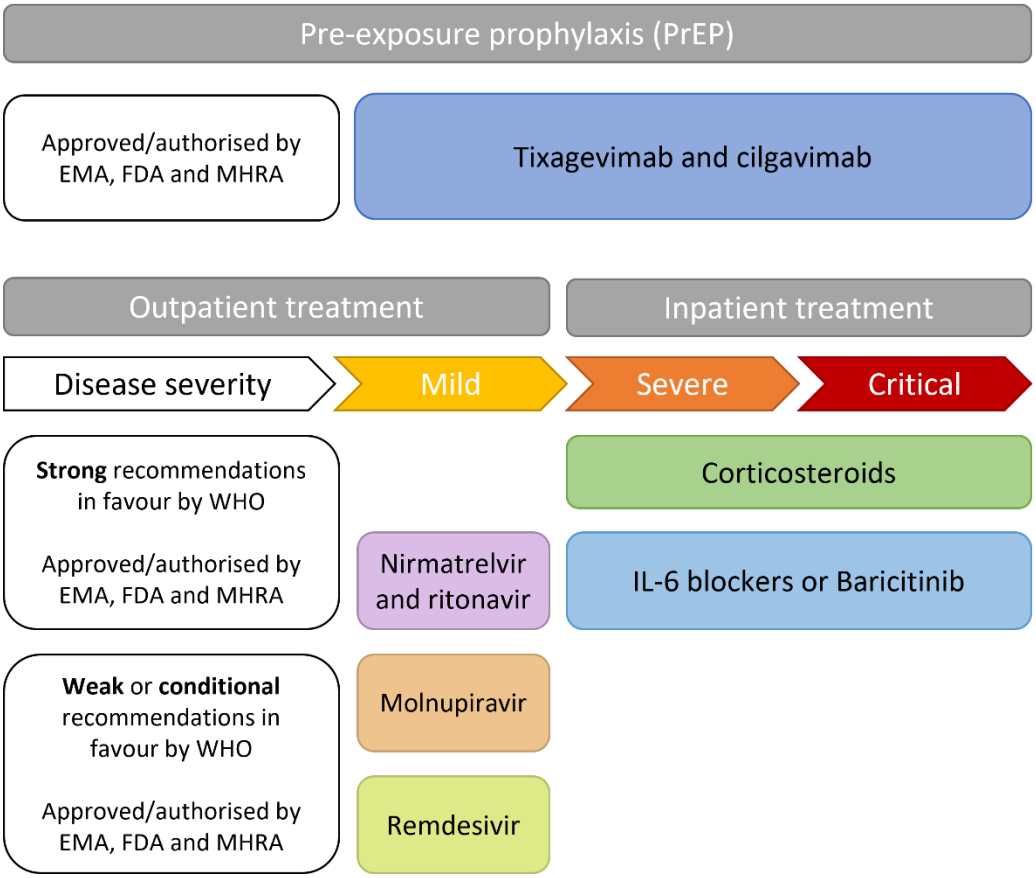

Figure 1 – Visual summary of prophylaxis and treatments for COVID-19, adapted from Agarwal *et al.* (2022) (17)**.** Two types of treatment are illustrated, pre-exposure prophylaxis and therapeutic treatment, which depending on severity of disease symptoms can be classified as outpatient or inpatient. Regarding therapeutic treatments, a further division is made based on WHO recommendations.

Furthermore, the WHO, through the “Living WHO guideline on drugs for COVID-19”, gives updated recommendations on the implementation of treatments for COVID-19. On April 22nd 2022, nirmatrelvir and ritonavir were strongly recommended for patients with mild disease and high hospitalisation risk, based on the analysis of trial data, but not recommended for low-risk patients. Additionally, an update on remdesivir and molnupiravir indicated a weak/conditional recommendation for high-risk patients with mild disease (17). However, once more there is a similar issue occurring with the roll out of treatments, and the WHO has recently made a statement requesting transparency in the process to guarantee drug availability in low- and middle-income countries (26).

Both vaccinations, prophylactic, and antiviral treatments when given at the correct time, have the capacity of reducing the risk of developing severe disease, consequent hospitalisation and death (27,28). From a public health perspective, it is important to avert the progress into severe disease and hospitalisation, which mostly likely occurs in the high-risk population. By preventing the need of hospital care, COVID-19 hospitalisation health care related costs are averted, and the burden on hospital capacity is reduced as a consequence, as well. Thus, it is important to understand the scope of the impact the prophylactic and antiviral treatments could have for settings with varying levels of vaccination coverage. Secondly, there is a knowledge gap regarding the scope of the impact would these or future treatments be made available to larger target populations.

Mathematical modelling is a useful and established tool when studying infectious disease transmission dynamics and guiding public health policy decisions (29). Within a public health scope, and throughout the current pandemic, mathematical models have been used as a support for policy makers in the decision of which control measures to implement (30–32). Additionally, it can also be used for cost-effectiveness analysis, to compare the costs and benefits of different public health measures. Outcomes can help policy makers with choosing the most impactful and cost-effective measure to reduce viral transmission and hospitalisations (33,34).

In the present research project, OpenCOVID, an individual-based model of SARS-CoV-2 transmission developed by the Swiss Tropical and Public Health Institute, will be used to explore the public health impact of different treatment strategies for COVID-19. The longer term public health impact of these treatments at a population level when used alongside vaccines, is not yet known and questions remain. Particularly, with different vaccine coverage between settings, as access to vaccines is not equitable, the impact of prophylactic and antiviral treatments might differ. Consequently, given what is known about these treatments, the goal of this project is to identify through mathematical modelling, how PrEP and antiviral treatments can prevent COVID-19 hospitalisations, in settings with different vaccination

coverages. Therefore, the following research question will be addressed: What is the impact of PrEP and antiviral treatments in preventing COVID-19 related hospitalisations, its associated costs, and how does that differ for settings with different vaccination coverage?

2. Methodology

The current research project was exclusively mathematical modelling based, in which a previously created mathematical transmission model was used to simulate and compare the impact of prophylactic and antiviral COVID-19 treatments. Firstly, a revision of available prophylactic and antiviral treatments against COVID-19 was conducted. The treatment selection was based on approval and/or authorisation by governmental medicine agencies, EMA, FDA and MHRA and recommended by the WHO. Afterwards, a literature search was carried out, in which trials and respective publications were analysed, and model parameter input was collected. Finally, scenarios were created, model simulations were conducted, and model output was analysed.

2.1. Model

The model used in the present project was the OpenCOVID model developed by the Disease Modelling Unit of the Swiss Tropical and Public Health Institute (SwissTPH) (30). The OpenCOVID model source code can be consulted at https://github.com/SwissTPH/OpenCOVID. The model is a stochastic individual-based transmission model of SARS-CoV-2 infection and COVID-19 disease. The model replicates the transmission of the virus through contacts between infectious and susceptible people. The variant simulated is the Omicron variant, and emergence of new VOIs or VOCs are not simulated in this study. A seasonal pattern is included, as seasonality also influences transmission, with less probability of infection during the summer months and higher during the winter months. Following infection, the model depicts a latency period and a pre-symptomatic phase that can lead to asymptomatic infection, and mild or severe disease. From severe disease, individuals can go to hospital, followed by intensive care, and eventually death (Figure 2). Viral load is represented as a function of time since infection (see Supplementary Figure 1). Immunity develops after recovery, and it is assumed that it wanes exponentially over time (Supplementary Figure 4). Initially the model was fitted to the Swiss national-level epidemic data, whereas the current version is setting agnostic, representing a Western/Northern hemisphere transmission setting. The contacts between individuals are characterised by an age-structured network (see Supplementary Figure 2 and 3). Further

details of model development and description can be consulted in the work of Shattock *et al.* (2022), Le Rutte *et al.* (2022), and Kelly *et al.* (2022) (30,35,36).

