Master of Public Health

Master de Santé Publique

Modeling of a SARS-CoV-2 epidemic: Consolidation of key parameters and the use of a multi-vaccine compartmental model on the impact assessment of a potential fourth COVID-19 wave in Ile-de-France

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List of acronyms

ACE2	Angiotensin-converting enzyme 2
ADE	Antibody-dependent enhancement
ANSM	Agence nationale de sécurité du médicament et des produits de santé
AP-HP	Assistance publique – Hôpitaux de Paris
ATU	Autorisation temporaire d'utilisation
CDC	Centers of Disease Control
CI	Confidence Intervals
CNR	Centre National de Référence des virus des infections respiratoires
COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
EHESP	École des Hautes Études en Santé Publique
EU	European Union
HAS	Haute Autorité de Santé
HR	Hazard Ratio
ICU	Intensive care unit
IDF	Ile-de-France
IFR	Infection-fatality ratio
INSERM	Institut national de la santé et de la recherche médicale
NPI	Non-pharmaceutical intervention
ODE	Ordinary differential equation
R, Rt, Re	Effective reproduction number
R0	Reproduction number
RBD	Receptor binding domain
RCT	Randomized controlled trial
RT- PCR	Reverse Transcription - Polymerase Chain Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
UK	United Kingdom
US	United States of America
VOC	Variants of concern
VOI	Variant of interest
VUM	Variant under monitoring
WHO	World Health Organization

Abstract

Introduction: Mathematical models have been progressively used in scientific research, and have assisted decision makers and public health policy on the study of the magnitude of outbreaks, as well as with the efficacy evaluation of interventions and resource allocation. Consequently, they have been great guiding instruments for the management of the COVID-19 health crisis. **Objective:** To provide a consolidated list of key parameters that influence the SARS-CoV-2 pandemic, and to use a mathematical model for the evaluation of the clinical impact of a fourth epidemic wave caused by the circulation of variants in partially vaccinated Ile-de-France. **Methods:** Parameters were gathered from online databases, scientific publications and grey literature. Equally, analyses of the clinical impact of a fourth wave consisted in simulating with a compartmental ODE model three epidemic scenarios based on different attained vaccination coverage using Comirnaty, COVID-19 Vaccine Moderna and Vaxzevria vaccines by early September 2021. **Results:** Twenty-five key parameters representing various aspects of the current pandemic were collected. Additionally, simulations run by the model predicted that a fourth surge of COVID-19 hospitalizations is very likely showing a peak of 713, 1,760 and 2,240 daily hospitalizations in the optimistic, realistic and pessimistic scenarios, respectively. Likewise, only the optimistic scenario did not show an overrun of Ile-de-France's intensive care unit, while the realistic and pessimistic scenarios showed an overrun by 11 Dec 2021 with a need of 5,144 daily beds, and on the 28 Nov 2021 with a need of 6,550, respectively. **Conclusion:** More than three quarters of Ile-de-France's population need to be vaccinated by 01 Sept 2021 if hospital saturation is to be avoided. Otherwise, an implementation of non-pharmaceutical interventions needs to be reinstituted during the autumn and winter 2021, at least until vaccines with higher efficacies and medical treatments are approved.

Keywords: mathematical model, SARS-CoV-2, vaccination, dynamics, clinical impact

Résumé

Introduction : Les modèles mathématiques ont été progressivement utilisés dans la recherche scientifique et ont aidé les politiques de santé publique à étudier l'ampleur des épidémies, ainsi qu'à évaluer l'efficacité des interventions et l'emploi des ressources. Par conséquent, ils ont été d'excellents instruments d'orientation pour la gestion de la crise sanitaire liée à la COVID-19. **Objectif :** Fournir une liste consolidée des paramètres clés qui influencent la pandémie de SARS-CoV-2, et utiliser un modèle mathématique pour l'évaluation de l'impact clinique d'une quatrième vague épidémique causée par la circulation de variants dans la population partiellement vaccinée d'Ile-de-France. **Méthodologie :** Les paramètres ont été recueillis à partir de bases de données en ligne, de publications scientifiques et de littérature grise. De même, les analyses de l'impact clinique d'une quatrième vague ont consisté à simuler avec un modèle ODE compartimental trois scénarios épidémiques basés sur des couvertures vaccinales différentes obtenues à l'aide des vaccins Comirnaty, COVID-19 Vaccine Moderna et Vaxzevria au début de septembre 2021. **Résultats :** Vingt-cinq paramètres clés représentant divers aspects de la pandémie actuelle ont été recueillis. De plus, les simulations effectuées à l'aide du modèle ont prédit qu'une quatrième vague d'hospitalisations liées à la COVID-19 devrait afficher un pic de 713, 1 760 et 2 240 hospitalisations quotidiennes dans les scénarios optimistes, réalistes et pessimistes, respectivement. De même, seul le scénario optimiste ne montrait pas de dépassement des capacités de soins intensifs d'Ile-de-France, alors que les scénarios réalistes et pessimistes montraient un dépassement au 11 décembre 2021 avec un besoin de 5144 lits par jour, et au 28 novembre 2021 avec un besoin de 6550, respectivement. **Conclusion** : Plus des trois quarts de la population d'Ile-de-France devra être vaccinée avant le 1er septembre 2021 pour éviter la saturation des hôpitaux. Sinon, des interventions non pharmaceutiques devront être mises en place au cours de l'automne et de l'hiver 2021, au moins jusqu'à ce que des et des traitements médicaux plus efficaces soient approuvés.

1 Introduction

In December 2019, a new coronavirus (later named SARS-CoV-2) emerged in China that has impacted the entire globe. Being declared as pandemic by the WHO on 11 Mar 2020, this novel coronavirus has affected more than 174 million people and caused about 3.7 million deaths in 219 countries, as of June 2021.[1] The latest coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 produces mild to moderate illness and people usually recover without any treatment. However, older people and individuals with certain underlying conditions are more likely to develop a serious disease with a higher risk of death, causing the saturation of health systems worldwide. SARS-CoV-2 is easily transmitted and infected individuals have the ability to spread the virus before showing any symptoms, or can even remain in an asymptomatic infectious state. This aspect has hindered the timely tracking and isolation of cases, which in combination with the appearance of new SARS-Co-V-2 variants that seem to be more transmissible and harmful, complicates the mitigation and control of the pandemic. Therefore, we need to rely on a combination of non-pharmaceutical interventions with efficient vaccination strategies to deal with the current health crisis, and prevent any pandemic resurgence.

1.1 France

The first COVID-19 cases in France were detected on 24 Jan 2020 in Bordeaux, yet further evidence showed that the virus had actually been circulating in the country since December 2019.[2] Up to early June 2021, about 110 thousand deaths and almost 6 million confirmed cases have occurred in the territory, which together with an overwhelmed health system and the SARS-CoV-2 Alpha, Beta, Gamma and Delta variants of concern already circulating in the country make France one of the most aggravated countries in Europe.[1] As result, a combination of pharmaceutical interventions like a national vaccination campaign and therapeutic treatments with non-pharmaceutical interventions such as social distancing measures, compulsory mask wearing, multiple lockdowns, curfews, school closures, and telework have been implemented to halt the spread of the virus.

France started its vaccination campaign on 27 Dec 2020, focusing on vaccinating individuals with a high risk of developing severe disease being the elderly, people with comorbidities, and exposed professionals (healthcare and frontline workers). Since then, vaccination eligibility has slowly included other groups in the population; hence, all people of legal age wishing to be vaccinated can do so since the end of May 2021, and minors older than 12 years old since mid-June 2021.

Four EU approved vaccines are being used in France as of June 2021: Comirnaty produced by BioNTech SE and Pfizer Inc., COVID-19 Vaccine Moderna produced by Moderna, Vaxzevria developed by AstraZeneca and Oxford University, and COVID-19 Vaccine Janssen by Janssen

Pharmaceutica (Johnson & Johnson Family of Companies). Vaxzevria and COVID-19 Vaccine Janssen are recommended for use on the >55 age groups presumed the risk/benefit analyses, and Comirnaty and COVID-19 Vaccine Moderna are to be used in the >18 age groups, with an addition of the 12-17 age group into the authorized age groups to be vaccinated with Comirnaty.

1.2 Mathematical modeling

The behavior of infectious diseases in a population is a complex subject to study. From understanding how they spread in host populations, to the ethical and economical consequences of what such research would implicate, infectious diseases are challenging to explore. On that account, mathematical models are the best, and often only, tools to help us understand and study epidemiological phenomena. Researchers are able to use mathematical modeling to test numerous hypotheses without having to undertake experimental or observational studies. For this reason, it is no surprise that models have been a great support during the COVID-19 health crisis for the evaluation of interventions, resource allocation and as counseling for policy-makers.

1.3 Objectives

(1) To identify and consolidate all the key parameters influencing the COVID-19 pandemic, to guide the development of the current mathematical model, and for the reference of future ones.

(2) To use a mathematical compartmental model for the evaluation of the clinical impact of a fourth epidemic wave caused by the circulation of the historical strain, the Alpha and the Delta variants in a partially vaccinated French region, Ile-de-France.

1.4 Current state of knowledge on the subject

Not a lot of work has been done to provide a full list of key parameters that could potentially be included in a mathematical model of SARS-CoV-2. Only the report created by Biggerstaff et al.[3] had as main objective to provide such material, however the collected information is limited to what was known at the beginning of the pandemic.

As regards to mathematical models, several models that include vaccination have been published such as the work done by Saad-Roy et al.[4], and Good and Hawks[5], but they have only considered a single vaccine. Analogously, models that have studied the impact of different vaccines with different efficacies on the current pandemic such as the ones developed by Nessma Adil et al.[6] and Kiem et al.[7], only did the analyses taking into account one vaccine at a time, and did not explore the effect of having multiple vaccines of different efficacies performed in a population at the same time.

2 Material and Methods

The development of the project was divided into two phases. The first phase comprised the literature review and the collection of all the important parameters that could be included in a model simulating the dynamics of SARS-CoV-2. Twenty-five main parameters were found to be the most relevant to consider for the modeling of SARS-CoV-2, and were grouped in eight categories: immunity, spatial mobility, social behavior, epidemiological parameters, impact on clinical care, risk factors, genetic evolution and interventions. The parameters were gathered from scientific publications and grey literature obtained from national and international institutional official websites such as WHO, ECDC, CDC, EMA, NGOs, Santé Publique France, ANSM, France's official websites, Public Health England, among others; and from online databases like PubMed, PMC, ScienceDirect, medRxiv, and Scopus.

In the second stage, a compartmental model of SARS-CoV-2 transmission, relying on a set of ordinary differential equations (ODE) and incorporating some of these parameters was used for evaluating the potential of a fourth COVID-19 wave in Ile-de-France. Analyses consisted in the simulation of three epidemic scenarios based on different vaccination strategies attaining realistic, optimistic and pessimistic vaccine coverage by early September 2021 (shown in Table 1). Only the Pfizer, Moderna and AstraZeneca vaccines were considered in the strategies, where Pfizer and Moderna vaccines were considered as one "mRNA vaccine" because of their similarities. Janssen's vaccine was not included in the model given that the small number of people vaccinated with it does not significantly impact the results. The hypothetical scenarios occurred between 01 Jul 2021 and 01 Sept 2021, and they began with the proportion of fully vaccinated people in July 2021 based on real-life data of people getting one dose on June 2020.

Table 1 Scenarios considering different attained vaccination coverage by September 2021

Proportion of population fully vaccinated by September 2021

	Pessimistic			Realistic			Optimisitic		
Age	Global	mRNA	AZ	Global	mRNA	AZ	Global	mRNA	AZ
0-4	**0.0**	0.0	0	**0**	0.0	0.0	**0**	0.0	0.0
5-9	**0.0**	0.0	0	**0**	0.0	0.0	**0**	0.0	0.0
10-14	**5.0**	5.0	0	**10**	10.0	0.0	**30**	30.0	0.0
15-19	**10.0**	10.0	0	**15**	15.0	0.0	**35**	35.0	0.0
20-24	**45.0**	45.0	0	**50**	50.0	0.0	**70**	70.0	0.0
25-29	**45.0**	45.0	0	**50**	50.0	0.0	**70**	70.0	0.0
30-34	**45.0**	45.0	0	**50**	50.0	0.0	**70**	70.0	0.0
35-39	**45.0**	45.0	0	**50**	50.0	0.0	**70**	70.0	0.0
40-44	**45.0**	45.0	0	**50**	50.0	0.0	**70**	70.0	0.0
45-49	**45.0**	45.0	0	**50**	50.0	0.0	**70**	70.0	0.0
50-54	**70.0**	70.0	0	**80**	80.0	0.0	**85**	85.0	0.0
55-59	**70.2**	33.2	37	**80**	37.9	42.1	**85**	40.3	44.7
60-64	**69.7**	30.7	39	**80**	35.1	44.9	**95**	41.7	53.3
65-69	**85.0**	43.0	42	**90**	45.5	44.5	**95**	48.1	46.9
70-74	**85.4**	59.4	26	**90**	62.9	27.1	**95**	66.4	28.6
75-79	**87.7**	79.7	8	**90**	81.5	8.5	**95**	86.0	9.0
80P	**87.6**	80.6	7	**90**	82.4	7.6	**95**	87.0	8.0

Note:
Results are presented as percentages (%)

The selected outcomes of interest were the number of hospital admissions and number of occupied ICU beds known that they are part of the indicators that trigger the implementation of control measures. All three scenarios considered the circulation of the historical virus along with two other variants with transmissibility similar to that of the Alpha and Delta variants. Additionally, no NPIs were taken into account in the scenarios to assess if vaccination alone could be able to prevent a fourth wave of COVID-19 cases that could spike the number of hospitalizations and ICU beds occupied by severe cases of this disease.

