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“OPTION CONTRACTS IN HEALTH CARE: THE PAXLOVID CASE ASSOCIATED WITH COVID-19”

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Contents

Abstracts

Abstract in English

Option contracts have begun to be employed quite recently in the healthcare sector, so the purchase of these financial instruments by healthcare institutions for the supply of treatments, like antivirals, is limited. This research tries to indicate benefits and limitations of the use of these contracts in such sector and, subsequently, calculates the value of an American Call option that has the price of Paxlovid as its underlying. Then, the outcome is multiplied by a probability of pandemic outbreak to align this value to pandemic expectations. Lastly, a comparative statics analysis attempts to examine which variables mostly influence option's value, whereas a case study of the Italian context helps to perform an economic analysis that describes advantages and disadvantages of different possible antiviral purchasing strategies that can be implemented by the Italian government through option contracts.

Abstract in Italian

L'utilizzo dei contratti d'opzione in ambito sanitario è assai recente, perciò l'acquisto da parte di istituzioni sanitarie di questi strumenti finanziari per l'approvvigionamento di farmaci, come ad esempio gli antivirali, è limitato. Questo studio intende indicare i benefici ed i limiti dell'uso di questi contratti nel settore menzionato e, successivamente, calcolare il valore di un'opzione finanziaria call americana che abbia come sottostante il prezzo dell'antivirale Paxlovid. Poi, il risultato è moltiplicato per una probabilità di scoppio della pandemia al fine di allineare questo valore con le aspettative riguardo a una possibile pandemia. Infine, un'analisi di statica comparata cerca di esaminare quali variabili possano maggiormente influenzare il valore dell'opzione stessa, mentre un caso di studio riguardante il contesto italiano permette di effettuare un'analisi economica che descriva vantaggi e svantaggi di alcune possibili strategie di acquisto dell'antivirale tramite contratti d'opzione da parte del governo italiano.

1. Introduction

Option contracts have been employed for decades in financial markets for purposes like speculation or hedging. The research on the use of these derivatives in the healthcare sector has expanded since mid-1990's.

An increasing number of articles has been published in the last two decades, recognizing that option contracts, when dealing with investments that are uncertain, irreversible and deferrable, add flexibility to decision strategies in the health sector. This last variable, according to Lakdawalla et al. (2018), should be annexed to the traditional methodologies in healthcare evaluations, that are based on Cost – Effectiveness Analysis (CEA).

In fact, the healthcare sector may struggle to cope with epidemiological threats when flexibility is missing in its decision-making framework. More precisely, countries' antiviral purchasing strategies overlooked option contracts as viable tools to obtain necessary number of therapies in case of need.

For instance, Italian government's approach for buying treatments of Paxlovid from Pfizer in the first months of 2022 resulted in an inefficient expense, with enormous quantities of antivirals unemployed. The Italian Pandemic Preparedness Plan 2021-23 asked for the inclusion of clauses that stabilized treatments' prices, thus improving readiness and preparedness of the response to a pandemic.

The aim of this research was to define a value of one option contract written on the price of the antiviral Paxlovid, that has proven to be effective against the Covid-19 pandemic. Prices were calculated in euro currency. The buyer was assumed to be a European community healthcare institution, like European Medicines Agency (EMA), whereas the issuer was supposed to be an insurance company. The American call option was the type of derivative designated for this intent since it could be exercised at any time prior to the maturity of the option. So, the buyer of the option had the possibility to obtain the stock of Paxlovid in any moment to curb virus diffusion or to limit consequences of a peak of contagion.

In addition, a comparative statics analysis was provided to distinguish which parameters mostly influenced the price of this derivative. Lastly, a case study of the Italian context helped to perform an economic analysis that examined advantages, disadvantages and implications of various buying procedures based on option contracts. Here, different scenarios of antiviral purchasing strategies by the Italian government have been presented.

The Barone-Adesi and Whaley (1987) approximation method was utilized to price the American call option, since it worked efficiently for maturities that were less than one year and it was suitable for comparative statics analysis.