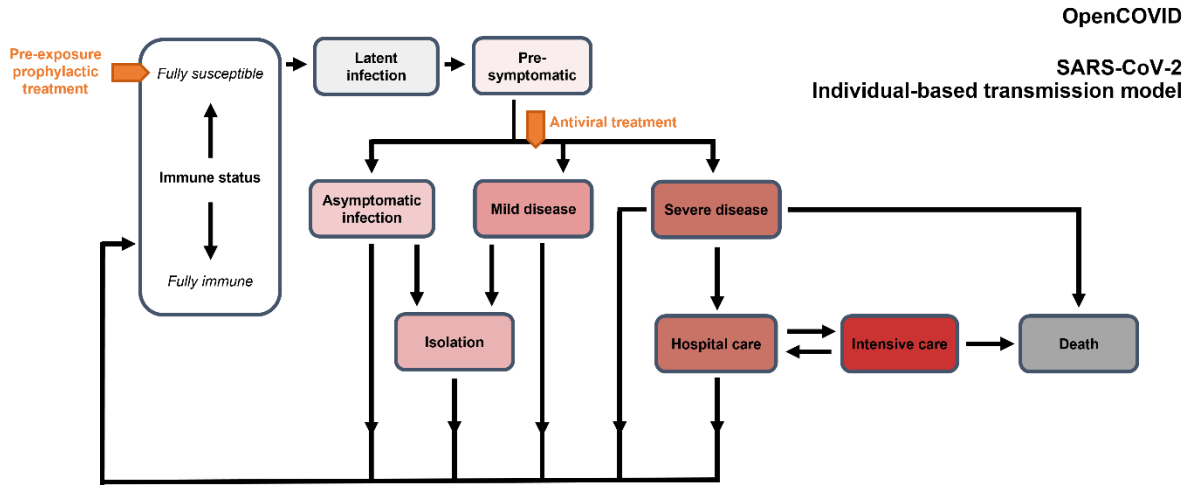

Figure 2 – Simplified flow-chart of OpenCOVID model structure, adapted from Shattock *et al*. (2022) (30)**.** The immune status varies from fully immune to fully susceptible, depending on vaccination status and naturally acquired immunity. From this state, an individual, once infected, goes to the latency period, then pre-symptomatic stage, after which some individuals will remain asymptomatic, others will develop mild or severe disease. Pre-exposure prophylaxis is administered to fully susceptible individuals, whereas antiviral treatment is given after development of mild symptoms, confirmed with a positive COVID-19 PCR test.

2.2. Interventions

In this project, the analyses consisted of simulations of PrEP (tixagevimab and cilgavimab) and oral antivirals (Nirmatrelvir and ritonavir, and Molnupiravir) for COVID-19 treatment, in settings with different COVID-19 vaccination coverage.

2.2.1. Pre-exposure prophylaxis (PrEP)

In the model, PrEP is considered to be a combination of monoclonal antibodies (tixagevimab and cilgavimab), as previously stated, and is available only to about 2% of the total population. This high-risk group eligible to receive PrEP consists of adults and adolescents aged 12 years and older weighing at least 40 kg, who are immunocompromised and therefore cannot receive COVID-19 vaccination, or that would experience adverse reaction to a COVID-19 vaccine (19,21). It is assumed that PrEP averts symptomatic disease. However, an individual can still become infected, and move into the asymptomatic infection compartment (Figure 2). Currently, the transmission blocking effect of PrEP is not yet known, and thus also not implemented in the model. Following administration of PrEP, its efficacy has an exponential

decay, starting at around 90%, reducing to 70% around 6 months post rollout, based on clinical trial results (22) (Supplementary Figure 4). Only one PrEP dose is implemented in the model, and an assumption of high coverage (98%) is made, because it is expected that individuals who cannot receive a vaccine and are at high-risk of developing severe COVID-19 disease are willing to receive a preventive medication, as these individuals are still often in isolation.

2.2.2. Oral antiviral treatments

As mentioned previously, three antiviral treatments have been authorised, but in the current project the focus is on the two oral antivirals available (Nirmatrelvir and ritonavir, and Molnupiravir). These treatments are aimed at those who have developed mild disease and tested positive for SARS-CoV-2, to prevent them from progressing into severe disease, and consequently hospitalisation (Figure 2). Additionally, both treatments need to be administered within 5 days of symptom onset (Supplementary Table 1). The high-risk group eligible to receive oral antivirals is adults older than 18 years of age with co-morbidities and/or adults over the age of 65, who are considered being at a higher risk of developing severe disease (17). Efficacy of antivirals is fixed in the model, based on clinical trial results. It is 89% for Nirmatrelvir and ritonavir, and 30% for Molnupiravir (23,24). These efficacy numbers are based on studies performed on unvaccinated high-risk individuals, here it is assumed that the efficacy remains similar when administered to those at low-risk and/or that are vaccinated. Antiviral coverage is assumed to be 75% for the high-risk group, and also for the low-risk group when expanded to the rest of the population. In the model, a 3-day delay from onset of symptoms to diagnosis is considered, as well as a delay from diagnosis to start of treatment of 2 days.

2.2.3. Vaccinations and boosters

Apart from treatment, vaccinations (both primary course and boosters) were also implemented in the model. The vaccines included in the model are mRNA vaccines. These have the capability of preventing new infections by developing immunity, as well as, protecting against progression into severe disease following infection, therefore reducing hospitalisation rate, ICU admissions, and deaths. After vaccination, it is assumed that there is still a probability of viral transmission if an individual is infected.

The considered individuals eligible to receive a vaccine range from fully susceptible, partially susceptible, as well as infected people who are not hospitalised. Primary vaccination is administered in two doses, with an interval of 28 days between doses. Roll-out starts in

December 2020 for high-risk group (older than 65 years of age and/or concurrent co-morbidities), and March 2021 for the low-risk individuals (18 to 64 years of age).

The same individuals who received the primary course are eligible to receive a booster dose. The equivalent priority groups are considered, high-risk individuals receive a third dose six months after the primary course, and individuals from low-risk group receive a booster once a year. It is considered that booster roll-out started in December 2021 and January 2022, respectively for high- and low-risk individuals.

The immunity conferred by vaccines wanes over time, and its implementation in the model has been previously described by Kelly *et al.* (2022) (36). To summarise, the induced immunity by vaccination wanes exponentially, with an immediate peak at 85%, and a reduction to 15% with a half-life of 105 days (see Supplementary Figure 4). Vaccine efficacy is considered to be 85%, of which 80% refers to transmission blocking properties.

2.3. Model initialisation

Simulations were considered to be somewhat representative of a general European setting, starting in December 2020, when the first vaccination rollout started. The simulations were run with a population size of 100 000 individuals. Between December 2020 up to June 2021, it is considered in the model that 30% of the population had been previously infected based on case data for the European Union (37). Simulations started in December 2020, up to June 2022 (day zero), continuing for another year until June 2023, concluding a total simulation time of 915 days (≈ 2,5 years).

An assumed effective reproduction number of 0.8 was used to represent the beginning of summer in the northern hemisphere, and exemplify the seasonality. In Supplementary Figure 5, the seasonality pattern can be observed for the whole year of simulation starting on day zero. No NPIs were considered in the future simulations, as currently most of these measures are not being implemented.

2.4. Analyses and Scenarios

Different scenarios were modelled to understand the impact of PrEP and oral antivirals, representing different vaccination and booster coverage settings, which will be referred only as vaccination coverage (Table 1). Three different coverages are considered, low, moderate, and high, based on data from European Centre for Disease Control (ECDC) in June 2022. These three levels align with vaccination coverages in Bulgaria, Slovakia, and Portugal,

respectively (38) (Table 1). A different vaccination coverage results in a different proportion of the population being susceptible to infection (Figure 3).

The baseline scenario does not include any prophylactic or antiviral treatment. For the three main scenarios, sub-scenarios were simulated, in which two antiviral efficacies are modelled, then two target populations are considered for each. Finally, the absence and presence of PrEP is simulated as well. To replicate chance in transmission dynamics, 20 stochastic simulations were implemented per scenario.

Table 1 – Main scenarios simulated in the current project. Baseline scenario only includes vaccination and boosters, and no prophylactic or antiviral treatments. The three main scenarios corresponding to different vaccination settings are then subdivided into sub-scenarios, in which two oral antivirals are simulated in two different target populations, including or excluding PrEP. This results in nine sub-scenarios for each vaccination setting.