The model used was an updated version of the deterministic, age-structured, compartmental model detailed by Crépey, Massonnaud and Roux.[8] As in the original model, the updated model (Figure 1) contemplated seventeen age groups of a five-year range from 0 through 80 years old with the last group being the people aged ≥80 years. It also considered the population to be divided into "compartments" depending on their status relative to a SARS-CoV-2 infection and its progression. As such, the model defines a compartment for susceptibles (S); exposed (E) that would become infectious in either an asymptomatic (As) state or step into a pre-symptomatic stage (Ips); pre-symptomatic individuals would then become infectious-symptomatic (Is) before arriving to either the hospitalized phase (Ih) or the infected non-hospitalized (Inh) one; and asymptomatic, infectious hospitalized and non-hospitalized individuals would then be removed (R) after recovering or dying from COVID-19.[9] Likewise, the upgraded model considered vaccination by adding vaccination flows parting from the S and R compartments of the unvaccinated branch to its analogous compartment in the vaccinated branch representing the individuals who are being vaccinated. Although other models have considered vaccination, they typically considered a single vaccine whereas this updated one contemplates multiple vaccines and several strategies into one vaccination campaign.

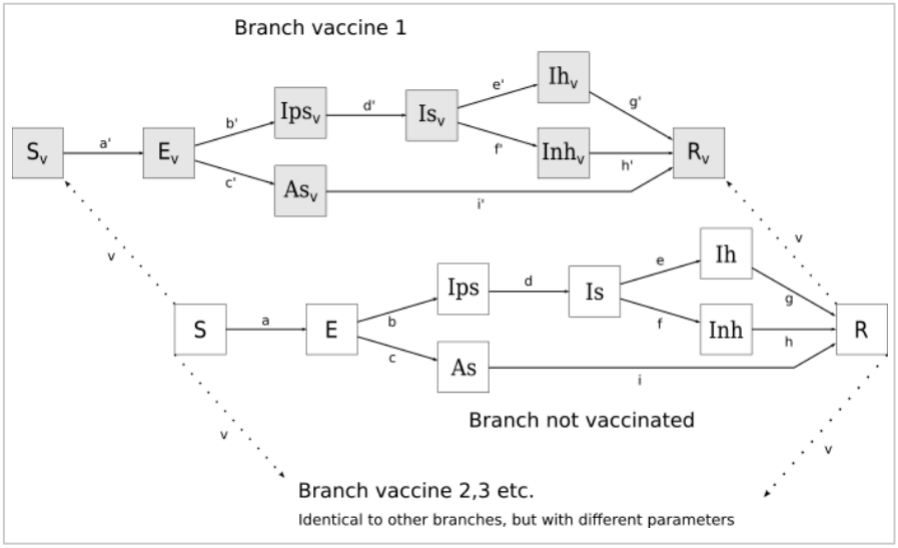

Figure 1 Multi-vaccine compartmental model used for the analyses

Some of the key parameters considered in the model shown in Figure 1 (either directly or indirectly) are natural immunity, infection-fatality ratio and pharmaceutical treatments in flows *g, h, i, g', h'* and *i'*; vaccine coverage and vaccine efficacy in flows *v* and *v'*; reproduction number, efficacy of NPIs, infectivity and transmissibility in flows *a* and *a'*; incubation period in flows *b, c, b'* and *c'*; infectious period in flows *d, e, f, I, g, h, d', e', f', i', g' and h'*; hospital saturation based on ICU occupancy and hospitalizations in flow *e* and *e'*; and lastly, morbi-mortalities per age group in flows *b, c, d, b' ,c'* and *d'.*

3 Results: phase I

3.1 Immunity

Natural immunity

Immunity acquired naturally occurs when an organism is exposed to a pathogen triggering an immune response. This will generate an immunological memory, where if the organism comes into contact with the pathogen in the future, it will recognize it and produce the necessary antibodies to fight the infection.

Concerning SARS-CoV-2, the duration of the conferred natural immunity and whether previous infection has an impact on the transmissibility of the virus are still unclear. According to an ECDC review, a decrease in the risk of reinfection during the first five to seven months of infection has been seen in cohort studies, yet these analyses occurred before the emergence of the currently circulating variants of concern. It is also hypothesized that natural immunity could last up to 1 year based on what is known from other betacoronavirus infections, meaning that SARS-CoV-2 could potentially remain in permanent circulation causing outbreaks ever so often.

Waning rate and duration of vaccine immunity

Defined as the rate of gradual loss of protective antibodies against a pathogen/antigen over time, the duration of protection against COVID-19 granted by vaccines remains unknown. Real-life data is still needed to determine the duration of immunity, which will then determine the frequency of vaccination so as to ensure continuous protection against SARS-CoV-2 infections. Given this uncertainty, past models have tested the waning rate of vaccine immunity with different values. Some examples are Goods and Hawks' model where they considered durations of immunity of 1 month, 1 year and a permanent one; and Saad-Roy and colleagues' model in which they used an immunity duration ranging from 0.25 to 10 years. [4,5]

Cross-immunity with other betacoronavirus

Considering the evidence of cross-immunity between other betacoronavirus, such as SARS-CoV-1 with HCoV-OC43 and vice versa, it is hypothesized that there could be a cross-immunity protection granted by a previous coronavirus infection against COVID-19. A cross-sectional observational study conducted by the Institut Pasteur and clinicians from the AP-HP, INSERM and the University of Paris demonstrated that there is no cross-protective immunity conferred by other coronaviruses in children[10], thus more studies are required to determine if such phenomenon occurs in the rest of the population. In addition, some modeling studies have considered different cross-immunity degrees against SARS-CoV-2 conferred by other betacoronavirus, such as the one by Kissler and colleagues, though its manifestation is still theoretical. [11]

Antibody-dependent enhancement

The ADE of an infection is a phenomenon wherein antibodies created during an immune response end up enabling the entry of the pathogen into the host cell. So far, there have not been instances of ADE reported during the COVID-19 vaccine's preclinical/clinical development, yet further research should be undertaken in order to prevent any potential side effects. Furthermore, the reduction in mortality due to immunization achieved through vaccination continuously outweighs the possible increased mortality due to ADE. This reassuring fact justifies disregarding antibody-dependent enhancement in upcoming models.[6,12]

3.2 Spatial mobility

Geographic spread

Communities are becoming more connected to each other as globalization continues to increase and enables infectious pathogens to spread more widely and faster. Some methods of studying the geographic spread of a pathogen through modeling are geographic and metapopulation networks. In the case of COVID-19, there have been a few models looking at the spatial dissemination of the virus. One of them is the metapopulation network model developed by Humphries et al., to study the spread of SARS-CoV-2 in Ireland. They split the population into several smaller communities based on geographic position, and used a mixed ODE model for the local levels; each community representing a node in the network and the edges representing travelling and commuting between locations. [13]

3.3 Social behavior

Vaccine hesitancy

Vaccine hesitancy refers to the delay in acceptance or refusal of vaccines despite the availability of vaccination services. France has historically been skeptical towards immunization, thus several surveys have been done to inquire about the acceptability level of COVID-19 vaccines in the general population. Among some of them, the CoVaPred survey conducted by Schwarzinger et al. collected responses from 1,942 working-age adults in July 2020 of whom 28.8% were likely to refuse vaccination outright[14,15]; the CoviPrev study involving 2000 people of 18 or more years old indicated on their results of the May 2021 survey that 24% of participants did not have an intention to get vaccinated, and surveyed for the first time parents of children under 17 where 47% had an intention of vaccinating their children[16]; Lazarus and colleagues, found that only 58.89% (n=669) of the participants living in France in June 2020 responded positively in regards to getting vaccinated[17]; and a cross-sectional study looking at the intention to get vaccinated against COVID-19 among healthcare professional done by Mueller et al during the summer of 2020, found that among 1509 participants, only 68% would be willing to get vaccinated.[18] These results indicating the national degree of vaccine hesitancy show the importance of promptly implementing strategies to address the issue if herd immunity is ever to be attained.

3.4 Epidemiological parameters

Seasonality

Refers to the periodic increase of disease incidence related to seasons or other calendar periods. It is important to understand the variability of the reproduction number throughout the seasons, as well as the time of the year when an outbreak occurs (e.g. winter, autumn, spring, summer); this is usually an estimated parameter. High seasonal variation leads to a greater accumulation of susceptibles during periods of low transmission, leading to recurrent outbreaks with higher peaks. Given that other betacoronavirus such as the common flu have shown seasonality in their dynamics, it is conceivable to think that SARS-CoV-2 could show it also, as described by Kissler et al on their model. [11]

R_o and R

A main indicator of a pathogen's transmissibility is its reproduction number. The basic reproduction number or "R-naught" (R_0) is the average number of persons infected by a single infected individual in a fully susceptible population and without control measures; whereas the effective reproduction number (R, R_t, R_e) consists on the average number of persons infected by an infected individual in a population in the context of changing transmission patterns, such as those resulting from interventions and acquired immunity. According to the Institut Pasteur, the R_0

of SARS-CoV-2 at the beginning of the first lockdown was estimated to be between 2.5 and 3 in France, and the effective reproduction number has ranged from 0.61 to 1.49 depending on the progress of the disease and the implemented interventions throughout the crisis. Thus, the reproduction number is a useful criterion not only for understanding the transmissibility of a disease, but also for estimating the likelihood of an epidemic to emerge and for the evaluation and comparison of the effectiveness of control measures. [3,7,19]

Serial interval

Refers to the average time between symptom onset in a primary case and symptom onset in linked secondary cases. According to a CDC report, the mean serial interval of SARS-CoV-2 ranges between 4 to 7 days. Knowing the serial interval of an infectious pathogen is of high importance in order to effectively implement control measures in a timely manner. [3]

Incubation period

Indicates the time between the infection and symptom onset. According to the WHO, the incubation period of SARS-CoV-2 is on average 5-6 days but it can be as long as 14 days. This indicator defines how much time an infected person would spend in the exposed compartment before going into the infectious compartments in compartmental models. [3,20]

Infectious period

Specifies the period during which an infected host, with or without symptoms, can transmit an infectious agent to susceptible persons, directly or indirectly. Based on current evidence, an individual with mild/moderate COVID-19 disease may shed viral SARS-CoV-2 loads for up to 10 days following symptom onset, while severe cases for up to 20 days.[3] However, a key aspect to consider about COVID-19 is that infectious individuals are able to transmit the virus before developing any symptoms, and they could even remain in an asymptomatic state until recovery. This particular characteristic is what has halted the control of the pandemic given that diseased individuals are able to transmit the virus without being detected. Therefore, even if it is thought that asymptomatic individuals are less contagious than symptomatic ones, it is still important to conduct further studies to better understand the relative infectiousness of asymptomatic individuals. [21]

Infectivity and transmissibility

Infectivity is defined as a pathogen's ability to invade a host and cause disease, while transmissibility is a pathogen's ability to spread to other hosts. In regards to SARS-CoV-2, there is still uncertainty whether pre-symptomatic and asymptomatic cases are less infectious than symptomatic cases, and even if they are still capable of transmitting the virus and causing disease, they may transmit the virus less than symptomatic cases due to the lack of expiratory symptoms

such as coughing and wheezing. Nevertheless, the fact that these cases usually go unnoticed allows them to keep mixing in society and thus increasing the possibility of spreading the disease. Further research is needed on the relationship between clinical symptoms, transmission and viral shedding in COVID-19 cases. [22–24]

3.5 Impact on clinical care

Infection-fatality ratio

The IFR refers to the proportion of all infections (confirmed, symptomatic and asymptomatic) that result in death, and it is an indicator that helps reflect the standard of care of the introduction of new therapeutics in a crisis. The IFR calculated from reported data in France may underestimate the real ratio given that many COVID-19 cases and related deaths went under-reported during the beginning of the pandemic, hence the use of mathematical models to estimate it. Salje and colleagues estimated an IFR of 0.53% (95% CI: 0.28-0.88), ranging from 0.001% in >20 years old to 8.3% (95% CI: 4.4- 13.9) in those >80 years old with their model; and Roques and colleagues estimated an IFR of 0.5% (95%-CI: 0.3–0.8) based on hospital death counting data and 0.8% (95%-CI: 0.45–1.25) adjusting for the number of deaths in nursing homes. [7,25,26]

Hospital saturation based on ICU occupancy

This parameter refers to the proportion of COVID-19 patients currently in the ICU or in a continuous monitoring unit in regards to the total available beds in baseline capacity, meaning before increasing ICU beds capacity in a hospital. It helps measure the national burden of disease of COVID-19, as well as the impact of control measures (NPIs and vaccination). This indicator is part of the indicators selected in France for the monitoring of the COVID-19 pandemic and there are three levels that have been set for its monitoring: green – occupancy proportion between 0 and 30%, orange – occupancy proportion between 30 and 60%, and red – occupancy proportion greater than 60%; and it has ranged from 6.8 to 138.8 since 18 Mar 2021. [3,19]

Hospitalization and ICU admission rates

These rates refer to the weekly new hospital and ICU admissions per 100k for COVID-19, and are also used to track a health system's capacity. They help measure the burden of disease of COVID-19, as well as the impact of control measures such as NPIs and vaccination. According to the ECDC, France's weekly new hospital admissions per 100k has ranged from 0.75 to 29.7 and weekly new ICU admissions per 100k from 0.11 to 200 since the beginning of the pandemic in mid-March 2020. [27]