Selections of the price of the underlying S, the riskless interest rate r, the cost of carrying the commodity b, the time to maturity of the option T, the volatility of the price of the underlying σ and the strike price X were required to calculate the value of such derivative. S was assumed to be 489.41 €, i.e. the price of Paxlovid on June 14th, 2023, when the report of Institute for Clinical and Economic Review (ICER) on the efficacy of treatments for patients that contracted Covid-19 virus was updated. The strike price X was chosen equal to S. The riskless interest rate r was aligned to the bond issuances in the euro area, so equal to 3%, while b was 1.5%, which was proportional to r, as indicated by Barone-Adesi and Whaley (1987). The designated time to maturity of the option T was two months, following studies like Swain, Lin and Wallentin (2024) and Zirilli, Limonti and Alibrandi (2022) on the waves of contagion observed in Italy at the beginning of the Covid-19 pandemic. A time series retrieved from Yahoo Finance of daily adjusted closing Pfizer prices from December 2007 to May 2024 in the Frankfurt Stock Exchange has been selected to obtain an approximation of the standard deviation of the price of Paxlovid. A yearly average of those daily observations has been performed for each year among 2008 and 2023. Then, growth rates of subsequent years have been computed to calculate their standard deviation, which resulted in a volatility of 16.73%.

Barone-Adesi and Whaley (1987) approximation provided a price of 13.95882 € for the American call option. However, this derivative could not be considered as just a financial contract. Its value is contingent on a probability of pandemic outbreak, because this deal is suited for antiviral purchases to face consequences of a pandemic burst.

If any pandemic does not occur before maturity, this option is not exercised, and it expires.

Therefore, a probability of pandemic outbreak should be incorporated into the evaluation. Two different studies of Attema, Lugnér and Feenstra (2010) and Marani et al. (2021) presented, respectively, probabilities of 0.75 % in a quarter and 44 % in a century. Their equivalent values for a maturity of two months have been computed. Those two p_{Attema} and p_{Marani}, multiplied by the price of the American call, resulted in option prices of 0.0698 € and 0.0134 €.

Let us now explain the structure of this research.

Chapter 2 is divided into two paragraphs: the first one portraited a literature review of articles on the evolution of pandemics, whereas the second one analysed how a Real Options Approach (ROA) has been used in the healthcare sector.

Paragraph 2.1 started with a description of the characteristics of influenza viruses, then defined typical patterns of epidemics and enumerated all the pandemics occurred from the beginning of the 20th century. Afterwards, it illustrated origins, transmission characteristics and effects of the SARS-COV-2 pandemic before reporting a literature review of articles and World Health Organization (WHO) guidelines on how to handle epidemic threats. A specific focus on the implications of antiviral treatment and prophylaxis is visible in articles like Longini et al. (2004), Longini et al. (2005), Biggerstaff et al. (2014), "A checklist for pandemic influenza risk and impact management" from WHO (2018) and the Italian Pandemic Preparedness Plan 2021-2023.

Instead, paragraph 2.2 examined financial derivatives, with a focus on main features of option contracts: differences among European and American options, as well as between Call and Put options, have been scrutinized through the books of Boyle and McDougall (2011) and Hull (2015). Subsequently, the framework for the application of the ROA was presented, explaining the main assumptions of this project evaluation method, as well as variations among financial options and real options through the books of Dixit and Pindyck (1994) and Copeland and Antikarov (2003). Then, this paragraph has drawn a literature review of the implementation of the ROA in the healthcare sector, with a special focus on the relationship among option contracts and antiviral supplies, as indicated in Attema, Lugnér and Feenstra (2010) and Harrington and Hsu (2010).

In paragraph 3.1, benefits of the introduction of new antiviral purchasing strategies for national governments were presented, then paragraph 3.2 underlined advantages and disadvantages of various therapies against Covid-19, presenting Paxlovid as well. The emphasis in paragraph 3.3 was shifted towards a broader investigation of the clinical gains of Paxlovid, whereas paragraph 3.4 discussed the cost-effectiveness of such drug.

Chapter 4 is divided into five units.

The first paragraph explained general characteristics of the financial contract, paragraph 4.2 defined the Barone-Adesi and Whaley (1987) approximation method, then paragraph 4.3 described how data has been selected and presented results. Paragraphs 4.4 and 4.5 are devoted to, respectively, the comparative statics analysis and the economic analysis.

Conclusive remarks are proposed in chapter 5, whereas the appendix specified all the calculations needed to compute the American call option price.

2. Literature review

2.1. Evolution of the studies on flu, pandemics and measures of pandemic prevention

Influenza viruses are described as respiratory diseases that can affect humans and animals with various levels of severity, usually occurring in the period among November and April in the Northern hemisphere, or between April and November in the Southern one, because of genetically drifting strains of influenza[1].