Scenario	Primary vaccination coverage	Booster vaccination probability	Antiviral treatments	Target population antivirals	Pre-exposure prophylaxis (PrEP)
1	Low: High-risk 0.4 Low-risk 0.35	High-risk 0.6 Low-risk 0.4	Nirmatrelvir and ritonavir Efficacy 0.89 Coverage 0.75 Molnupiravir Efficacy 0.30 Coverage 0.75	**a) Only high-risk vaccinated and unvaccinated** groups receive antivirals b) **High- and low-risk vaccinated and unvaccinated** groups receive antivirals	c) **Without** PrEP d) **With** PrEP
2	Moderate: High-risk 0.75 Low-risk 0.6	High-risk 0.8 Low-risk 0.6			
3	High: High-risk 0.99 Low-risk 0.95	High-risk 0.95 Low-risk 0.85			
Baseline	Same as alternative scenarios	Same as alternative scenarios	None	Not applicable	None

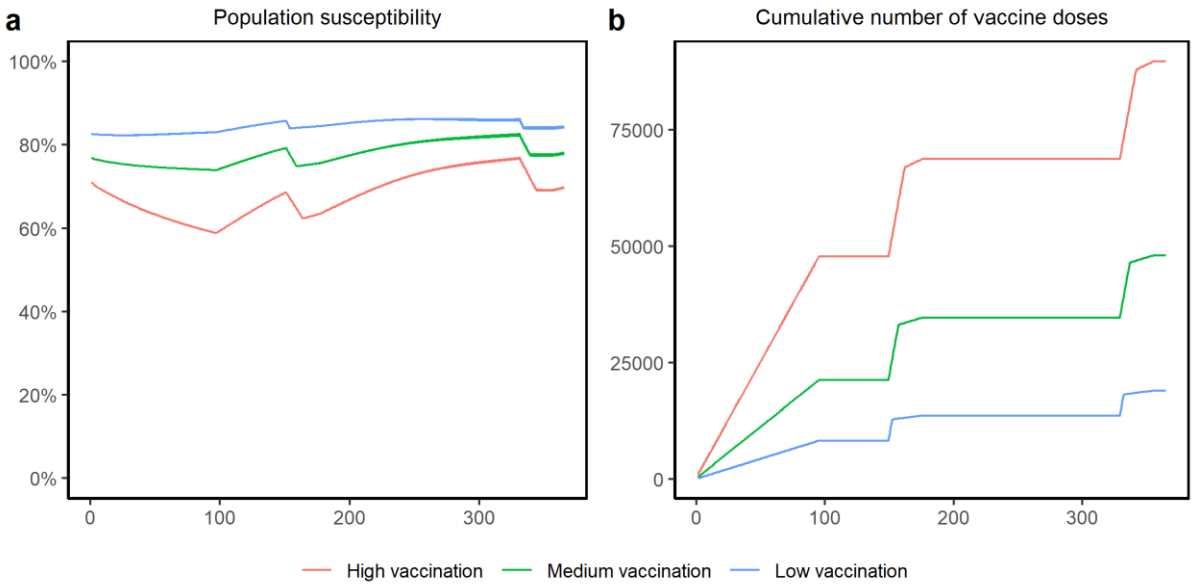

Figure 3 – Characteristics of the three different vaccination coverage settings simulated. (a) Susceptibility of the population across one year simulation, and (b) the cumulative number of vaccine doses given in one year simulation.

2.1. Economic analysis

A simple economic analysis was undertaken to better understand the possible economic benefits and drawbacks of prophylactic and antiviral treatment. A comparison between treatment and hospitalisation costs was performed, based on number of hospitalisations averted (number of hospitalisations in the baseline scenario minus number of hospitalisations with antivirals and PrEP).

PrEP with the combination of tixagevimab and cilgavimab is completed with two consecutive intramuscular injections. Currently, this monoclonal antibody seems to be priced at 1000 United States Dollars (USD) per dose (39). For antivirals, the number of doses included in a nirmatrelvir and ritonavir treatment course is in total 30 tablets (3 tablets twice a day for 5 days), with a total cost of USD 530. For molnupiravir, a total of 40 tablets is required (4 tablets twice a day for 5 days), with a total cost of USD 700 (40). Original costs are illustrated in USD as no cost/price was found for the European Union. These were converted in euros (EUR) using the exchange rate (as of August 1st, 2022) of 0.98 for USD. Therefore, the final price used was EUR 975, EUR 517, EUR 683, for tixagevimab and cilgavimab (PrEP), nirmatrelvir and ritonavir (antiviral 89% effective), and molnupiravir (antiviral 30% effective), respectively.

Hospitalisation costs were based on a health care cost model by Czernichow *et al.* (2021) (41). The authors used data of health costs from Denmark, France, Spain and the UK in publicly funded hospitals, then modelled it based on Body Mass Index (BMI) during the first

half of 2020. The average hospitalisation cost per day was EUR 883, and ICU cost was EUR 1925 (41). The duration of hospitalisation in the work of Czernichow *et al.* was estimated at an average of 13 days based on the report from Moriconi *et al.* (2020) (42), and these references are similar to other reports of 11 days (43), 10 days during the first wave, and 15 during second/third wave (44). Therefore, in the present project, based on the references above, the rounded final cost per hospitalisation was EUR 11,500, and for ICU was EUR 25,000. Lastly, vaccination price was set to EUR 20 (45). In this economic analysis, other costs such as lost productivity due to disease, as well as, the logistics of vaccination implementation (facilities, distribution, medical staff), were not included.

3. Results

The usage of two different antiviral treatments with two distinct efficacies, as well as the administration of PrEP, was explored for three different vaccination coverage settings. Future disease transmission dynamics were simulated with a start in June 2022, and followed through for one full year. Omicron was the variant considered, and no other variants or new variants were simulated or introduced. The initial effective reproduction number considered was 0.8, and no NPIs were included in the simulation.

In the three vaccination coverages considered, a peak in number of SARS-CoV-2 infections can be observed in the winter months of the year, with lower numbers in the warmer months of the year. With decreasing vaccination coverage, an increase in number of infections can be observed. The same situation occurs for number of cases in hospital and ICU, with a lower number of cases when the vaccination coverage is higher. Number of infections is not majorly impacted by antiviral treatment between each scenario with different antiviral efficacy, as these treatments are given after an individual becomes infected. Additionally, shortening the duration of infection will not largely impact the infectiousness of the individual, and in spite of a small impact on transmission, it is not visibly reflected in the figures. Furthermore, only a small proportion of the population receives PrEP (2% of the total population), which once more does not greatly impact incidence, as observed in Figure 4 (and Supplementary Figures 6 and 7).

Not giving any treatment produces the highest number of cases in hospital and ICU, across all vaccination coverage settings. Comparing between vaccination coverage settings, in the peak, with no treatment, there are approximately 15, 35 and 55 daily cases in hospital in high, moderate, and low vaccination coverage settings, respectively (Figure 4, Supplementary Figures 6 and 7). As can be observed in Figure 4, in a high vaccination coverage setting,

number of cases in hospital and ICU in the peak, decreases with the introduction of antiviral treatment and PrEP. Antiviral treatment with 30% efficacy given only to the high-risk group yields a higher number of cases in hospital and ICU compared to increasing coverage to the total population, and increasing efficacy to 89%. In contrast, antiviral treatment with 89% efficacy given to the total population results in the highest decrease in hospital and ICU cases compared to 30% efficacy, and administering antiviral treatment to high-risk group only. This can be similarly observed for moderate and low vaccination coverage settings (Supplementary figures 6 and 7).

The number of antiviral treatments administered also fluctuates proportionally to the number of infections and cases. In addition, this number is lower when antivirals are given to the high-risk group only (Figure 4, Supplementary Figures 6 and 7).