3.6 Risk Factors

Morbi-mortality and transmissibility by age group

It has been noted that the risk of death and the risk of developing a severe case of COVID-19 increase with age and with the number of underlying medical conditions. The >75 age group is the most susceptible group to develop a severe case of disease and has a higher risk of death, followed by the 65-74 age group, 50-64 age group and 18-49 age group. Similarly, the transmission dynamic of SARS-CoV-2 also varies with age, being the 18-49 age group the one who contributes the most to COVID-19 transmission as opposed to other age groups. [28,29]

Comorbidities

Certain medical conditions increase the risk of developing a severe case of COVID-19, and the accumulation of comorbidities is associated with an even higher risk of developing severe and life-threatening cases of disease. Among some of the comorbidities related to severe COVID-19 cases include hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immunocompromised status, cancer, smoking and obesity among adult patients. [30]

3.7 Genetic evolution

Mean evolutionary rate

As explained by Stern and Andino in their book *Viral Pathogenesis*, the mean evolutionary rate refers to the average rate at which mutations accumulate per base pair in the genome over the course of a year, and it is measured by comparing different viral genomes isolated at different time points. These mutations create genetic diversity in the viral population that can modify the features of the original strain. Some of the most significant changes conferred by these mutations are the ability to escape the natural immune response of the host, escape from immunity granted by vaccines, and the ability to escape from antiviral drugs. The natural selection of the genetic alterations regulates which mutations will persist in the viral population. Therefore, it is presumed that there is a relationship between the evolutionary rate of a virus, the viral population diversity and its pathogenicity, reflecting the importance of having continuous surveillance and monitoring systems on SARS-CoV-2's evolution. [31]

Pereson et al estimated an evolutionary rate of SARS-CoV-2 for its spike protein as 1.08×10^{-3} nucleotide substitutions/site/year after analyzing two thousand and one hundred sequences representing seven main clades of SARS-CoV-2. As the spike protein is the main target of vaccines and other pharmaceutical therapies, it is of utmost importance that the genomic region of the virus coding for the protein keeps being monitored for the prompt identification of any structural change in the protein. [32]

Notable mutations of concern

These are the mutations in the SARS-CoV-2 genome, especially in the receptor binding domain (RBD) region that could affect the transmissibility, virulence and ability to escape immunity of the virus. Some most concerning mutations in the RBD region are:

- E484K – mutation that allegedly allows the virus to escape the host's immune system
- N501Y– mutation in the receptor-binding domain that presumably increases binding affinity to ACE2 receptor of human cells
- N439K – mutation likely to grant the virus the ability to escape antibodies as well as a greater affinity to ACE2 receptor
- L452R – potential increase in binding affinity to ACE2. Associated with an increase of 18-24% in viral transmissibility and slight immune escape
- Y453F – increased binding affinity to ACE2 and possible evasion of some human antibodies

As well as a deletion of concern:

- 69-70del – deletion that possibility allows the virus to escape antibodies

And another mutation in the S protein where the RBD region is located:

- D614G – assumed to have a moderate effect on the virus transmissibility [33–35]

Other important mutations of concerns such as P681H, K417N, K417T, A701V, H655Y, and T478K, lineages and tracking of variants are registered by the interactive SARS-CoV-2 mutation tracker 'CovMT' developed by Alam and colleague. This system summarizes the genomes of more than 450 000 isolates to track and monitor the spread of the variants worldwide, as well as to identify any possible hazardous mutation, particularly in the RBD region as these could have an impact on the efficacy of pharmaceutical interventions. [33]

SARS-CoV-2 variants

In France, there are three categories to classify SARS-CoV-2 variants defined by *Santé Publique France* and the *Centre National de Référence des virus des infections respiratoires (CNR)* [36]:

I. Variants of concern (VOC): variant that has shown an increase on its transmissibility or has shown an unfavorable impact on COVID-19 epidemiology; increase in the seriousness of the disease or a change in clinical symptoms; a decrease in the efficacy of control measures such as diagnostic tests, NPIs and pharmaceutical interventions; or a variant that has been classified as VOC by the WHO. Variants of concern in France:
    - The B.1.1.7 lineage, known as the Alpha variant originated in the UK, spreads easier and faster than other variants. Preliminary evidence suggests an increase of risk of death by B.1.1.7 and it is currently the most predominant variant in France accounting

for 85% of the sequenced positive RT-PCRs. Notable spike mutations: N501Y, D614G, P681H [37,38]

- The B.1.1.7 lineage plus the additional mutation E484K, is considered as an additional variant of concern as it shows high transmissibility and potentially causes more severe disease, evidence of neutralization studies suggest it has an impact on vaccine efficacy[38]

- The B.1.351 lineage, known as the Beta variant originated in South Africa has increased transmissibility and potentially causes a more severe disease. This variant has drastically impacted the immunity granted by the AstraZeneca vaccine, and affected other vaccine efficacies. Notable spike mutations: K417N, E484K, N501Y, D614G, A701V [37,38]
- The P.1 lineage, known as the Gamma variant originated in Brazil. Evidence showing that it contains a set of mutations that may affect its ability to be recognized by antibodies and its transmissibility has been found. Raises concerns for potentially re-infection of SARS-CoV-2. Notable spike mutations: K417T, E484K, N501Y, D614G, H655Y. [37,38]
- The B.1.617.2, known as the Delta variant originated in India. There has been evidence showing higher transmissibility and an ability to escape vaccine immunity, but not on severity of infection. Notable spike mutations: L452R, T478K, D614G, P681R[38]

II. Variant of interest (VOI): variant that has a phenotypic change or a mutation leading to a amino acid change associated with confirmed or suspected phenotypic implications; and is responsible for viral transmission in a community, caused clusters or has been detected in other countries; or has been classified as VOI by the WHO. CNR and Santé Publique France have classified variant B.1.617 originated in India, as VOI in France on 21 Apr 2021.

III. Variant under monitoring (VUM): absence of virological, epidemiological or clinical evidence indicating an impact on France's public health, despite having mutations that are also present in one or more VOIs.

The epidemiological situation in France as of 02 June 2021 is shown in Figure 2 extracted from Santé Publique France's official website:

Classement des variants du SARS-CoV-2 en France, 02/06/2021		
Variants préoccupants (VOC)	**Variants à suivre (VOI)**	**Variants en cours d'évaluation (VUM)**
20I/501Y.V1 (B.1.1.7, Alpha) 84,9% des séquences (Flash #9)	20C/484K ou 20C/477N (B.1.526, Iota) Cas sporadiques	20C/452R (B.1.526.1) Cas sporadiques
sporadiques20H/501Y.V2 (B.1.351, Beta) 8,8% des séquences (Flash #9)	20C/655Y (B.1.616) Clusters en Bretagne (Côte d'Armor)	20A/214Ins (B.1.214.2) 0,1% des séquences (Flash #9)
20J/501Y.V3 (P.1, Gamma) 0,5% des séquences (Flash #9)	20A/484K (B.1.525, Eta) 1,1% des séquences (Flash #9)	20A/440K (B.1.619) 0,3% des séquences (Flash #9)
20I/484K ou 484Q (B.1.1.7 + E484K/Q)* 20I/484K : 2,6% des séquences20I/484Q : 0,1% des séquences (Flash #9)	20B/681H (B.1.1.318) Non détecté lors de Flash #9	20A/477N (B.1.620) 0,6% des séquences (Flash #9)
21A/478K (B.1.617.2, Delta)** 0,1% des séquences (Flash #9) Majorité de cas importés d'Inde	21A/154K (B.1.617.1, Kappa)** Non détecté lors de Flash #9	20I/452R (B.1.1.7 + L452R) Cas sporadiques
		20A/145Ins (B.1.621) 1 cas détecté en IDF
		IDF20C/452R (B.1.427 / B.1.429, Epsilon) Cas sporadiques
		19B/501Y (A.27) 0,1% des séquences (Flash #9)
		20B/484K (P.2, Zeta) Non détecté lors de Flash #9

Figure 2 SARS-CoV-2 variant classification in France as of 02Jun21[36]

3.8 Interventions

Pharmaceutical treatments

On 25 Feb 2021, France's Health Minister Olivier Véran announced during a press conference that France approved two therapeutic treatments against sever COVID-19:

- Treatment with interferons, which are already used to treat diseases like hepatitis and some cancers, they are signaling proteins that are involved in the immune system's fight against pathogens. There are some people who do not produce enough of these proteins, and become eligible to receive this treatment whenever they develop a severe case of COVID-19. [39]
- Roche's and Lilly France's dual monoclonal antibody therapies. Both were granted a Temporary Authorization for Use "ATU" by the ANSM and their use is intended only for people over 80 years old; people aged 70-80 with a chronic disease and any other person with a compromised immune system caused by a pathology or a treatment; or having a high risk of complications. [39–41]

Vaccine coverage

Estimated percentage of people who have received a complete vaccination cycle, that is people who have had COVID-19 and those receiving the Janssen vaccine getting only one vaccine dose; severely immunocompromised people receiving three vaccine doses, and the rest of the

population receiving two vaccine doses. In France, no official targets have been established yet, although a 70% vaccination coverage was considered to be enough for the attainment of herd immunity in 2020. Nevertheless, it is possible that herd immunity will not be achieved given the high levels of vaccine hesitancy in the country, in addition to the younger population not being included into the vaccine campaign, and the different efficacies of the vaccines currently being used. Furthermore, the emergence of more transmissible variants, namely Alpha and Delta, raises the level of immunity needed to achieve herd immunity, hence 70% of vaccination coverage may not be enough anymore.

Vaccine efficacy against disease

Represents the percentage reduction in disease incidence in a vaccinated group compared to an unvaccinated group under optimal conditions (e.g. RCTs).

Table 2 Summary of evidence on vaccine efficacy per variant (95% confidence intervals)

Vaccine	Historical Strain	Alpha United Kingdom B.1.1.7 lineage Variant: 202012/01, or 501Y.V1	Beta South Africa B.1.351 lineage Variant: 501Y.V2	Gamma Brazil P.1/P.2 lineage Variant: 501Y.V3	Delta India B.1.617 lineage Variant: B.1.617.2
Pfizer-BioNTech: Comirnaty BNT162b2	7 days through up to 6 months after second dose: Overall efficacy 91.3% [CI, 89.0-93.2][42] Severe disease 100% [CI, 88-100] as defined by the U.S CDC[43] and 95.3% [CI, 71.0-99.9] as defined by the U.S FDA[44].	Real-world data collected from Israel MoH surveillance system between 17 Jan and 06 Mar 2021 reported an efficacy of 97% (symptomatic, severe/critical disease and death) and 94% (asymptomatic) cases when more than 80% of tested specimens were positive for the B.1.1.7	100% [CI, 53.5-100.0] (800 trial participants in South Africa) according to Pfizer [42] A study in Qatar found a 75.0% [CI, 70.5-78.9] at 14 or more days after the second dose. Vaccine effectiveness against severe,	Unknown. Neutralizing viral studies show that antibodies produced by the BNT162b2 vaccine are still active although slightly less effective against the mutations found in the P.1 lineage. More real-life data and research is needed. [49,50]	A test negative case control study conducted by Public Health England found an 87.9% [CI, 78.2-93.2] effectiveness against symptomatic disease two weeks after the second dose. Effectiveness was notably

		variant in the country. [45] A test negative case control study conducted by Public Health England found a 93.4% [CI, 90.4-95.5] effectiveness.[46] A study in Qatar found an 89.5% [CI, 85.9-92.3] at 14 or more days after the second dose. Vaccine effectiveness against severe, critical, or fatal disease found was 97.4% [CI, 92.2-99.5]. [47] A summary of evidence on vaccine efficacy (related to the period when Alpha variant was dominant) done by PHE reported a 85-90% Efficacy against symptomatic disease after two doses and 55-70% after one dose. [48]	critical, or fatal disease found was 97.4% [CI, 92.2-99.5][47]		lower after 1 dose of vaccine with B.1.617.2 cases 33.5% (95%CI: 20.6 to 44.3) compared to B.1.1.7 cases 51.1% (95%CI: 47.3 to 54.7) with similar results for both vaccines (BNT162b2 and ChAdOx1) [46]
Moderna: mRNA-1273	From 14 days after second dose:	In an in vitro neutralizing study	Moderna COVID-19 vaccine has a 6x reduction in	Unknown. In vitro and at a high titer,	Unclear.