The annual vaccination campaign helps to contain the diffusion of the influenza across the population, but relevant differences among the strains can cause the outbreak of epidemics or, in the worst case, pandemics[2].

Genetic mutations can be sometimes so deep that they can create an alarm for a "false pandemic", or it may also happen that novel viruses are isolated from human being but, without the capacity to spread worldwide, they result in a "pandemic scare"[3].

In this context, huge concern by both World Health Organization (WHO) and national governments is put in place to face bursts of influenza A viruses, that can affect human, avian and some mammalian species: these epidemics happen due to the acquired capacity of the influenza A viruses, to which humans have almost no existing immunity, to cause sustained human-to-human transmission[4]. In the worst-case scenario, outbreaks of the epidemic in single areas, regions or countries may result in a pandemic whether the spread of this virus is quickly extended on a worldwide basis, causing social and economic impacts and stressing health care systems[5].

Hence, pandemics are unpredictable but recurring events of different ranges of transmissibility and clinical severity[6], with unknown timing and impact, that periodically affect either the entire world or specific areas, regions or countries at intervals of 10 to 50 years.[7]

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[1] The source is Longini et al. (2004).
[2] While Longini et al. (2004) focuses on annual influenza vaccines, Germann et al. (2006) remarks the importance of rapid production and distribution of targeted vaccines in the case of pandemic outbursts.
[3] The source is WHO (2004).
[4] The source is WHO (2017) "Pandemic influenza risk management. A WHO guide to inform & harmonize national & international pandemic preparedness and response".
[5] See WHO (2018) "A checklist for pandemic influenza risk and impact management: building capacity for pandemic response".
[6] See Biggerstaff et al. (2014).
[7] The source is WHO (2009), which expresses that this trend has been observed since the 16th century.

The conversion of the animal influenza virus into a human one can be obtained, at a genetic level, in two different ways, which are defined as genetic reassortments and genetic mutations: in the first case, the genes from animal and human influenza viruses blend together, whereas in the second one genes from an animal influenza virus change and become capable of affecting humans and transmitting among them[8].

Even if various areas of the world may encounter different dynamics, a typical pattern of pandemics is composed by multiple waves[9], with different numbers of cases at peak for each wave. From the beginning of the 20th century, five pandemics have occurred because of antigenic shifts: the 1918-1919 “Spanish flu” A (H1N1), the 1957-1958 “Asian flu” A (H2N2), the 1968-1969 “Hong Kong flu” A (H3N2), the 2009-2010 “Swine flu” A (H1N1) and the severe acute respiratory syndrome SARS-COV-2[10].

In addition, albeit the quick spread of the 2003-2004 “Avian flu” A (H5N1) caused at least 800 deaths and alarmed the health care systems worldwide[11], measures of surveillance and containment, like isolation of symptomatic infected individuals and a tracing system for their contacts, demonstrated to be sufficient to limit the proliferation of the epidemic, due to the virus long incubation period and the fact that almost all cases were symptomatic and easy to be detected[12].

While origins of the 1918-1919 “Spanish flu” remains unknown[13], the literature agrees on the dynamics and the impact of such pandemic. Three waves of illnesses have been observed: the first wave started in spring 1918 in the Northern Hemisphere, whereas the second wave affected North America, Europe and Africa in fall 1918 and the third one was present in some parts of the world in winter 1919[14]. Young adults between 20 and 40 have been the most affected age group, causing over than 20 million deaths with an estimated case fatality rate, i.e. the conditional probability of death given infection or disease, that ranged among 2 and 3%[15].

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[8] The source is WHO (2017) “Pandemic influenza risk management. A WHO guide to inform & harmonize national & international pandemic preparedness and response”.

[9] The source is WHO (2004).

[10] See Biggerstaff et al. (2014), “Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023” and WHO (2017) “Pandemic influenza risk management. A WHO guide to inform & harmonize national & international pandemic preparedness and response” for an overview on these five pandemics.

[11] The source is Fraser et al. (2004).

[12] See Longini et al. (2004) for further explanation of containment measures of the SARS.

[13] The source is WHO (2009).

[14] See Biggerstaff et al. (2014).

[15] See Longini et al. (2004), “Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023” and WHO (2017) “Pandemic influenza risk management. A WHO guide to inform & harmonize national & international pandemic preparedness and response”.
The source for the definition of case fatality rate is, instead, Ejima et al. (2012).