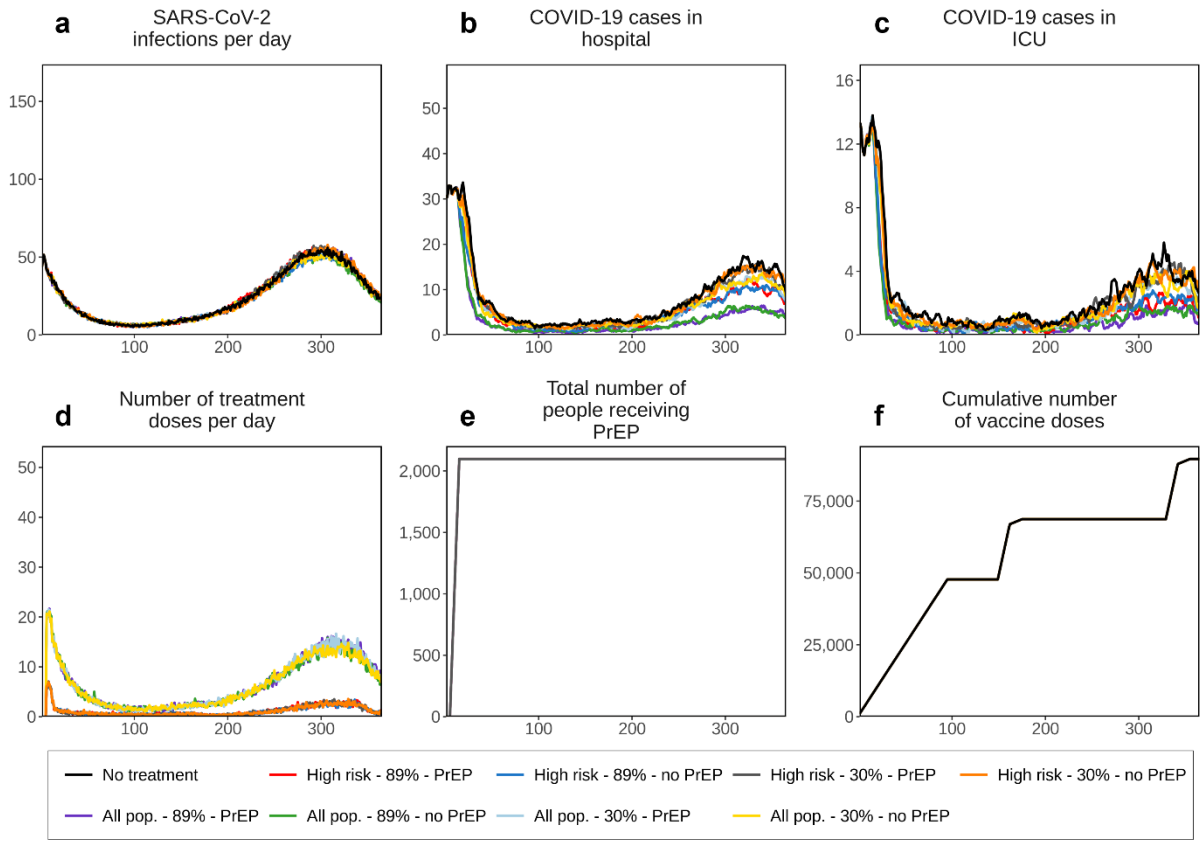

Figure 4 – **Projected epidemiological characteristics (top row) and number of treatment and vaccination doses given (bottom row) in the high vaccination coverage setting over 1-year simulation.** (a) Number of daily SARS-CoV-2 infections, (b) number of COVID-19 cases in hospital, (c) number of COVID-19 cases in ICU, (d) number of antiviral treatment doses given per day, (e) cumulative number of PrEP doses given , and (f) cumulative number of vaccine doses given. Results of the moderate and low vaccination coverage settings are provided in Supplementary Figures 6 and 7.

As the goal of antiviral treatment is to prevent severe disease and hospitalisations, looking at the averted hospitalisations is a good public health measure to analyse its effectiveness. Figure 5 shows the proportion of averted hospitalisations when compared to not giving any treatment, across all three vaccination coverage settings. It can be observed that administering antivirals always results in averted hospitalisations in all three settings.

Antivirals with a lower efficacy (efficacy of 30%) only avert between 8% and 23% hospitalisations, if given only to high-risk and total population, respectively, when compared to the baseline of no treatment. Whereas, an antiviral treatment with an efficacy of 89% averts between 28% if given to high-risk group, to 63% hospitalisations if given to the whole population, when compared to no treatment. For antiviral treatment with 30% efficacy, there is between 4 to 12% increase in averted hospitalisations when coverage increases from high-risk group only to total population. If antiviral efficacy is 89%, then averted hospitalisations increase between 25 to 29% with an increased coverage to the total population.

The current situation, which is antiviral treatment with 89% efficacy given to the high-risk group, with administration of PrEP, leads to 29%, 32%, and 36% reduction in hospitalisations in high, moderate, and low vaccination coverage settings, respectively. Including the total population averts 56%, 60%, and 63% of hospitalisations in each vaccination setting, compared to not giving treatment. Similar reductions in hospitalisations can be observed if PrEP is not included. When PrEP is administered, there is between 1 to 5% increase in averted hospitalisations when compared to not giving PrEP (Figure 5).

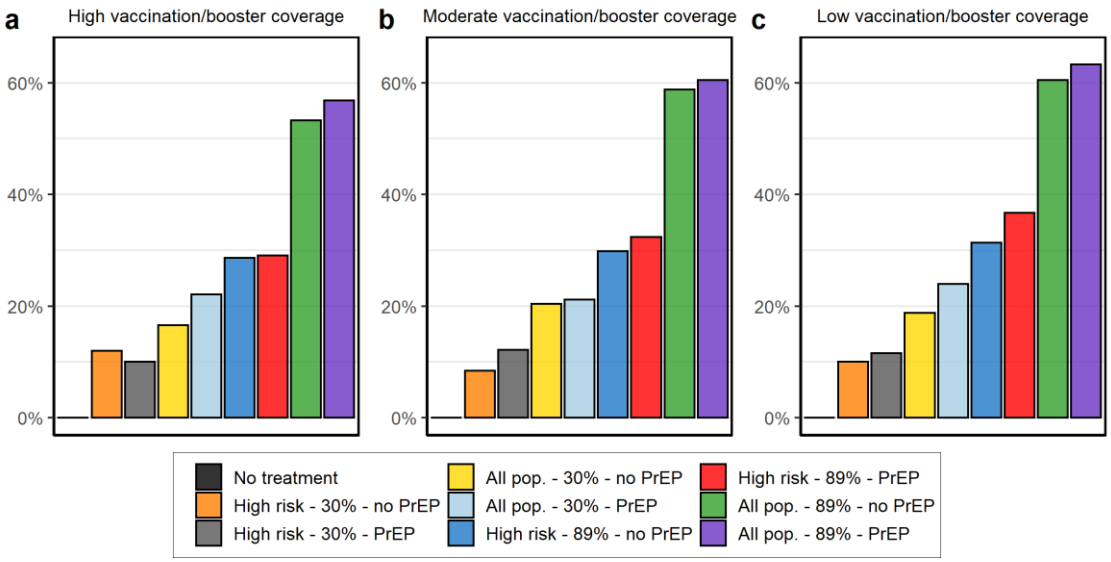

Figure 5 – Total of hospitalisations averted for each scenario with a 30% or a 89% antiviral efficacy given to the high-risk group or whole population, with or without PrEP, relative to the no treatment scenario. (a) High vaccination/booster coverage setting, (b) moderate vaccination/booster setting, and (c) low vaccination/booster setting.

The costs of vaccination and PrEP are constant in the population within each vaccination setting. Vaccination costs however decrease with decreased vaccination coverages. In contrary, ICU and hospitalisation costs increase with decreased vaccination coverage (Figure 6).

Overall, giving antiviral treatment with 89% efficacy to the whole population results in approximately 10% decreased total costs when compared to only giving antiviral treatment with 89% efficacy to the high-risk group. However, regarding antivirals with 30% efficacy, an opposite effect can be observed: the costs increase by approximately 11% when administering antivirals to the whole population, instead of high-risk group only. This same effect is observed for both scenarios with or without PrEP, across all vaccination settings. Within all vaccination settings, the investment of providing an antiviral with 89% efficacy to the high-risk group, and PrEP to those eligible, which is the current practiced situation, results in lower total costs compared to the same situation without antivirals and PrEP (baseline of no treatment), because of the reduction in hospitalisations and ICU costs.

The most cost-effective scenario identified in this analysis is administering antiviral treatment with 89% efficacy to the whole population. Extending antiviral treatment beyond the high-risk groups to total population resulted in 30%, 38% and 42% costs averted compared to no treatment, in high, moderate, and low vaccination coverage settings, respectively. With the provision of PrEP, and giving antiviral treatment with 89% efficacy to the total population, costs averted decrease to 17%, 27%, and 36% in high, moderate, and low vaccination coverage settings, respectively, when compared to the baseline of no treatment (Figure 7). However, when analysing spending and averted hospitalisations, the benefit of PrEP can be highlighted. In a high vaccination coverage setting, increasing spending on antiviral treatment with higher efficacy (89%) by 84% to increase the coverage from high-risk group to total population could avert an additional 34% of hospitalisations, leading to a reduction in total costs of 15%. Additionally, an increase of 83% in the costs of antiviral treatment (89% efficacy) in the same setting with PrEP, to increase the coverage to the total population, could avert an extra 39% hospitalisations, leading to a reduction of 8% in total costs. Regarding antiviral treatment with lower efficacy (30%), costs increase by 85% when given to the total population to possibly avert 5% of hospitalisations. A similar increase in costs adding PrEP leads to 13% additional hospitalisations averted.

A similar trend is observed for moderate and low vaccination settings, in which increasing the spending on antiviral treatment by 80%, on average, to increase antiviral treatment coverage from high-risk group to total population, with higher and lower efficacy, including or excluding PrEP, leads to an average of 10% less hospitalisations with antiviral with 30% efficacy, and 40% less with antiviral with 89% efficacy.