	Overall 94.1% [CI, 89.3-96.8] 18-64 yr 95.6% [CI, 90.6-97.9] ≥65 yr 86.4% [CI, 61.4-95.2] 65-74 yr 82.4% [CI, 48.9-93.9] ≥75 yr 100.0% [CI, NE-100.0] [51] Approx. 6 months median after second dose: >90% against COVID-19 cases and >95% against severe COVID-19 cases. Update on the ongoing COVE phase III study. [52]	conducted by Moderna, Moderna COVID-19 vaccine produced neutralizing titers against all key emerging variants tested, including B.1.1.7 and B.1.351. The study showed no significant impact on neutralizing titers against the B.1.1.7 variant relative to prior variants. [53]	neutralizing titers against with the B.1.351 variant, but still above protective levels, shows in-vitro study. [53] Booster vaccines are being developed, one targeted against the SA variant (mRNA-1273.351), and a multivalent booster combining the original vaccine with the mRNA-1273.351 vaccine (mRNA-1273.211). Preclinical data shows that booster candidates increase neutralizing titers against VOC. Following the mRNA-1273.351 boost, neutralizing titers were comparable between the ancestral strain and the new B.1.351 variant. Phase 2 study is currently ongoing. [52]	antibodies induced by Moderna's vaccine still show a neutralizing activity. Vaccine appears to work although with decreased efficacy. [50,54]	
AstraZeneca/ Oxford:	From 15 days of second dose	70.4% [CI, 43.6–84.5]	10.4% [CI, −76.8 to	Unknown. An in-vitro study	A test negative case control

Vaxzevria ChAdOx1 nCoV-19 (AZD1222)	(updates of the primary analysis of the ongoing USA phase III trial): Overall symptomatic 76% [CI, 68-82] Severe disease 100% Symptomatic among ≥65 yr 85% [CI, 58-95][55] From 15 days of second dose (pooled efficacy analysis of UK phase II/III and Brazil phase III trials): Overall 59.5% [CI, 45.82-69.72] Age groups 56-65 yr and ≥65yr did not have enough subjects recruited, hence efficacies could not be estimated. [56]	in an exploratory analysis of an RCT in the UK.[57] A test negative case control study conducted by Public Health England found a 66.1% [CI, 54.0-75.0] effectiveness.[46] A summary of evidence on vaccine efficacy (related to the period when Alpha variant was dominant) done by PHE reported a 65-90% efficacy against symptomatic disease after two doses and 55-70% after one dose.[48]	54.8] efficacy in an RCT placed in South Africa.[58]	showed that antibodies created by the Oxford vaccine are still active against the P.1 variant, although somewhat less efficient. [59]	study conducted by Public Health England found a 59.8% [CI, 28.9-77.3] effectiveness against symptomatic disease two weeks after the second dose. Effectiveness was notably lower after 1 dose of vaccine with B.1.617.2 cases 33.5% (95%CI: 20.6 to 44.3) compared to B.1.1.7 cases 51.1% (95%CI: 47.3 to 54.7) with similar results for both vaccines (BNT162b2 and ChAdOx1)[46]
Janssen Johnson & Johnson: Ad26.COV2.S	From 28 days after the second dose: Global 66.1% [CI, 55.0- 74.8] 18-64 yr 65.1%	Unknown. Preliminary data show that neutralizing capacity created by the	64.0%[CI, 41.2-78.7] efficacy against moderate to	68.1% [CI, 48.8-80.7] efficacy against moderate to	Unclear

	[CI, 52.91-74.45] ≥65 yr 64.0% [CI, 34.40-91.35] Severe disease 85.4% [CI, 54.2-96.9] [60]	J&J vaccine are still active against the B.1.1.7 lineage, although somewhat less efficient. [60]	severe-critical COVID-19. 81.7% [CI, 46.2-95.4] against severe-critical disease after 28 days of administration of vaccine. [61] (95% of the Covid-19 cases in South Africa were caused by the 20H/501Y.V2 variant)	severe-critical COVID-19. 87.6% [CI, 7.8-99.7] against severe-critical disease after 28 days of administration of vaccine. P.2 lineage carrying the E484K mutation was identified in 69% of the cases.[61]	

Vaccine efficacy against transmission

Refers to the percentage reduction in ability to transmit the virus in a vaccinated group compared to an unvaccinated group under optimal conditions (e.g. RCTs). Given that SARS-CoV-2 is spread through droplets of saliva from an infected person to another, it is thought that any vaccine that reduces the duration of infection, the viral load or the amount of times an infected person coughs could potentially decrease transmission. However, none of the COVID-19 vaccine trials targeted the evaluation of decrease in transmission as the primary goal, so a vaccine efficacy against transmission was not estimated. Nevertheless, the ECDC conducted a literature review on the available information on SARS-CoV-2 transmission from previously infected or vaccinated individuals as of 29 Mar 2021, and only one large study done in Scotland on household transmission of healthcare workers was found as direct evidence on vaccine reducing viral transmission. The study suggested a 30% decrease (HR 0.70, 95% CI 0.63 to 0.78)[63] in the risk of infection among household members of vaccinated individuals compared to those of unvaccinated individuals, yet evidence is still limited and more studies looking at the impact of vaccines on viral transmission are still needed. [64]

Non-pharmaceutical interventions (NPIs)

Referring to the actions taken to slow the spread of COVID-19, outside of vaccines or medical treatments. These include lockdowns, curfews, school closures, wearing masks, social distancing,

among others, and their efficacy depends on the timing and duration of the application, along with their combination. NPIs recommended by the ECDC relative to SARS-CoV2 transmission characteristics are listed in Figure 3.[65]

Table 1. Characteristics of SARS-CoV-2 transmission and relevance for NPI

	Value/description (+ ref)	Relevance for NPI
Main transmission routes	Respiratory droplets (large and aerosols), fomites [3]	Mask wearing, hand and respiratory hygiene, avoid indoor and crowded places
Incubation period	Range: 1-14 days [8-11] Median: 5-6 days	Duration of quarantine Follow-up of contacts
Infectious period	1-2 days before symptom onset 10 days after symptom onset in mild cases, 14-20 days in severe cases [12,13]	Duration of isolation, duration of quarantine
Basic reproduction number	2-4 [14,15]	All NPI
Infectiousness by age	Unclear	School measures
Proportion of asymptomatic cases	30-40% [16,17]	Mask wearing, hand hygiene, avoid indoor and crowded places, testing strategy, quarantine
Transmission by asymptomatic cases	Yes	Quarantine, testing strategy
Risk factors for transmission (personal)	Activities, number of contacts	Physical distancing, hand and respiratory hygiene, contact tracing
Risk factors for transmission (setting)	Close contact, indoor settings, crowding, travel	Physical distancing, mass gatherings, travel restrictions
Risk factors for severity (personal)	Old age, underlying diseases	Protection of vulnerable groups

Figure 3 Characteristics of SARS-CoV-2 transmission and relevance for NPI

4 Results: phase II

4.1 Vaccination strategies

The initial step for running the simulations of the three vaccination coverage scenarios was for the model to be able replicate Ile-de-France's vaccination campaign from 03 Jan 2021 up to 12 Jun 2021. The three hypothetical scenarios were run for the summer 2021 period. Illustrated in Figure 4, the observed vaccination campaign is represented in dotted lines and the simulated one by the model in a continuous line. Based on the proposed scenarios (Table 1), the global vaccination coverage for Ile-de-France's population of people over 10 years old achieved by 01 Sep 2021 was 72.5% in the optimistic scenario, 57.6% in the realistic scenario, and 51.8% in the pessimistic scenario.

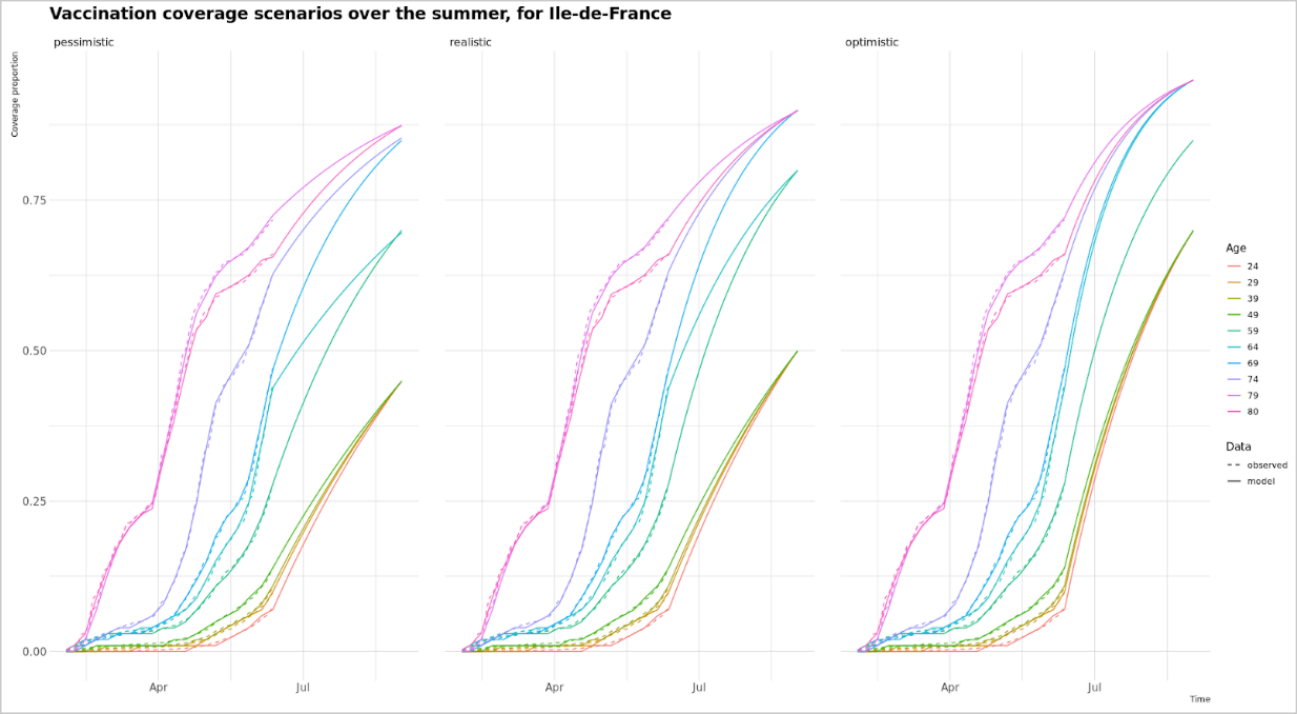

Figure 4 Vaccination coverage scenarios for each age group. The three scenarios based on the observed vaccination campaign run until 01 Sept 2021. Real-life data on the vaccination campaign is represented by the dotted lines, and the one simulated by the model one by the continuous lines.

4.2 Hospital admissions

As illustrated in Figure 5, the simulation's results estimated that even for high levels of vaccination coverage attained by September 2021, if no control measure are put into place while two variants similar to the Alpha and Delta are circulating in the population along with the historical strain, a fourth wave of COVID-19 hospitalizations in Ile-de-France is highly possible. They indicated that COVID-19 hospitalizations would start surging around Nov 2021 and ending by Jul 2022 in the optimistic scenario, with a peak of 713 daily hospitalizations on 25 Feb 2022; from Oct 2020 to April 2022 in the realistic scenario, with a peak of 1,760 daily hospitalizations on 24 Dec 2021; and starting in Oct 2020 through Feb 2022 in the pessimistic scenario, with a peak of 2,240 daily hospitalizations in 13 Dec 2021.

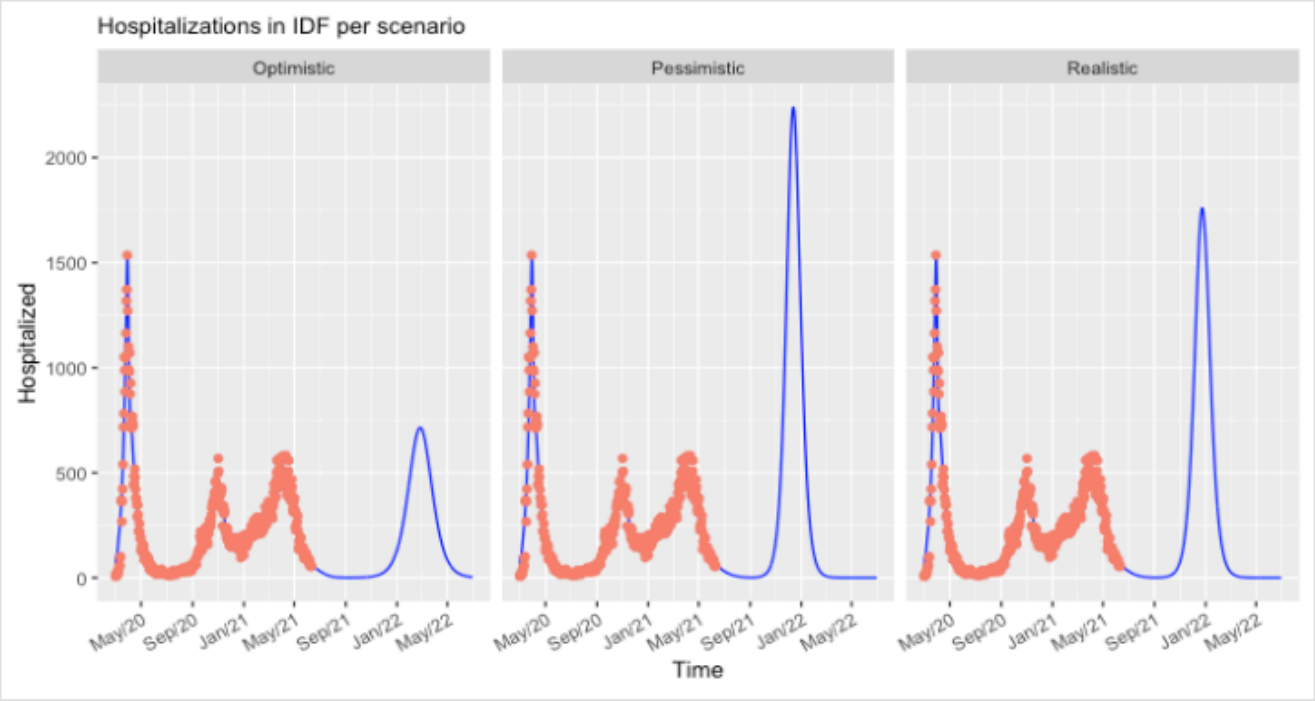

Figure 5 Number of COVID-19 hospital admissions per attained vaccination coverage scenario. The blue line stands for the simulated number of hospitalizations by the model from 01 Mar 2020 to 30 Jun 2022, the orange dots representing the real-life data on number of hospitalizations from 01 Mar 2020 to 11 Jun 2021.