The outbreak of the avian originated 1957-1958 "Asian flu" A (H2N2) pandemic was in Southern China in February 1957, then in the Northern hemisphere a second wave occurred in October 1957 and, lastly, a third wave in January 1958[16]. It affected all age groups, especially individuals with pre-existing medical conditions and elderly[17], causing a number of deaths that ranged approximately between one and four million people with an estimated case fatality rate lower than 0.2 %[18].

The dynamics of the avian originated 1968-1969 "Hong Kong flu" A (H3N2) pandemic have been slightly different, since in some countries the burst of the epidemic was delayed and other countries dealt with large single waves. More precisely, whereas the Hong Kong area experienced a wave in July 1968, in the United States local bursts were present from October 1968 until March 1969 and United Kingdom did not cope with a pandemic outbreak until the winter of 1969-1970; furthermore, countries in the Southern hemisphere encountered the same threat among June and September 1969[19]. All age groups were affected, particularly elderly and people with pre-existing medical conditions[20], causing approximately among one and four million of deaths with an estimated case fatality rate lower than 0.2 %[21].

A first wave of the swine originated 2009-2010 influenza A (H1N1) pandemic was firstly described in spring 2009 in Mexico and the United States, then followed by a second wave in the fall of the same year, while some countries in the Southern hemisphere only dealt with a single wave[22]. The worldwide impact of that pandemic was moderate compared to the other ones: as children aged 0 to 14 and young adults between 20 and 40 have mostly been affected, the range of deaths has approximately been among 100,000 and 400,000 people, with 0.02 % estimated case fatality rate[23].

Lastly, SARS-COV-2, identified through a study of illness individuals with some sort of pneumonia coming from seafood market at Wuhan city in China, due to a peak of contagion that almost coincides with the onset of symptoms, in addition to the vast presence of

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[16] See Biggerstaff et al. (2014).
[17] See WHO (2004).
[18] The sources for the data are "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023" and WHO (2017) "Pandemic influenza risk management. A WHO guide to inform & harmonize national & international pandemic preparedness and response".
[19] See Biggerstaff et al. (2014) and Germann et al. (2006).
[20] See WHO (2004).
[21] The sources for the data are "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023" and WHO (2017) "Pandemic influenza risk management. A WHO guide to inform & harmonize national & international pandemic preparedness and response".
[22] See Biggerstaff et al. (2014).
[23] The sources for the data are "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023" and WHO (2017) "Pandemic influenza risk management. A WHO guide to inform & harmonize national & international pandemic preparedness and response".

asymptomatic and pauci-symptomatic individuals[24], which limited the effectiveness of containment measures, have resulted in a pandemic outburst. SARS-COV viruses are one of the four types of human coronaviruses of the beta class of them, which, together with the alpha class, is able to affect humans[25].

Some authors describe bats as a natural host for SARS-COV-2, but more than one intermediary host can be present, as, for example, pangolins, which are taken into consideration; on the contrary, the possibility of a laboratory escape of such virus is excluded[26].

Other authors discovered that Covid-19 incidence is negatively correlated with humidity and rainfall, while they also noticed that temperature is positively correlated with COVID-19 mortality rates[27].

Its transmission potentially occurred via droplets, direct contact and, probably, through polluted surfaces[28], hence national authorities suggested people to avoid staying in poorly ventilated enclosed spaces, crowded public places, and close-contact settings[29], whereas its basic reproduction number R_0 is estimated to be between 2 and 3[30].

It affected all age groups, with main symptoms like high fever, dyspnoea, pneumonia, and lung problems, albeit it has revealed to be more dangerous for old people over 60 years of age and people with comorbidities such as diabetes, high blood pressure or kidney problems[31]. More than 5 million deaths have been estimated by WHO over the years 2020 and 2021[32], with a case fatality rate that drastically declined over the course of the pandemic, ranging between 20% or more in the early phase of the pandemic and less than 0.5 % at the end of 2022[33].

According to Horita and Fukumoto (2023), the prevalence of the Omicron variant[34] led to an overall decrease of the case fatality rate around the world.

[24] The source is "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023".
[25] See Bharati et al. (2022).
[26] The source is Asghar et al. (2022).
[27] The source is Basray et al. (2021).
[28] See Bharati et al. (2022).
[29] The source is Furuse et al. (2020).
[30] See Bharati et al. (2022).
[31] The source is Bharati et al. (2022).
[32] The source is Msemburi et al. (2023).
[33] The source is Horita and Fukumoto (2023).
[34] See Asghar et al. (2022) for a broader description of the Omicron variant.