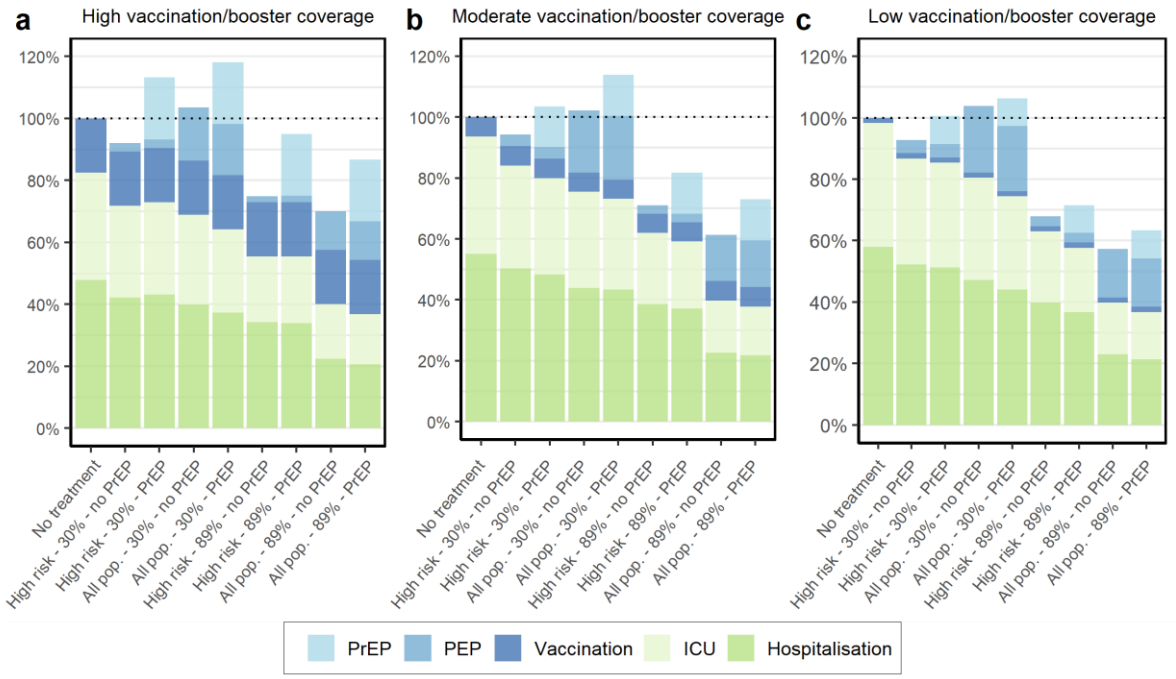

Figure 6 – Total costs stacked by type of cost for each scenario with a 30% or a 89% antiviral efficacy given to the high-risk group or whole population, with or without PrEP, compared to the no treatment scenario. (a) High vaccination/booster coverage setting, (b) moderate vaccination/booster setting, and (c) low vaccination/booster setting. Blue colours represent PrEP, treatment and vaccination costs, and green colours represent ICU and hospitalisation costs. The black dotted line represents 100% costs which correspond to the baseline scenario with no treatment.

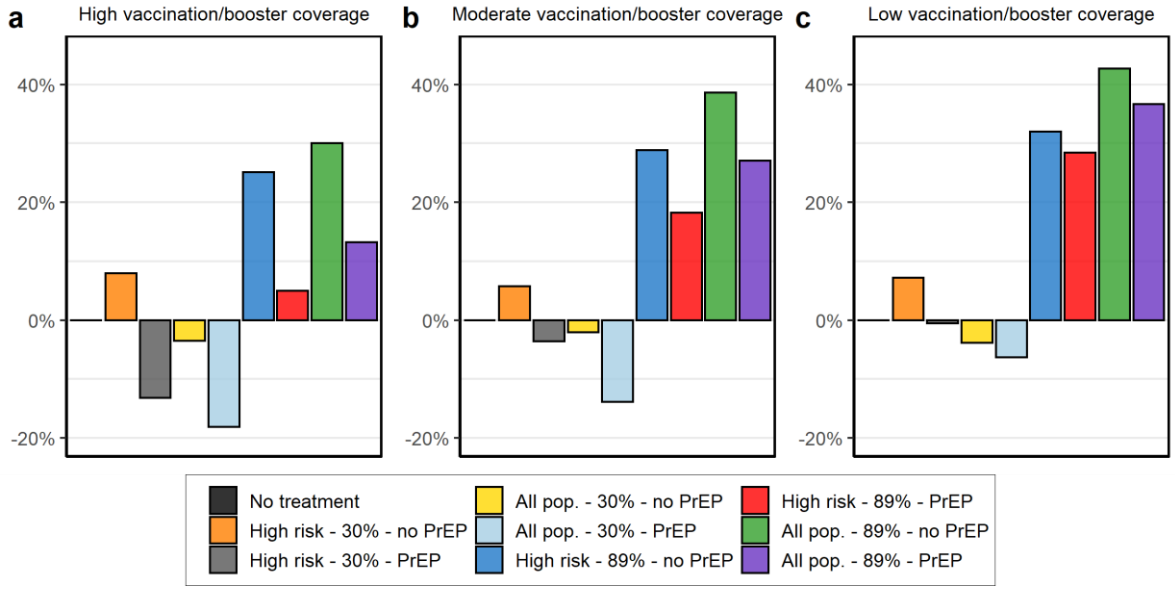

Figure 7 – Total of costs averted for each scenario with a 30% or a 89% PEP efficacy given to the high-risk group or whole population, with or without PrEP, compared to the no treatment scenario. (a) High vaccination/booster coverage setting, (b) moderate vaccination/booster setting, and (c) low vaccination/booster setting.

In a high vaccination coverage setting, when antiviral treatment with an 89% efficacy is given to the total population, and PrEP is administered as well, there is approximately a 20% increase in total costs, but 7% less hospitalisations, compared to not administering PrEP. If antiviral treatment (89% efficacy) is only given to high-risk group, then there is a similar increase in costs if PrEP is also administered, but only 0.6% less hospitalisations compared to no PrEP. In the scenarios in which antiviral treatment has a 30% efficacy and PrEP is given, for high-risk group only there are 18% more costs and no averted hospitalisations, and for total population the costs increase in 12%, and there are 6% less hospitalisations, when comparing to no PrEP. Overall, in moderate and low vaccination coverage settings, in scenarios in which PrEP is included, the same effect of increased costs and lower hospitalisations is observed.

4. Discussion

The present research project, which uses OpenCOVID, an individual-based mathematical transmission model, simulated the introduction of pre-exposure prophylactic treatment (PrEP) and two oral antivirals in three different vaccination settings. Additionally, a preliminary economic analysis was conducted.

The two distinct treatments have different effects, PrEP, a combination of monoclonal antibodies, reduces the probability of infection, and this effect wanes over time. Antiviral treatments reduce the individual's viral load, and therefore reduces the probability of an individual developing severe symptoms and being hospitalised. Among all three vaccination settings modelled in the project, both PrEP and antiviral treatment did not greatly impact the incidence of SARS-CoV-2 when compared to the scenario in which no treatment was given, as expected. Because PrEP only covers 2% of total population in the simulation, therefore even if efficacy is assumed to be high, coverage in total population remains low, as it is only given to a very specific target group within the total population. Furthermore, antiviral treatment is only given after testing positive with SARS-CoV-2. Additionally, it reduces viral load, leading to a shorter infection duration, but only having a small impact on transmission. Therefore, not greatly influencing the incidence of new SARS-CoV-2, and mostly preventing hospitalisations. As expected, the incidence of SARS-CoV-2 increases with decreased vaccination and booster coverage. Therefore, it is important to reach higher vaccination coverage across all target groups.

Since PrEP and antiviral treatments have been authorised, it is important to remark that a scenario in which no treatment is administrated, and only vaccinations and boosters are being

implemented, is never preferred nor ethical. However, this scenario is still representative of many countries in the world where these treatments have not been authorised yet, or where there is inequitable access to them. The pharmaceutical companies that manufacture both antiviral treatments recommended by the WHO, and simulated here, molnupiravir, and nirmatrelvir and ritonavir, together with the Medicines Patent Pool, have signed agreements with 27 and 35 generic companies to produce and supply the treatments to low- and middle-income countries (LMICs) (46,47). This is a step forward in the control of COVID-19, as LMICs would benefit immensely due to the low vaccination coverages observed in these regions. Contrarily, mainly in a Western World setting, PrEP is currently being rolled out, and antiviral treatment with an 89% efficacy is made available to high-risk groups, as referred in the methods.