When looking at the number of hospitalizations by vaccination status, illustrated in Figure 6, analyses revealed that vaccinated individual with COVID-19 will still be hospitalized in the three scenarios, and because the majority of the at-risk population will be vaccinated at that time, they will represent the majority of the hospitalizations. Likewise, the age patterns of hospitalizations found in previous COVID-19 waves appear to remain constant in this potential fourth wave and throughout all scenarios, the elderly representing the largest number of hospital admissions.

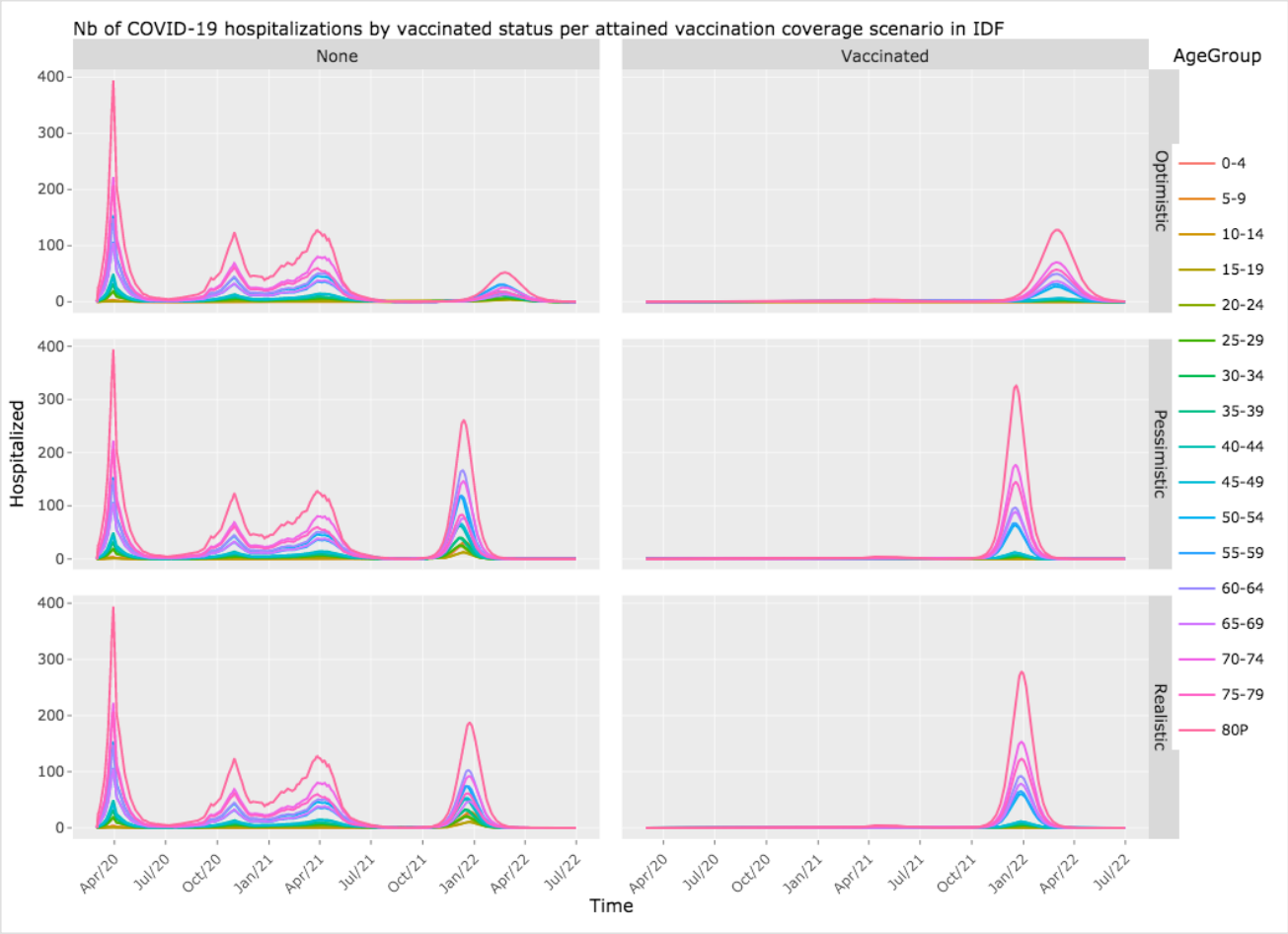

Figure 6 Number of daily hospital admissions categorized by vaccinated status and vaccination campaign scenario in Ile-de-France, presented by age groups.

Despite the unaffected age-group pattern of hospital admissions in a potential fourth wave in the population of Ile-de-France, it is the younger age groups (0 to 19 years old) that will have the most notorious shift in the number of hospitalizations in comparison to preceding COVID-19 outbreaks. As seen in Figure 7 and Table A 1, the 0-4 and 5-9 age groups have between 960 and 1,370 hospitalizations in the potential fourth wave in comparison to <150 hospitalizations in the last observed wave; and the 10-14 and 15-19 age groups have between 330 and 550 hospitalizations compared to <80 hospitalizations in the last observed COVID-19 surge. For the rest of the age groups, the estimated number of hospitalizations in the optimistic scenario was comparable to the observed number of hospitalizations of the previous wave, the >80 age group reaching the highest number of hospitalizations with almost 22,250 hospital admissions in the realistic scenario, followed by the 75-79 and 70-74 age groups with approximately 8,740 and 11,730 hospitalizations respectively in the same scenario.

Figure 7 Comparison of the total observed number of hospital admissions of previous waves to the estimation of number of hospital admissions of the three scenarios of the potential fourth wave in Ile-de-France. Results shown by age group. "O", optimistic; "R", realistic; "P": pessimistic.

4.3 Required amount of intensive care unit (ICU) beds

The simulations on the number of occupied ICU bed by COVID-19 cases estimated that only the scenario with the highest level of vaccination coverage attained by September 2021 could avoid the overrun of Ile-de-France's ICU estimated capacity of 2,500 beds; whereas in the realistic scenario ICU capacities would be surpassed by 11 Dec 2021 with a need of 5,144 daily beds, and on the 28 Nov 2021 with a need of 6,550 daily beds in the case of the pessimistic scenario (Figure 8). Results are assuming that no intervention is put into place other than the vaccination campaign, and that similar variants to the Alpha and Delta variants are circulating in the population of Ile-de-France.

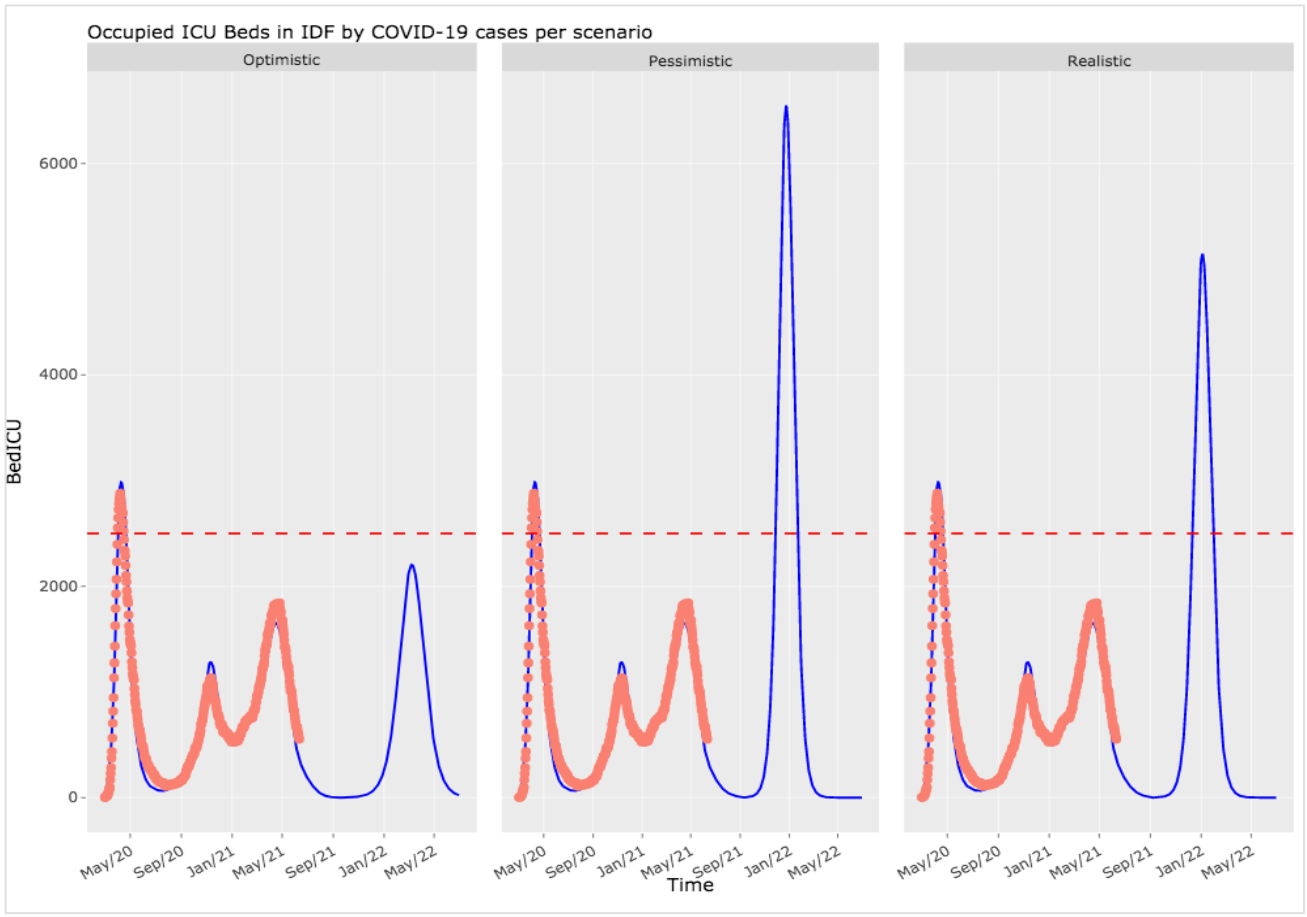

Figure 8 Number of required ICU beds in Ile-de-France by COVID-19 patients per attained vaccination coverage scenario. The blue line stands for the simulated number of required ICU bed by COVID-19 patients from 01 Mar 2020 to 30 Jun 2022, the orange dots represent the real-life observed number of critical COVID-19 patients occupying an ICU bed in Ile-de-France during previous waves, and the red dotted line stands for the theoretical ICU capacity limit of Ile-de-France.

Furthermore, the age group distribution of the required ICU bed by COVID-19 patients seemed to remain unchanged. In all scenarios, it is still the older individuals that will largely be admitted into critical care, and being the 70-74 year old group who will require the most amount of ICU beds compared to other age groups (Figure 9). Likewise, the optimistic scenario did not only show a reduction on the number of occupied ICU beds by vaccinated people in comparison to other scenarios and to non-vaccinated individuals, but also indicated that the need for ICU beds for vaccinated people will come later than the one of non-vaccinated individuals. The highest number of ICU beds needed by COVID-19 vaccinated patients would peak by mid-March 2022, approximately 2.5 months after the highest number of ICU beds is needed by the non-vaccinated patients. Results of the other scenarios did not show any difference in these timing between the vaccinated and non-vaccinated groups, where the greatest requirement for ICU beds for the realistic and pessimistic scenarios will be needed by early Jan 2022.

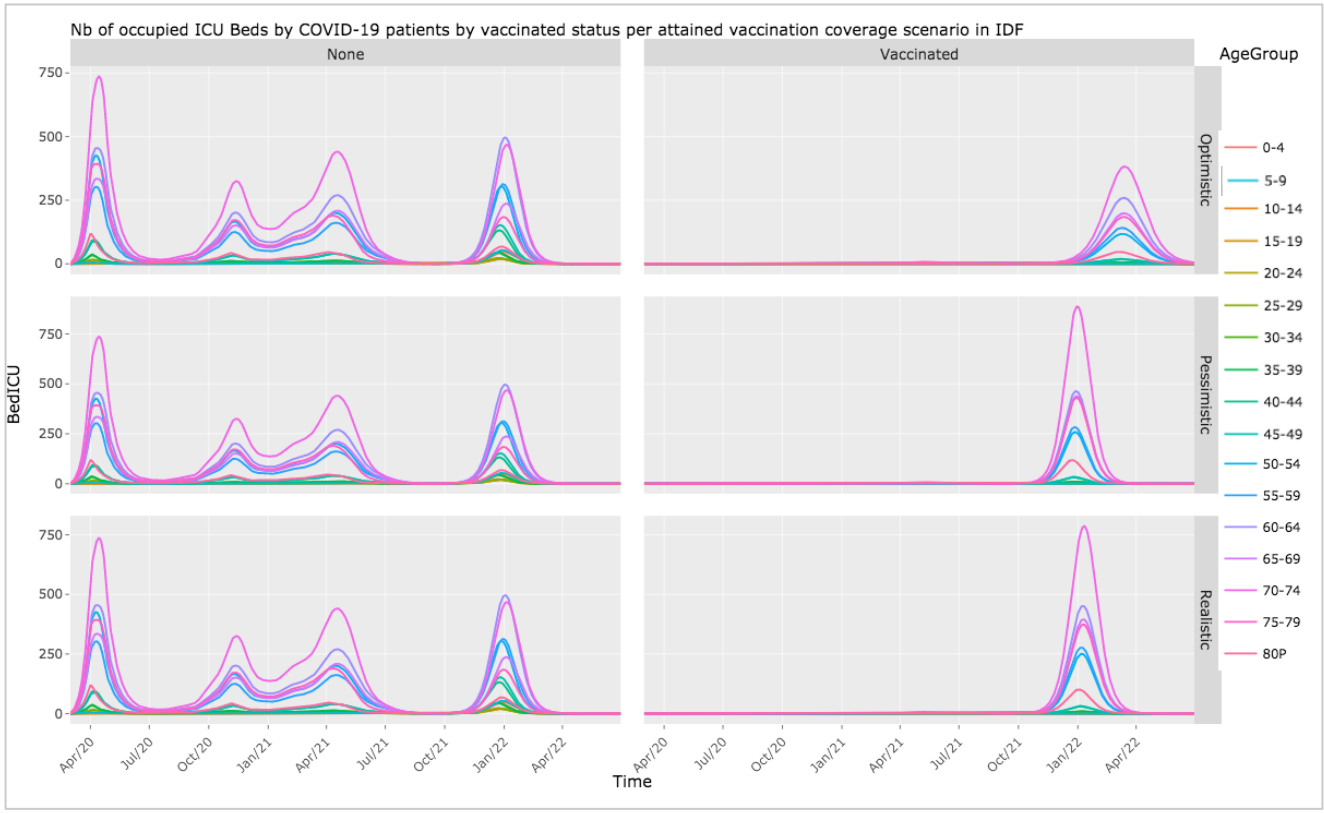

Figure 9 Number of daily required ICU beds by COVID-19 patients categorized by vaccinated status and vaccination campaign scenario in Ile-de-France, presented by age groups.