Therefore, while the recurring nature of these events have alarmed WHO and governments[35], scientific literature as well has incremented the interest and the number of articles about pandemic influenza prevention.

Even if a pandemic guidance was published by WHO in 1999, articles and regulations have been produced more often since the burst of the 2003-2004 "Avian flu" A (H5N1), since it has been realized that the higher international travel would have increased, compared to the past century, the risk and the speed of transmission of a pandemic influenza[36].

The contribute of WHO is mainly linked to the creation of continuously updated preparedness plans and guidelines to be implemented in the case of pandemic outbreaks, as well as checklists of specific activities that should be adopted.

In 2004 the WHO issued a guidance on the use of influenza vaccines and antivirals during influenza pandemics, which attempts to distribute recommendations to improve overall supply of both those crucial medicines to face pandemic outbursts.

The document suggests to include antiviral stockpiling within national pandemic plans, since they will be the single virus-specific intervention during the initial response, until the arrival of a vaccine, and their protection is virtually immediate. The decision to stockpile antivirals and their deployment during a pandemic should depend on various factors like characteristics of the specific agent, chemical stability of raw materials or formulated drug, potential for antiviral drug resistance, drug costs and their reimbursement, rapid access to drugs, rationing or distribution of limited drug supplies[37]. Antivirals are supposed to be used for both treatment and prophylaxis, although the second strategy can be more expensive, due to the requirement of greater supply.

In fact, guidelines suggest, for countries with scarce supply, to resort to the first option.

Antiviral drugs for treatment can be administered twice daily both to sick people within the first 48 hours of their illness and to exposed people with a contraindication for vaccination; whereas, the use for prophylaxis requires daily administration for either long-term, in the case of seasonal prophylaxis, or short-term, to provide rapid onset of protection. The antivirals specifically analysed are oseltamivir, rimantadine and zanamivir.

[35] See Germann et al. (2006).
[36] See Germann et al. (2006).
[37] The source is WHO (2004).

National governments and healthcare institutions should deliver available medicines according to the epidemiology of the pandemic, in particular the groups most seriously affected, and to prioritized goals, such as reduction of mortality, reduction of morbidity, limiting social disruption, ensuring maintenance of health care systems, ensuring integrity of social infrastructure and limiting economic losses[38].

Moreover, the document recommends further research on dosage and possible side effects on high-risk individuals as pregnant women, immunocompromised individuals, elderly people with underlying diseases and infants. Scientific literature has contributed in various aspects of pandemic prevention, such as through the study of possible mitigation strategies or analyses of previous pandemics.

In this context, Fraser et al. (2004) have evaluated the effectiveness of containment measures put in place, in the case of no vaccines availability, to limit the proliferation of the Avian flu epidemic of 2003-2004, i.e. the isolation of symptomatic individuals, the tracing of their contacts and the quarantine for them. Through a comparison of basic reproduction number R_0[39] and θ, which is defined as the proportion of diffusion prior to symptoms, among four different viral infections, i.e. SARS, smallpox, 1978 H1N1 flu and human immunodeficiency virus, they have found that the low R_0 and θ of the SARS played a huge role in boosting the efficacy of containment measures, especially the isolation of symptomatic people[40]. Unfortunately, as it has been observed for the SARS-COV-2 pandemic[41], their conclusion is that an epidemic influenza with higher transmissibility cannot be equally contained with just the beforementioned measures.

In the same year, Hufnagel et al. (2004) have published a simulation model on the SARS epidemic that accounts for worldwide travel[42] and which lead to an evaluation of control strategies to limit pandemic spread, focusing on vaccination and different types of travel restrictions. Regarding vaccination, they suggest to use international travel to quantify the necessary portion of the population that should receive doses, in order to reduce the amount of vulnerable individuals and, so, limiting proliferation of the epidemic. Moreover, two

[38] The source is WHO (2004).
[39] See Biggerstaff et al. (2014) for the definition and a broader explanation of the concept.
[40] See Fraser et al. (2004) for the estimates of the two parameters R_0 and θ.
[41] Recall "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023".
[42] The proxy used by Hufnagel et al. (2004) is the global aviation network, examined through an investigation on civil flights among the 500 largest airports in the world.

alternatives are presented to diminish such portion: isolation of the largest cities and social distancing.