From the model projections, it is clear that adding antiviral treatments to vaccination as an additional public health measure results in lower hospitalisations, and averts total costs spent. It was observed that an antiviral treatment with higher efficacy leads to less hospitalisations than a lower efficacy, as expected. Also, increasing coverage to include total population results in further hospitalisations averted. The proportion of hospitalisations averted with the introduction of antivirals increases to some extent with decreasing vaccination coverage. Thus, antivirals are even more impactful in reducing hospitalisations in low vaccination coverage settings. However, antiviral treatment should never be a substitute for vaccines, but used as an additional measure, as vaccinations have shown a substantial reduction in COVID-19 severe cases and deaths. Therefore, it is very important to achieve vaccine equity, and increase global vaccination coverage to curb the pandemic (48).

The introduction of antiviral treatment has shown to avert total costs (cost of interventions plus healthcare costs). Increasing the coverage of antivirals from the current high-risk group to the total population results in less hospitalisations, and a reduction in total costs, in all vaccination coverage settings. An antiviral with 89% efficacy resulted in less hospitalisations, and less costs, when compared to a treatment with a lower efficacy, as expected. A study carried out in Korea also reported a public health and cost benefit from using antiviral treatment. Administering antiviral treatment with 87% efficacy to the total population resulted in 80% reduction in hospital cases, and 17% less hospitalisations if given only to the elderly population. A treatment with 30% efficacy led to 25% and 4% reduction, if given to total population, and elderly population, respectively. Regarding costs, authors reported that the higher efficacy antiviral treatment was more cost-effective than lower efficacy antiviral treatment (49). Higher treatment efficacy clearly resulted in better outcomes, however, it is arguable that the lower efficacy treatment should not be completely discarded as it still yields benefits relative to no treatments. As demands of production and distribution of antivirals

increase worldwide, it could be beneficial to use a lower efficacy treatment, when a higher efficacy treatment is not available.

Similarly, as with the antiviral treatments, the introduction of PrEP as an additional public health measure also averts hospitalisations, even though the total costs increase, this measure has many benefits. In this preliminary economic analysis, PrEP is not a cost-effective measure. However, there is a reduction of symptomatic disease, and thus also severe disease, averting hospitalisations. This was observed in the model outcome, as introduction of PrEP resulted in less hospitalisations in comparison to a scenario without PrEP. Therefore, even if costs increase, it is important to provide PrEP to the part of the population at need. The treatment that is currently authorised for SARS-CoV-2 PrEP usage is more expensive than antiviral treatment, and takes two consecutive intramuscular injections as one dose. In the simulations, these additional costs of administration, delivery, shipping and any potential wastage of the treatments were not included, which most likely will increase even further the cost of PrEP. However, PrEP is still a very beneficial measure on an individual level, besides its health impact at population level. As it is targeted at immunocompromised individuals to whom vaccination is not recommended, it can allow these people to re-join societal life, and consequently ease any potential mental health repercussions derived of isolation, in which many still remain. Furthermore, it has been reported that immunocompromised people (e.g., transplant patients, untreated or uncontrolled HIV patients) have a higher risk of prolonged SARS-CoV-2 infection, which has been shown to enable the emergence of new viral variants (50,51). Therefore, and of extreme public health importance, PrEP could potentially reduce the arrival of new variants.

This modelling project obtained a preliminary idea of the impact of prophylactic and antiviral treatment for COVID-19 in averting hospitalisations, and related costs. Nonetheless, several limitations can be reported. The model was calibrated for a general western European setting, and was not country specific, which might not fully represent the epidemiological characteristics of individual countries in the continent. The same aspect applies to health service costs, and targeted costs. The costs for the two oral antiviral treatments were based on publicly available information. These same costs have been recently evaluated by the US Institute for Clinical and Economic Review (ICER), and were considered reasonable. However, some differences between markets can arise due to confidential pricing agreements between manufacturers and individual countries (52). An average for health service costs was used based on reported literature; however, hospitalisation and ICU costs may vary between countries, which could most likely result in differences of averted costs between countries. Additionally, certain costs, such as additional costs of administration, delivery, shipping and

wastage of the treatments and vaccines were not included in these analyses. By including these the economic analysis could be improved.

The introduction of new variants was not considered over the simulation period of 2.5 years. As seen through the pandemic, new variants have emerged approximately every 6-7 months (5). The emergence of new immune escaping variants could change the efficacy of both PrEP and antiviral treatment. Matrajt *et al.* (2022) simulated antiviral treatment in a scenario with a variant with high viral transmissibility and a low vaccine effectiveness, reporting a reduced impact of the treatments on transmission (53). Therefore, modelling the impact of these treatments with introduction of new variants could provide more realistic insights.

Long COVID was not considered in the model, but modelling this clinical outcome could be of interest. Long COVID is characterised by prolonged symptoms, which can include among others fatigue, breathlessness, and cognitive dysfunction (54). The effect of antivirals on long COVID is not yet known. If these treatments could be effective in reducing the chance of developing long COVID, this could support the increase in coverage of antivirals to the whole population, not only from a public health perspective, but also from a cost-effectiveness standpoint.

Recently, there have been reports of disease rebound after finishing antiviral treatment, particularly in high-risk patients (55,56). It was reported that both available oral antiviral treatments led to similar rebound rates (55). However, rebound causes are still not fully known, therefore further investigation is needed (55,56). When more data become available, this phenomenon could be considered in future modelling work to analyse the benefits of these treatments.

The indication for the two oral antiviral treatments modelled in the present project is that it should be administered within five days of symptom onset. Additionally, through modelling, it has been recently reported that early treatment is necessary to better control transmission (53). In the current model, a two-day delay from diagnosis to start of treatment was considered. However, a longer delay in treatment administration could possibly have a different effect on viral load, transmission, and the probability of developing severe symptoms, which could potentially lead to more hospitalisations.

Lastly, efficacies of antiviral treatment were based on clinical trial results, and not on real world effectiveness, and a sensitivity analysis was not conducted in the present project. Additionally, only two antiviral treatment efficacies on two extreme ends were simulated. Adherence to treatment in both high-risk and low-risk groups was not considered, as well as, different treatment coverage rates in both groups. Consequently, as a following modelling work, a sensitivity analysis with a range of antiviral treatment efficacies would be extremely valuable,

along with a range for adherence to treatment, and varied treatment coverage rates, analysing what would the most optimal and realistic outcome be. Additionally, in the present work, an average cost for treatments, vaccinations, and health services was used, and as costs may vary between different settings, it is important to carry out a sensitivity analysis with a range of costs, for a better applicability of results.

5. Conclusion

The results in the present project suggest that both prophylactic and antiviral treatments can be useful additional public health measures to decrease hospitalisations, and consequently ICU cases and deaths. Overall, PrEP and antiviral treatments prevent more COVID-19 related hospitalisations, and avert its associated costs, when compared with a scenario with no treatment, within all vaccination coverage settings. These treatments are to some extent more impactful, with more averted hospitalisations and costs, in a low vaccination coverage setting. Additionally, across all vaccination coverage settings there is an added benefit of adding PrEP, with further hospitalisations being averted. Both treatments can be a useful tool to prevent the overburdened health care systems around the world. Nonetheless, it is still of utmost importance to increase COVID-19 vaccination coverage.

As a preliminary analysis, this project showed a cost benefit of highly effective antiviral treatment. It is important to carry out a more in-depth analysis to understand at which efficacy antiviral treatment will result in the most cost-effective solution. As more results from real world application of these treatments appear, mathematical modelling will be a valuable tool to explore its benefits and drawbacks. Furthermore, models can help identify the optimal target product profile (TPP) for COVID-19 antiviral treatments. Thus, informing policy makers on how to best implement antivirals that lead to the most optimal public health and cost-effective outcome.