Concerning the analyses on the age distribution, the same age pattern in the analyses for the number of hospital admissions was found for the results of the number of required ICU bed by COVID-19 patients. With the circulation of Alpha and Delta-like variants, more individuals from the younger population will require ICU beds in a fourth resurgence of COVID-19 cases than in previous ones, if no control measures are implemented, as illustrated in Figure 10 and Table A 2. The 0-4 and 5-9 age groups will have a need of between 1,890 and 2,690 ICU beds in a potential fourth wave in comparison to <290 ICU beds observed in the last wave, and between 640 and 1,080 ICU beds compared to <150 observed for the 10-14 and 15-19 age groups. Nevertheless, only the optimistic scenario resulted in having a need for ICU beds of approximately the number of occupied ICU beds observed in previous COVID-19 outbreaks for the rest of the age groups. The 70-74 age group is the group with the largest need for ICU beds with more than 66,670 ICU beds needed in the realistic scenario, followed by the 60-64 and 65-69 age groups with 50,270 and 33,880 ICU beds needed respectively in the same scenario.

Figure 10 Comparison of the total observed number of required ICU beds by COVID-19 patients of previous waves to the estimated number by the model of the three scenarios of the potential fourth wave in Ile-de-France. Results shown by age group. "O", optimistic; "R", realistic; "P": pessimistic.

5 Discussion

5.1 Key parameters

Predicting the transmission dynamics of an infectious disease through mathematical modeling can be a challenging task, especially when it comes to novel pathogens such as SARS-CoV-2. There are many factors involved in the behavior of an epidemic that do not exclusively pertain to the infectious agent, but that are also context-dependent. Disentangling their associations and understanding how all these parameters influence the dynamics of an outbreak is the basis for the mathematical modeling of an infectious disease.

In the context of COVID-19, estimates for some of its parameters are still limited and not fully understood, but thanks to collective and worldwide contributions enough information has been gathered in order to produce insightful SARS-CoV-2 epidemic models, such as the one described in this work. As further research is completed and more data is collected on the key parameters influencing the COVID-19 health crisis, models will be able to reproduce more accurately the dynamics of SARS-CoV-2 in a determined population, thus more efficient strategies can be developed so to achieve a better prevention and control of SARS-CoV-2 epidemics.

5.2 Model outcomes

Initial results indicated that with a higher level of vaccination coverage such as the one considered in the optimistic scenario, the arrival of a fourth COVID-19 wave could be delayed in comparison to the other two scenarios, but would still be highly possible if no control measures are implemented. Additionally, the results of the realistic and pessimistic scenarios exhibited the importance of implementing timely interventions, since not doing so could cause an abrupt and significant increase on the number of hospital admissions and on the need for ICU beds, which could potentially be even higher than the ones seen during the three previous COVID-19 waves, as observed in Figure 5 and Figure 8. Moreover, only a high level of vaccination coverage such as the one proposed in the optimistic scenario could potentially prevent an overrun of the ICU capacities with no interventions implemented after September 2021.

Analyses done over the vaccination status of individuals and number of hospitalizations and ICU beds needed reinforced the argument that vaccination alone will not be able to stop an upcoming potential surge of COVID-19 cases, and that interventions that reduce SARS-CoV-2 transmission must continue to be applied after the summer of 2021 if a further public health crisis is to be avoided in Ile-de-France. Even in a population with high vaccination coverage such as in the optimistic scenario, individuals are still prone to developing severe disease that end up in hospital and ICU admissions because no vaccine completely prevents from developing severe COVID-19. Therefore, it is substantial to continue with the implementation of interventions that reduce viral spread, as individual protection is not enough to halt the onset of a fourth surge of COVID-19 cases. Nonetheless, vaccines are still successful at containing the escalation of the number of severe COVID-19 cases, even with the efficacy decrease caused by the arrival of the new variants. Though the number of vaccinated individuals who are hospitalized and need an ICU bed is generally larger than the number of non-vaccinated individuals (Figure 6 and Figure 9), the proportion of such admissions in regards to the total number of vaccinated individuals in each age group is smaller than in the non-vaccinated category, as illustrated in Figure A 1 and Figure A 2 for all age groups and all scenarios. For instance, the >80 vaccinated age group in the realistic scenario could reach almost 300 hospitalizations per day in comparison to almost 200 of the >80 non-vaccinated age group, yet vaccinated individuals represent 90% of the population of this age group whereas the non-vaccinated group only 10% (Figure 6).

Parallel results were obtained regarding the ICU beds needed, yet the optimistic scenario showed that the number of ICU beds for non-vaccinated and vaccinated patients will be staggered, meaning that vaccination does not only contain the number of hospital and ICU admissions but that it delays their influx. Subsequently, it is to expect that a large portion of hospitalizations and ICU patients in a fourth COVID-19 wave will be vaccinated individuals as the majority of the at-risk

population will be vaccinated, however this is in a situation where no mitigation measures are implemented and where the fourth outbreak is left to cease on its own.

Lastly, the vast amount of hospitalizations and required ICU beds regarding the younger age groups in a potential fourth COVID-19 surge can be explained by the fact that these groups have the least amount of vaccinated individuals, which in addition to being exposed to more transmissible variants such as the Alpha and Delta variants, leave them more vulnerable to develop a more severe form of COVID-19.

5.3 Strengths

To our knowledge, there are not a lot of studies done exclusively to consolidate all key aspects of a SARS-CoV-2 epidemic for its mathematical modeling. As of the time of writing this manuscript, only the report done by Biggerstaff et al[3] at the CDC had the most comprehensive list of parameters, although it only includes information of the very beginning of the pandemic. Our work was able to identify additional parameters, and since the project was completed a year after the pandemic began, updated data has also been able to be reported. Additionally, given how the SARS-CoV-2 pandemic performs differently depending on the setting, an attempt was made to gather as much information as possible exclusively to the epidemic in France in order to get a more representative explanation of the country's health crisis.

Regarding the second phase of the study, the main strength was the feature of the mathematical model to consider the impact of vaccinating individuals with more than one vaccine, as well as the inclusion of Alpha-Delta-like variants into the modeling of the SARS-CoV-2 epidemic until mid-2022 in the country. These features allowed for a more accurate representation of the situation in France, aside from obtaining more realistic results on how the epidemic will unwind after the summer of 2021.

5.4 Limitations

The limitations of the first phase comprise the inclusion of reports that have not yet been peer reviewed and that no formal assessment of biases on the cited works was done. Similarly, as the SARS-CoV-2 is still ongoing at the time of writing this work, some of the estimates may evolve as more data is collected on the different parameters of the epidemic.

Some of the second phase limitations include the continuous change in vaccine efficacy with the emergence of new SARS-CoV-2 variants, the inclusion of values that do not concern solely France's population and seasonality not being included in the model. Additionally, even if the vaccination coverage scenarios were based on factual data on the number of vaccinated people in June 2021 when vaccination eligibility was including the majority of the population, the proposed attained vaccination coverage levels for the three scenarios by September 2021 remains

theoretical. Similarly, consideration of the Alpha and Delta-like variants into the model was not completely representative. The circulation of the variants in the population of Ile-de-France was pondered from September 2021 onwards, but the variants had been introduced into the population beforehand. Likewise, their dynamics were not modeled per se for simplification purposes, but rather the relative increase in transmission compared to the historical variant was considered to account for them within the overall epidemic dynamic, where the Alpha-like variant was considered to be 60% more transmissible than the historical strain and the Delta-like variant 40% more transmissible than the Alpha-like variant.

Furthermore, a lot of uncertainties regarding the population's behavior and sentiment towards vaccines still exist. Even if vaccination hesitancy seems to have reduced in the last months, there is a possibility that the summer vacations will have an influence on people's desire to get vaccinated or on their compliance with self-control measures, which altogether could have a conceivable impact on the epidemic's dynamic as control measures have been drastically relaxed since the beginning of the summer 2021.

6 Conclusion

Analyses clearly demonstrated that relying only on vaccination campaigns that attain a total vaccination coverage of between 51.5% and 72.5% is not enough to prevent another COVID-19 resurgence when highly transmissible variants are circulating in the population. If further saturation of the hospital services is to be avoided, more individuals need to be vaccinated by either advocating the importance of vaccination and promoting vaccination campaigns, or by ensuring that people will still be able to get vaccinated after the end of the summer 2021. On the other hand, the implementation of non-pharmaceutical interventions that limit the transmission of the virus in combination with the proposed vaccination campaigns could help prevent another public health crisis, at least until vaccines with higher efficacies and pharmaceutical treatments are approved for authorization.

Modeling the dynamics of infectious diseases is a powerful tool that helps implement effective control and mitigation measures. As demonstrated by the results shown previously, mathematical models can provide valuable insights without having to expend many resources and in a relatively short period of time. They can estimate the magnitude of a potential outbreak, and are able to explore and evaluate different interventions, as well as when it is most effective to implement them, all in a theoretical milieu, so to guide decision makers and health policy to make educated decisions for the better handling of health crises.

7 References

1. Santé Publique France. Coronavirus : chiffres clés et évolution de la COVID-19 en France et dans le Monde. Santé Publique France. Published February 18, 2021. https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-chiffres-cles-et-evolution-de-la-covid-19-en-france-et-dans-le-monde

2. Roberts M. Coronavirus: France's first known case "was in December."https://www.bbc.com/news/world-europe-52526554. Published May 5, 2020. Accessed February 18, 2020.

3. Biggerstaff M, Cowling BJ, Cucunubá ZM, et al. Early Insights from Statistical and Mathematical Modeling of Key Epidemiologic Parameters of COVID-19. *Emerg Infect Dis*. 2020;26(11). doi:10.3201/eid2611.201074

4. Saad-Roy CM, Wagner CE, Baker RE, et al. Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years. *Science*. 2020;370(6518):811-818. doi:10.1126/science.abd7343

5. Good MF, Hawkes MT. The Interaction of Natural and Vaccine-Induced Immunity with Social Distancing Predicts the Evolution of the COVID-19 Pandemic. Sher A, ed. *mBio*. 2020;11(5):e02617-20, /mbio/11/5/mBio.02617-20.atom. doi:10.1128/mBio.02617-20

6. Nessma Adil MY, Christian H, Obama T, et al. *The Impact of COVID-19 Vaccination Campaigns Accounting for Antibody-Dependent Enhancement*. Immunology; 2021. doi:10.1101/2021.01.04.425198

7. Salje H, Kiem CT, Lefrancq N, et al. Estimating the burden of SARS-CoV-2 in France. Published online April 20, 2020:44.

8. Roux J, Massonnaud C, Crépey P. *COVID-19: One-Month Impact of the French Lockdown on the Epidemic Burden*. Epidemiology; 2020. doi:10.1101/2020.04.22.20075705

9. Massonnaud C, Roux J, Crépey P. *COVID-19: Forecasting Short Term Hospital Needs in France*. Epidemiology; 2020. doi:10.1101/2020.03.16.20036939

10. Sermet-Gaudelus I, Temmam S, Huon C, et al. *Prior Infection by Seasonal Coronaviruses Does Not Prevent SARS-CoV-2 Infection and Associated Multisystem Inflammatory Syndrome in Children*. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.06.29.20142596

11. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science*. 2020;368(6493):860-868. doi:10.1126/science.abb5793

12. ACROBiosystems. SARS-CoV-2 Infection: Do You Know About the Antibody-Dependent Enhancement (ADE)? *News-Medical*. https://www.news-medical.net/whitepaper/20201223/SARS-CoV-2-Infection-Do-You-Know-About-the-Antibody-Dependent-Enhancement-(ADE).aspx. Published December 23, 2020.