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Supplementary Material

MSc One Health

Minor Research Project (Research Profile)

The impact of prophylactic and antiviral treatments for COVID-19: a modelling study

Inês da Silva Soleiro Nunes Marcelino

Student nr. 9983759

Daily supervisor: Dr. Epke Le Rutte, Swiss TPH

Examiner: Dr. Ganna Rozhnova, UMC Utrecht

Utrecht

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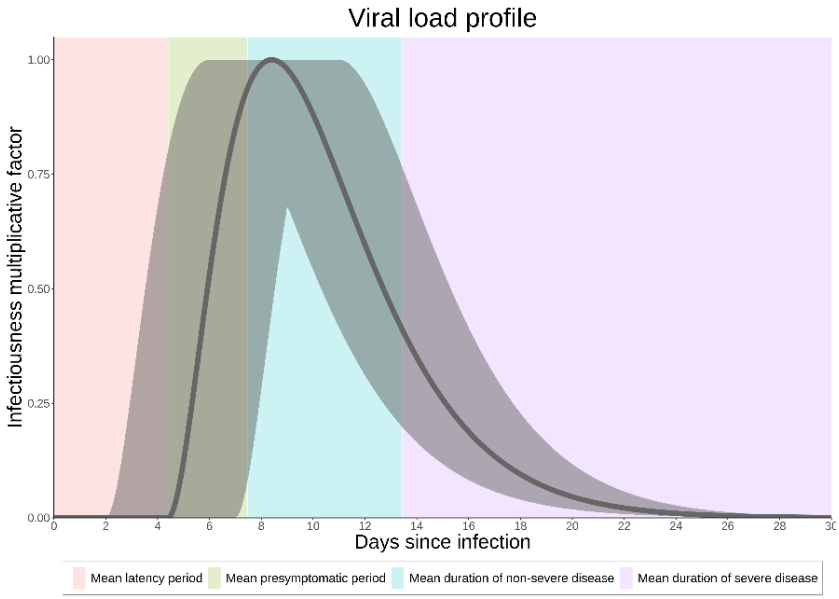
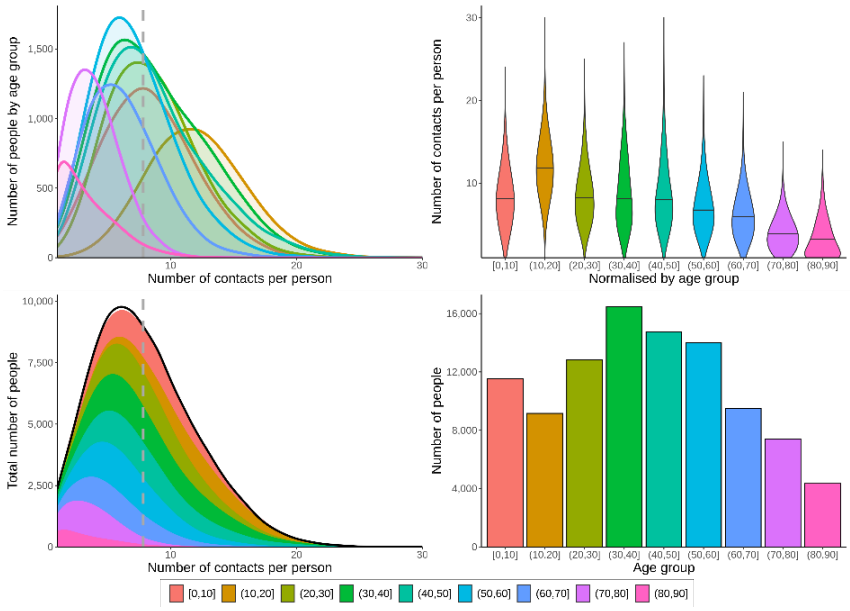
Supplementary Table 1– Overview of authorised and/or approved prophylactic treatments for Covid-19.

Commercial name	**Evusheld**	**Paxlovid**	**Lagrevio**	**Veklury**
Active substance	Tixagevimab and cilgavimab	Nirmatrelvir and ritonavir	Molnupiravir	Remdesivir
Medication class	Monoclonal antibody	Antiviral	Antiviral	Antiviral
Prophylaxis type	Pre-exposure	n/a	n/a	n/a
Manufactured by	AstraZeneca	Pfizer	Merck Sharp & Dohme	Gilead Sciences
Authorisation and/or approval	FDA, US: authorised Dec 8th 2021 (19) MHRA, UK: approved Mar 17th 2022 (20) EMA, EU: authorised Mar 24th 2022 (21)	FDA, US: authorised Dec 22nd 2021 (57) MHRA, UK: approved Dec 31st 2021 (58) EMA, EU: authorized Jan 28th 2022 (59)	MHRA, UK: approved Nov 4th 2021 (60) FDA, US: authorised Dec 23rd 2021 (61) EMA, EU: still under revision (62)	MHRA, UK: approved May 26st 2020 (63) EMA, EU: authorised Jul 3rd 2020 (64) FDA, US: approved Oct 22nd 2020 (65)
Trial Phase	Phase 3	Phase 2/3	Phase 3	Phase 3
Study population	High-risk of inadequate response to vaccination or exposure to SARS-CoV-2	Non-hospitalised unvaccinated high-risk patients		
Type of medication	Intramuscular injection	Oral tablets	Oral tablets	Intravenous infusion
Dosing	Two consecutive injections (150mg tixagevimab + 150mg cilgavimab)	Three tablets (150mg nirmatrelvir + 100g ritonavir), every 12 hours for 5 days, within 5 days of symptom onset	Four 200mg capsules, every 12 hours for 5 days, within 5 days of symptom onset	200mg on day 1 100mg on days 2 and 3, as early as possible in the course of disease
Overall efficacy reported in trial	77% risk reduction of development of symptomatic Covid-19	89% risk reduction of Covid-19 related hospitalisation by day 28	30% risk reduction of Covid-19 related hospitalisation by day 29	87% risk reduction of Covid-19 related hospitalisation by day 28
Trial reference (clinicaltrials.gov)	NCT04625725 (66)	NCT04960202 (67)	NCT04575597 (68)	NCT04501952 (69)
Publication reference	Levin *et al.* (2022) (22)	Hammond *et al*. (2022) (23)	Jayk Bernal *et al*. (2022) (24)	Gottlieb *et al*. (2022) (25)

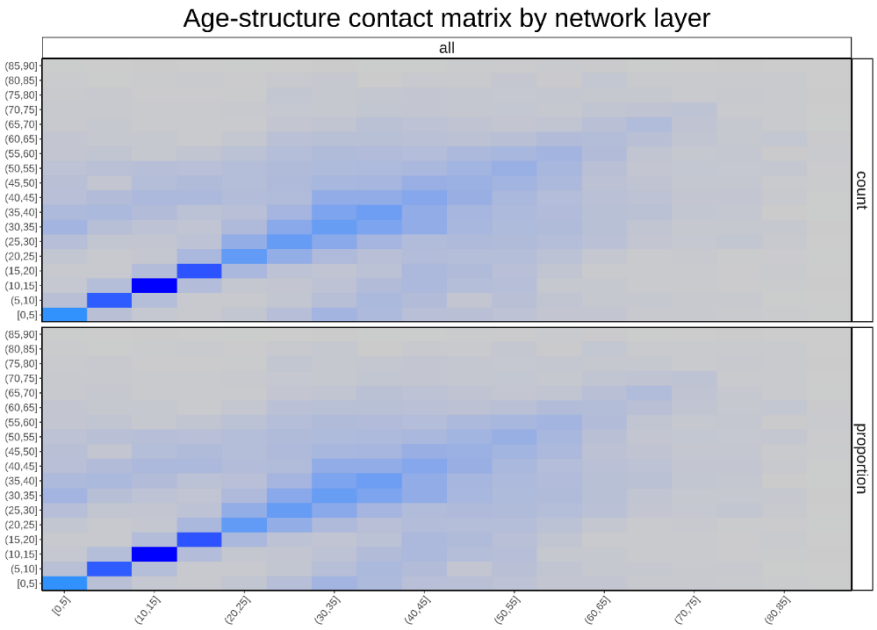
*EMA: European Medicines Agency, FDA: Food and Drug Administration, MHRA: Medicines and Healthcare products Regulatory Agency, US: United States, UK: United Kingdom, EU: European Union.



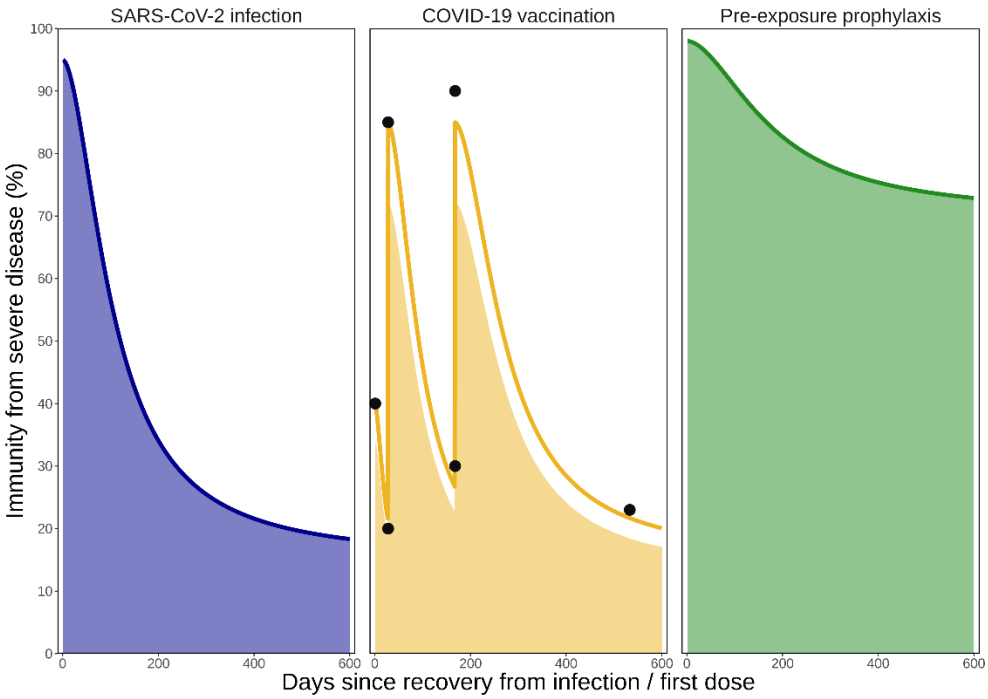
Supplementary Figure 1 – Profile for viral load since day of infection. Between day 6 and 14 post infection, peak infectivity is reached.