13. Humphries R, Spillane M, Mulchrone K, Wieczorek S, O'Riordain M, Hövel P. A metapopulation network model for the spreading of SARS-CoV-2: Case study for Ireland. *Infect Dis Model*. 2021;6:420-437. doi:10.1016/j.idm.2021.01.004

14. Santé Publique France. CoVaPred : comment se protège la population et quelle est l'intention de vaccination contre la COVID-19 quand le vaccin sera disponible ? Santé Publique France. Published December 9, 2020. https://www.santepubliquefrance.fr/etudes-et-enquetes/covapred-comment-se-protege-la-population-et-quelle-est-l-intention-de-vaccination-contre-la-covid-19-quand-le-vaccin-sera-disponible

15. Schwarzinger M, Watson V, Arwidson P, Alla F, Luchini S. COVID-19 vaccine hesitancy in a representative working-age population in France: a survey experiment based on vaccine characteristics. *Lancet Public Health*. 2021;6(4):e210-e221. doi:10.1016/S2468-2667(21)00012-8

16. Santé Publique France. CoviPrev : une enquête pour suivre l'évolution des comportements et de la santé mentale pendant l'épidémie de COVID-19. Santé Publique France. Published June 4, 2021. https://www.santepubliquefrance.fr/etudes-et-enquetes/coviprev-une-enquete-pour-suivre-l-evolution-des-comportements-et-de-la-sante-mentale-pendant-l-epidemie-de-covid-19#block-242830

17. Lazarus JV, Ratzan SC, Palayew A, et al. A global survey of potential acceptance of a COVID-19 vaccine. *Nat Med*. 2021;27(2):225-228. doi:10.1038/s41591-020-1124-9

18. Mueller JE, Olivier C, Diaz Luevano C, et al. Étude transversale des intentions de vaccination contre la grippe saisonnière et la COVID-19 des professionnels de santé : quels leviers pour la promotion vaccinale ? Bulletin épidémiologique hebdomadaire, 2021, n°. 2-série Covid-19, pp. 2-9. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/article/etude-transversale-des-intentions-de-vaccination-contre-la-grippe-saisonniere-et-la-covid-19-des-professionnels-de-sante-quels-leviers-pour-la-pr

19. data.gouv.fr. Indicateurs de suivi de l'épidémie de COVID-19. Published April 18, 2021. https://www.data.gouv.fr/fr/datasets/indicateurs-de-suivi-de-lepidemie-de-covid-19/

20. World Health Organization. *Transmission of SARS-CoV-2: Implications for Infection Prevention Precautions*.; 2020. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions#:~:text=The%20incubation%20period%20of%20COVID,to%20a%20confirmed%20case

21. Mc Evoy D, McAloon CG, Collins ÁB, et al. *The Relative Infectiousness of Asymptomatic SARS-CoV-2 Infected Persons Compared with Symptomatic Individuals: A Rapid Scoping Review*. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.07.30.20165084

22. Sayampanathan AA, Heng CS, Pin PH, Pang J, Leong TY, Lee VJ. Infectivity of asymptomatic versus symptomatic COVID-19. *The Lancet*. 2021;397(10269):93-94. doi:10.1016/S0140-6736(20)32651-9

23. Gao M, Yang L, Chen X, et al. A study on infectivity of asymptomatic SARS-CoV-2 carriers. *Respir Med*. 2020;169:106026. doi:10.1016/j.rmed.2020.106026

24. Tan J, Liu S, Zhuang L, et al. Transmission and clinical characteristics of asymptomatic patients with SARS-CoV-2 infection. *Future Virol*. 2020;15(6):373-380. doi:10.2217/fvl-2020-0087

25. CDC. COVID-19 Pandemic Planning Scenarios. Centers for Disease Control and Prevention. Published March 19, 2021. https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html

26. Roques L, Klein EK, Papaïx J, Sar A, Soubeyrand S. Using Early Data to Estimate the Actual Infection Fatality Ratio from COVID-19 in France. *Biology*. 2020;9(5):97. doi:10.3390/biology9050097

27. ECDC. Data on hospital and ICU admission rates and current occupancy for COVID-19. Published online April 15, 2021. https://www.ecdc.europa.eu/en/publications-data/download-data-hospital-and-icu-admission-rates-and-current-occupancy-covid-19

28. Kiem C, Massonnaud C, Levy-Bruhl D, et al. Evaluation des stratégies vaccinales COVID-19 avec un modèle mathématique populationnel. Published online December 23, 2020:42.

29. Oster AM, Caruso E, DeVies J, Hartnett KP, Boehmer TK. Transmission Dynamics by Age Group in COVID-19 Hotspot Counties — United States, April–September 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(41):1494-1496. doi:10.15585/mmwr.mm6941e1

30. ECDC. Risk factors and risk groups COVID-19. European Centre for Disease Prevention and Control. Published November 16, 2020. https://www.ecdc.europa.eu/en/covid-19/latest-evidence/epidemiology

31. Stern A, Andino R. Viral Evolution. In: *Viral Pathogenesis*. Elsevier; 2016:233-240. doi:10.1016/B978-0-12-800964-2.00017-3

32. Pereson MJ, Flichman DM, Martínez AP, Baré P, Garcia GH, Di Lello FA. Evolutionary analysis of SARS-CoV-2 spike protein for its different clades. *J Med Virol*. 2021;93(5):3000-3006. doi:10.1002/jmv.26834

33. Alam I, Radovanovic A, Incitti R, et al. CovMT: an interactive SARS-CoV-2 mutation tracker, with a focus on critical variants. *Lancet Infect Dis*. 2021;21(5):602. doi:10.1016/S1473-3099(21)00078-5

34. Chand M, Hopkins S, Dabrera G, et al. *Investigation of Novel SARS-COV-2 Variant Variant of Concern 202012/01*. Public Health England; 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959438/Technical_Briefing_VOC_SH_NJL2_SH2.pdf

35. COG-UK. *COG-UK Update on SARS-CoV-2 Spike Mutations of Special Interest*. COVID-19 Genomics UK Consortium; 2020. https://web.archive.org/web/20201225050316/https://www.cogconsortium.uk/wp-content/uploads/2020/12/Report-1_COG-UK_20-December-2020_SARS-CoV-2-Mutations_final_updated2.pdf

36. Santé Publique France. Coronavirus : circulation des variants du SARS-CoV-2. Santé Publique France. Published April 23, 2021. https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-circulation-des-variants-du-sars-cov-2

37. CDC. Science Brief: Emerging SARS-CoV-2 Variants. Centers for Disease Control and Prevention. Published January 28, 2021. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-emerging-variants.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fmore%2Fscience-and-research%2Fscientific-brief-emerging-variants.html

38. ECDC. SARS-CoV-2 variants of concern as of 3 June 2021. European Centre for Disease Prevention and Control. Published June 3, 2021. https://www.ecdc.europa.eu/en/covid-19/variants-concern

39. FranceInfo. Anticorps monoclonaux et Interféron : ce que l'on sait des "traitements innovants" contre le Covid-19 évoqués par Olivier Véran.https://www.francetvinfo.fr/sante/maladie/coronavirus/anticorps-monoclonaux-et-interferon-ce-que-l-on-sait-des-traitements-innovants-contre-le-covid-19-evoques-par-olivier-veran_4311899.html. Published February 26, 2021.

40. Ministère des Solidarités et de la Santé. Traitement par anticorps monoclonaux. Published February 24, 2021. https://solidarites-sante.gouv.fr/soins-et-maladies/maladies/maladies-infectieuses/coronavirus/tout-savoir-sur-la-covid-19/article/traitement-par-anticorps-monoclonaux

41. ANSM. Anticorps monoclonaux : l'ANSM permet l'utilisation en accès précoce de deux bithérapies contre la COVID-19. Agence nationale de sécurité du médicament et des produits de santé. Published March 15, 2021. https://ansm.sante.fr/actualites/anticorps-monoclonaux-lansm-permet-lutilisation-en-acces-precoce-de-deux-bitherapies-contre-la-covid-19

42. Pfizer Inc. Pfizer and BioNTech Confirm High Efficacy and No Serious Safety Concerns Through Up to Six Months Following Second Dose in Updated Topline Analysis of Landmark COVID-19 Vaccine Study. Pfizer. Published April 1, 2021. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious

43. CDC. COVID-19 Medical Conditions. Centers for Disease Control and Prevention. Published March 29, 2021. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

44. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry. Published online February 2021. https://www.fda.gov/media/137926/download

45. Pfizer Inc. Real-World Evidence Confirms High Effectiveness of Pfizer-BioNTech COVID-19 Vaccine and Profound Public Health Impact of Vaccination One Year After Pandemic Declared. Pfizer. Published

March 11, 2021. https://www.pfizer.com/news/press-release/press-release-detail/real-world-evidence-confirms-high-effectiveness-pfizer

46. Bernal JL, Andrews N, Gower C, et al. *Effectiveness of COVID-19 Vaccines against the B.1.617.2 Variant*. Epidemiology; 2021. doi:10.1101/2021.05.22.21257658

47. Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. *N Engl J Med*. Published online May 5, 2021:NEJMc2104974. doi:10.1056/NEJMc2104974

48. Public Health England. *COVID-19 Vaccine Surveillance Report*. Public Health England; 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/995101/Vaccine_surveillance_report_-_week_24_v2.pdf

49. Liu Y, Liu J, Xia H, et al. Neutralizing Activity of BNT162b2-Elicited Serum. *N Engl J Med*. 2021;384(15):1466-1468. doi:10.1056/NEJMc2102017

50. Heart Matters Magazine. Covid variants: latest on the Indian, Brazilian, UK and South African variants. *Br Heart Found*. Published online April 26, 2021. https://www.bhf.org.uk/informationsupport/heart-matters-magazine/news/coronavirus-and-your-health/covid-variant#BRApfizer

51. European Medicines Agency. *COVID-19 Vaccine Moderna: EPAR - Product Information*. Committee for Medicinal Products for Human Use (CHMP); 2021:7. https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-epar-product-information_en.pdf

52. Moderna. Moderna Provides Clinical and Supply Updates on COVID-19 Vaccine Program Ahead of 2nd Annual Vaccines Day. Moderna Inc. Published April 13, 2021. https://investors.modernatx.com/news-releases/news-release-details/moderna-provides-clinical-and-supply-updates-covid-19-vaccine

53. Moderna. Moderna COVID-19 Vaccine Retains Neutralizing Activity Against Emerging Variants First Identified in the U.K. and the Republic of South Africa. Moderna Inc. Published January 25, 2021. https://investors.modernatx.com/news-releases/news-release-details/moderna-covid-19-vaccine-retains-neutralizing-activity-against/

54. Conseil scientifique. LE VARIANT « BRESILIEN » P1 : ANTICIPER POUR L'ETE. Published online April 16, 2021. https://solidarites-sante.gouv.fr/IMG/pdf/avis_conseil_scientifique_16_avril_2021.pdf

55. AstraZeneca. AZD1222 US Phase III primary analysis confirms safety and efficacy. AstraZeneca. Published March 25, 2021. https://www.astrazeneca.com/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html

56. European Medicines Agency. *COVID-19 Vaccine AstraZeneca*. Committee for Medicinal Products for Human Use (CHMP); 2021:114-115 & 120-121. https://www.ema.europa.eu/en/documents/assessment-report/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf

57. Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *The Lancet*. 2021;397(10282):1351-1362. doi:10.1016/S0140-6736(21)00628-0

58. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med*. Published online March 16, 2021:NEJMoa2102214. doi:10.1056/NEJMoa2102214

59. Dejnirattisai W, Zhou D, Supasa P, et al. *Antibody Evasion by the Brazilian P.1 Strain of SARS-CoV-2*. Microbiology; 2021. doi:10.1101/2021.03.12.435194

60. European Medicines Agency. *COVID-19 Vaccine Janssen: EPAR - Product Information*. Committee for Medicinal Products for Human Use (CHMP); 2021:8. https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf

61. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med*. Published online April 21, 2021:NEJMoa2101544. doi:10.1056/NEJMoa2101544

62. Infovac. Vaccins contre le COVID-19 : liste des essais cliniques. Published April 29, 2021. https://www.infovac.ch/fr/infovac/actualites/955-vaccins-contre-le-covid-19-liste-des-essais-cliniques

63. V Shah AS, Gribben C, Bishop J, et al. *Effect of Vaccination on Transmission of COVID-19: An Observational Study in Healthcare Workers and Their Households*. Public and Global Health; 2021. doi:10.1101/2021.03.11.21253275

64. ECDC. *Risk of SARS-CoV-2 Transmission from Newly- Infected Individuals with Documented Previous Infection or Vaccination*. European Centre for Disease Prevention and Control (ECDC); 2021. https://www.ecdc.europa.eu/sites/default/files/documents/Risk-of-transmission-and-reinfection-of-SARS-CoV-2-following-vaccination.pdf

65. ECDC. *Guidelines for the Implementation of Non- Pharmaceutical Interventions against COVID-19*. European Centre for Disease Prevention and Control (ECDC); 2020. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-guidelines-non-pharmaceutical-interventions-september-2020.pdf

66. Luo J. Forecasting COVID-19 pandemic: Unknown unknowns and predictive monitoring. *Technol Forecast Soc Change*. 2021;166:120602. doi:10.1016/j.techfore.2021.120602

67. Sun J, Chen X, Zhang Z, et al. Forecasting the long-term trend of COVID-19 epidemic using a dynamic model. *Sci Rep*. 2020;10(1):21122. doi:10.1038/s41598-020-78084-w

68. Petter E, Mor O, Zuckerman N, et al. *Initial Real World Evidence for Lower Viral Load of Individuals Who Have Been Vaccinated by BNT162b2*. Epidemiology; 2021. doi:10.1101/2021.02.08.21251329

69. Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. *N Engl J Med*. 2020;383(16):1544-1555. doi:10.1056/NEJMoa2024671

70. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577

71. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389

72. Santé Publique France. COVID-19 : point épidémiologique du 18 février 2021. Santé Publique France. Published February 18, 2021. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-18-fevrier-2021

73. Lauerman J, Gale J. Can a Vaccinated Person Still Spread the Coronavirus? *The Washington Post*. https://www.washingtonpost.com/business/can-a-vaccinated-person-still-spread-the-coronavirus/2021/02/22/00d4f6a8-7551-11eb-9489-8f7dacd51e75_story.html. Published February 23, 2021.