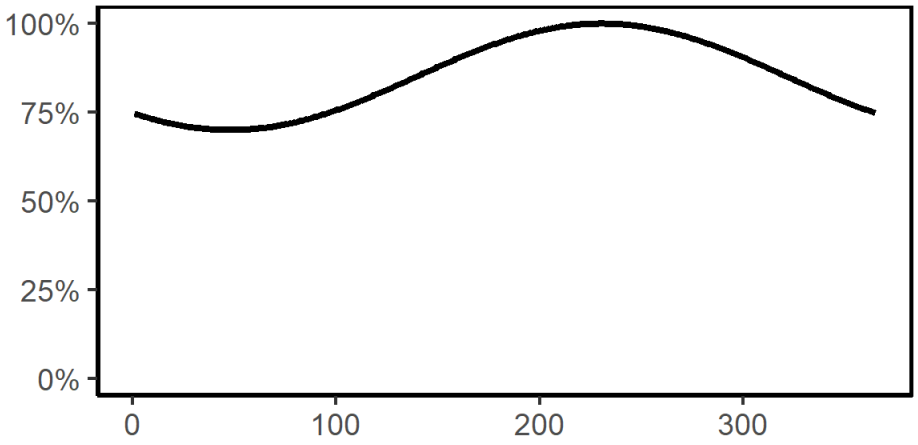
Supplementary Figure 2 – Contact properties by age group in OpenCOVID representing an agnostic Western/Northern hemisphere setting. Top panel shows the number of people in age group against number of contacts per person. Top right panel displays normalized number of contacts per person against age group. Bottom left panel shows total number of people against number of contacts per person. And bottom right panel shows the distribution of age group sizes.



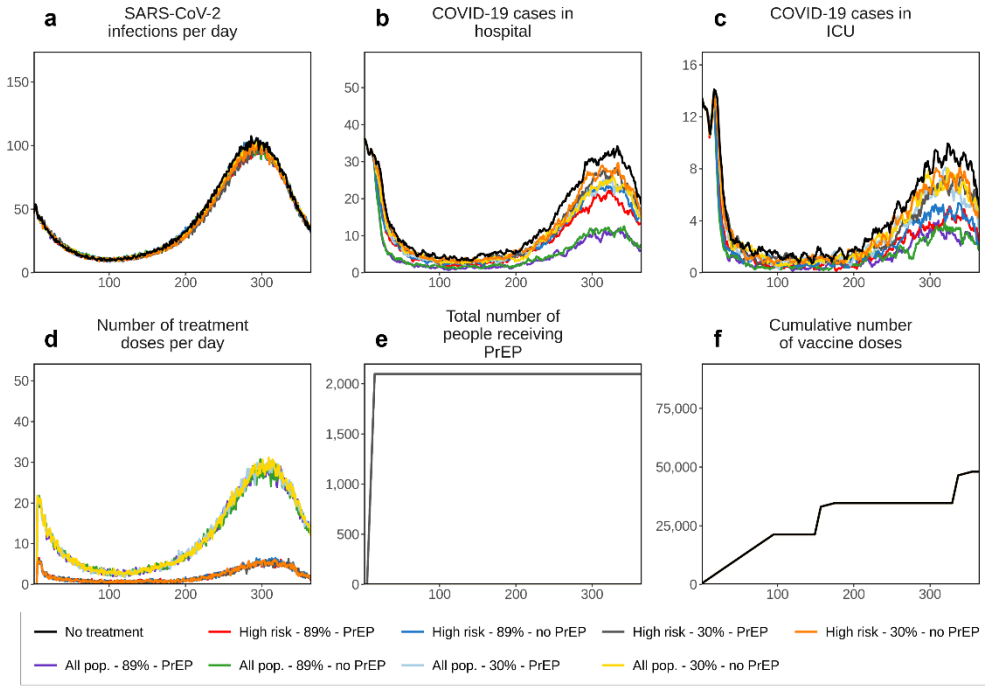
Supplementary Figure 3 – Age-structured contact matrix network for OpenCOVID in an agnostic Western/Northern hemisphere setting. It can be noted that the younger age groups have a higher number of contacts, and generally most group ages have higher contact with the same age group.



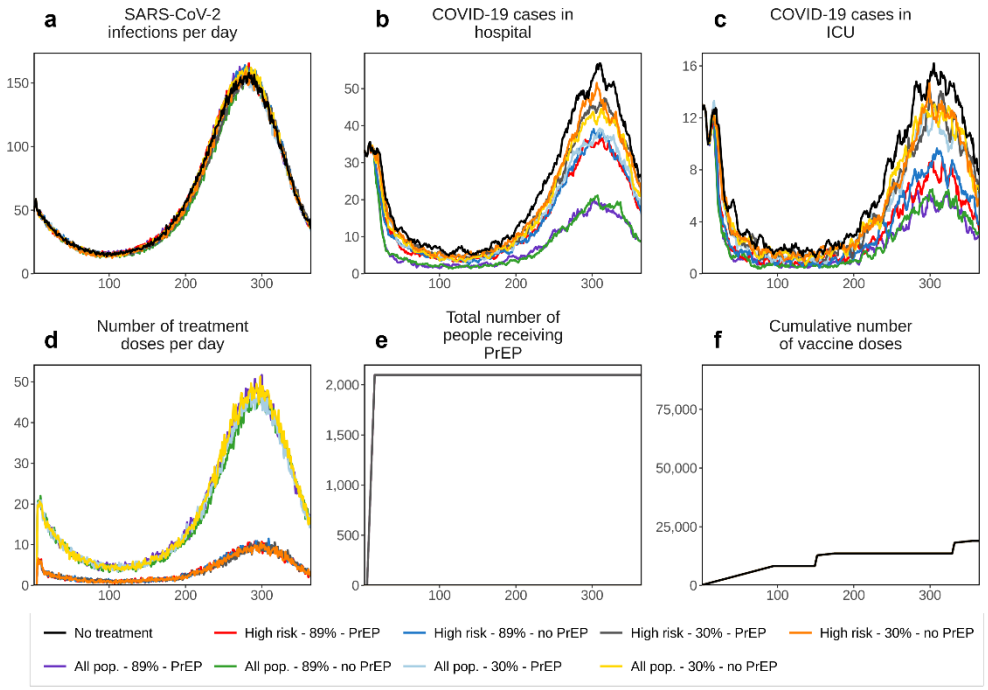
Supplementary Figure 4 – Profile for immunity developed from natural SARS-CoV-2 infection (first panel), COVID-19 vaccination (middle panel), and PrEP (third panel). The points in the middle panel show the initial efficacy with exponential decay, and following booster dose efficacy with similar decay.



Supplementary Figure 5 – Increased or decreased additional probability of transmission between two contacts. Seen across seasons in one-year simulation based on the input provided in the model, and a reproductive effective number of 0.8 in the beginning of summer.



Supplementary Figure 6 – Projected epidemiological characteristics (top row) and number of treatment and vaccination doses given (bottom row) in the moderate vaccination coverage setting over 1-year simulation. (a) Number of daily SARS-CoV-2 infections, (b) number of COVID-19 cases in hospital, (c) number of COVID-19 cases in ICU, (d) number of antiviral treatment doses given per day, (e) cumulative number of PrEP doses given, and (f) cumulative number of vaccine doses given.



Supplementary Figure 7 – Projected epidemiological characteristics (top row) and number of treatment and vaccination doses given (bottom row) in the low vaccination coverage setting over 1-year simulation. (a) Number of daily SARS-CoV-2 infections, (b) number of COVID-19 cases in hospital, (c) number of COVID-19 cases in ICU, (d) number of antiviral treatment doses given per day, (e) cumulative number of PrEP doses given, and (f) cumulative number of vaccine doses given.