74. L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). *PROTOCOLE D'UTILISATION THÉRAPEUTIQUE ET DE RECUEIL D'INFORMATIONS Bamlanivimab 700 Mg/20 ML (35mg/ML) Solution à Diluer Pour Perfusion*.; 2021. https://www.ansm.sante.fr/var/ansm_site/storage/original/application/b15191dc7046163dc3c81aba0d1272f2.pdf

75. Diebold A, Jaby F, Rozier G, Souvy M. *CovidTracker*. https://covidtracker.fr/vaccintracker/

76. Tirado SMC, Yoon K-J. Antibody-Dependent Enhancement of Virus Infection and Disease. *Viral Immunol*. 2003;16(1):69-86. doi:10.1089/088282403763635465

77. The Lancet Public Health. COVID-19 in France: challenges and opportunities. *Lancet Public Health*. 2021;6(4):e192. doi:10.1016/S2468-2667(21)00054-2

78. Serhan Y. The Vaccine-Hesitant Man of Europe. *The Atlantic*. https://www.theatlantic.com/international/archive/2021/03/france-vaccine-hesitancy-astra-zeneca/618316/. Published March 18, 2021.

79. Gauchon R, Ponthus N, Pothier C, et al. *Lessons Learnt from the Use of Compartmental Models over the COVID-19 Induced Lockdown in France*. Epidemiology; 2021. doi:10.1101/2021.01.11.21249565

80. Gauchon R, Ponthus N, Pothier C, et al. *Lessons Learnt from the Use of Compartmental Models over the COVID-19 Induced Lockdown in France*. Epidemiology; 2021. doi:10.1101/2021.01.11.21249565

81. Pageaud S, Ponthus N, Gauchon R, et al. *Adapting French COVID-19 Vaccination Campaign Duration to Variant Dissemination*. Infectious Diseases (except HIV/AIDS); 2021. doi:10.1101/2021.03.17.21253739

82. Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*. 2021;372(6538):eabg3055. doi:10.1126/science.abg3055

83. Stern A, Andino R. Viral Evolution. In: *Viral Pathogenesis*. Elsevier; 2016:233-240. doi:10.1016/B978-0-12-800964-2.00017-3

84. Clinical trials for SARS-CoV-2 OR Covid-19 AND treatment. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/search?query=SARS-CoV-2+OR+Covid-19+AND+treatment&status=ongoing&phase=phase-three&resultsstatus=trials-with-results

85. Liu Y, Liu J, Xia H, et al. Neutralizing Activity of BNT162b2-Elicited Serum. *N Engl J Med*. 2021;384(15):1466-1468. doi:10.1056/NEJMc2102017

86. European Medicines Agency. *COVID-19 Vaccine Janssen*. Committee for Medicinal Products for Human Use (CHMP); 2021:88. https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-janssen-epar-public-assessment-report_en.pdf

87. European Medicines Agency. *Comirnaty : EPAR - Product Information*. Committee for Medicinal Products for Human Use (CHMP); 2021:8. https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

88. Ministère des Solidarités et de la Santé. Indicateurs de suivi de l'épidémie de COVID-19. Accessed June 1, 2021. https://www.data.gouv.fr/fr/datasets/indicateurs-de-suivi-de-lepidemie-de-covid-19/

89. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021;384(15):1412-1423. doi:10.1056/NEJMoa2101765

90. Cherian S, Potdar V, Jadhav S, et al. *Convergent Evolution of SARS-CoV-2 Spike Mutations, L452R, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India*. Molecular Biology; 2021. doi:10.1101/2021.04.22.440932

91. Grassly NC, Fraser C. Mathematical models of infectious disease transmission. *Nat Rev Microbiol*. 2008;6(6):477-487. doi:10.1038/nrmicro1845

8 Appendices

8.1 Appendix 1: Total number of hospitalizations

Table A 1 Total number of hospitalizations by age group per COVID-19 wave

Total number of hospitalizations by age group per COVID-19 wave

				4th Wave		
Age	1st Wave	2nd Wave	3rd Wave	Optimistic	Pessimistic	Realistic
0-4	90	70	150	960	1230	1180
5-9	90	70	150	1130	1370	1340
10-14	30	30	60	350	550	520
15-19	50	40	80	330	520	490
20-24	430	300	520	640	1160	1070
25-29	460	320	550	670	1240	1130
30-34	720	510	860	1100	1940	1790
35-39	770	540	890	1100	1860	1730
40-44	1180	830	1380	1720	2990	2770
45-49	1010	730	1260	1770	3190	2930
50-54	3670	2600	4310	4170	7470	6180
55-59	2560	1910	3350	4530	7830	6520
60-64	3550	2680	4730	4900	11220	9200
65-69	2530	1950	3520	3700	7160	6000
70-74	5340	4120	7260	7090	14000	11730
75-79	4970	3690	5540	5550	9800	8740
80P	9470	7390	11820	13310	25570	22250

8.2 Appendix 2: Total number of ICU beds occupied by COVID-19 patients by age group

Table A 2 Total number of occupied ICU beds by age group per COVID-19 wave

Total number of required ICU Beds by age group per COVID-19 wave

				4th Wave		
Age	1st Wave	2nd Wave	3rd Wave	Optimistic	Pessimistic	Realistic
0-4	180	140	290	1890	2410	2320
5-9	180	140	290	2220	2690	2620
10-14	70	50	110	690	1080	1010
15-19	90	80	150	640	1020	960
20-24	480	340	590	730	1300	1200
25-29	510	360	620	750	1400	1280
30-34	1020	710	1230	1580	2770	2550
35-39	1100	750	1270	1580	2660	2470
40-44	3210	2200	3820	4760	8250	7620
45-49	3000	2110	3820	5330	9560	8770
50-54	16150	11050	19490	18740	33460	27670
55-59	11550	8310	15540	20910	35970	29940
60-64	18980	13730	26140	26880	61320	50270
65-69	13970	10310	20090	21000	40470	33880
70-74	29630	21890	42060	40420	79570	66670
75-79	16440	11760	19250	18820	33150	29560
80P	3500	2690	4440	4950	9500	8270

8.3 Appendix 3: Comparison of the proportion of hospitalized individuals in each age group by vaccine status per scenario in Ile-de-France

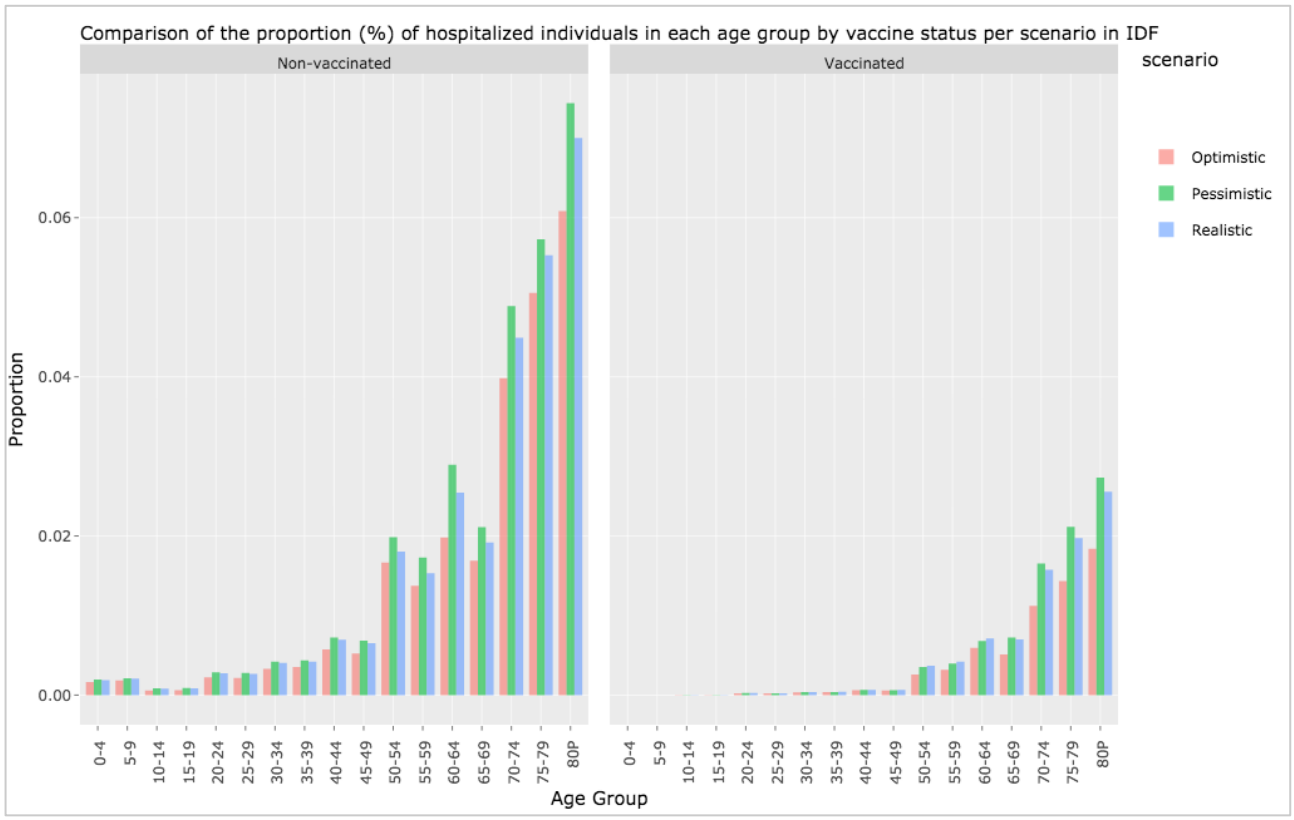

Figure A 1 Comparison of the proportion of hospitalized people in each age group by vaccine status per scenario in Ile-de-France

8.4 Appendix 4: Comparison of the proportion of the population of each age group requiring an ICU bed by vaccine status per scenario in Ile-de-France

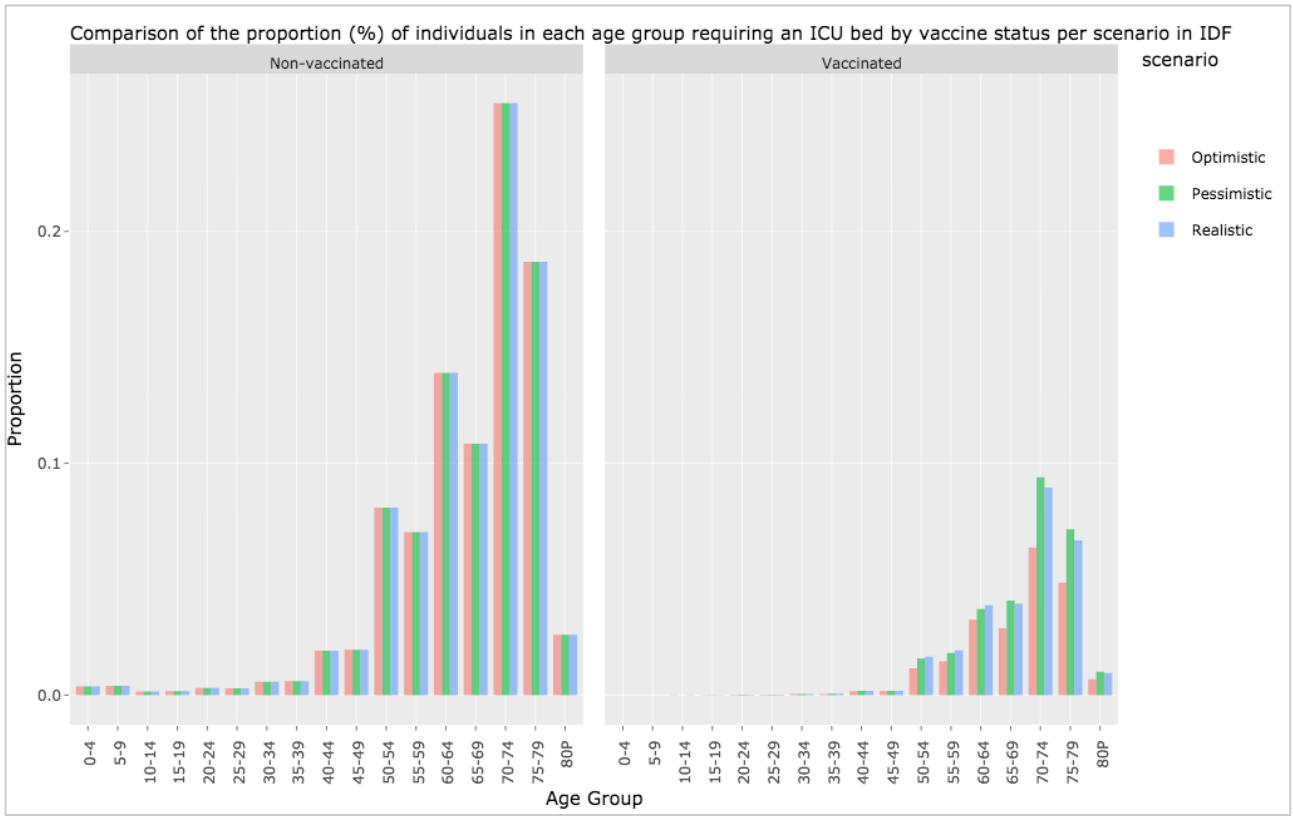

Figure A 2 Comparison of the proportion of individuals in each age group needing an intensive care unit bed by vaccine status per scenario in Ile-de-France