The first option is proven by the model to be the most effective one, since an isolation of only 2% of the largest cities can reduce by approximately 37% the fraction of the population that requires vaccination in the case of pandemic burst[43].

Other authors, instead, like Longini et al. (2004) have focused on the use of targeted antiviral prophylaxis (TAP) to control the escalation of pandemic influenza, and they demonstrate that such action can successfully contain the diffusion of a virus until the arrival of a vaccine. Authors choose the epidemiology of the 1957-1958 "Asian flu" A (H2N2) as the strain to be analysed in their simulation model. They show that proper timing and duration of this intervention, i.e. a prophylaxis between four and eight weeks for contacts of symptomatically infected individuals, is as effective as a vaccination of 80% of the entire population of the United States, due to multiple effects of antiviral agents, such as preventing infection given exposure and reducing both possibility of transmission to others given infection and possibility of clinical illness given infection[44].

Other interesting strategies are the geographically targeted antiviral prophylaxis (GTAP) and pre-vaccination (Pre-Vac), both presented by Longini et al. (2005) that have compared the effectiveness of various different combinations of strategies to prevent the diffusion of an influenza with a pattern between influenza A (H3N2) and influenza A (H2N2)[45].

GTAP involves the administration of one course of antiviral, in that case oseltamivir, to a fraction of individuals, quantified through a sensitivity analysis, that lives in an area in which an infected index case is identified. Pre-Vac, instead, consists of an injection with poorly matched, low-efficacy vaccine before the pandemic outbreak in order to obtain immunity to the virus by a part of the population, hence containing spread of the disease at the source[46]. The other two measures taken into consideration by Longini et al. (2005) are TAP and household quarantine. Authors emphasize the key element of timing for the implementation of TAP and GTAP. Results of the study show that Pre-Vac helps to decrease the basic reproduction number, while TAP or GTAP alone can contain pandemic with R_0 up to approximately 1.6, even though

[43] See Hufnagel et al. (2004) for the graphical representation of the effectiveness of both control measures, as well as for a comparison among them.
[44] See Longini et al. (2004) to review the effectiveness of different intervention durations for two classes of antivirals, i.e. adamantanes and neuraminidase inhibitors.
[45] The model used in the analysis is an extension of a previous one presented by Longini et al. (2004).
[46] The source for the concepts of GTAP and Pre-Vac is Longini et al. (2005).

a combination of one of these two interventions with Pre-Vac and household quarantine can limit pandemics with R_0 until 2.4[47].

Even Germann et al. (2006) have assessed and compared the benefits stemming from four different measures, such as social distancing, school closures, dynamic mass vaccination and TAP. Authors simulate, through a stochastic model[48], pandemic outbreaks of flu A H5N1 in the United States for various reproductive numbers, mimicking different transmission intensities. The mitigation procedures are deemed to be effective in this case whether they decrease the attack rate to the one of the annual influenza, close to 10% of the United States overall population. They have found that intervention policies can be very sensitive to the transmission level of the epidemic, but, on the other hand, a quick implementation of a mixture of school closures, social distancing and TAP may contain, also without available vaccines, epidemics with R_0 equal to 2.4[49], which is greater than the highest basic reproduction number observed up to the moment of publication of that study.

The growing importance of antiviral agents has been incorporated in the update of WHO pandemic preparedness plan in 2009, which also clarifies roles and responsibilities of governments, health and non-health care sectors, communities, individuals, families and WHO itself during the pandemic preparedness and response, suggesting a "whole-of-society" approach in addressing epidemic outbreaks[50]. A relevant update that can be found in this document is a precise clarification of the structure of pandemic phases, which is important to distinguish the exact activities that must be undertaken by each agent during every phase of the pandemic.

Overall, eight phases are described within this framework:

1. Phase one occurs when animal influenza viruses still have not infected humans.

2. In the phase two animal influenza viruses infect people.

3. During phase three the virus forms small clusters of infection in humans.

4. Phase four is defined through the confirmation of human-to-human transmission of the virus able to end up in "community-level" outbreaks.

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[47] See Longini et al. (2005) for a broad description of the outcomes of all possible combinations of strategies.
[48] Germann et al. (2006) asserts that such model can also take into consideration the international travel presented by Hufnagel et al. (2004).
[49] See Germann et al. (2006) for the model limitations.
[50] WHO (2009) emphasizes the involvement of each group within the society in order to coordinatively respond to a pandemic threat.

5. When human-to-human transmission in at least two countries of one WHO region is proven, phase five is proclaimed.

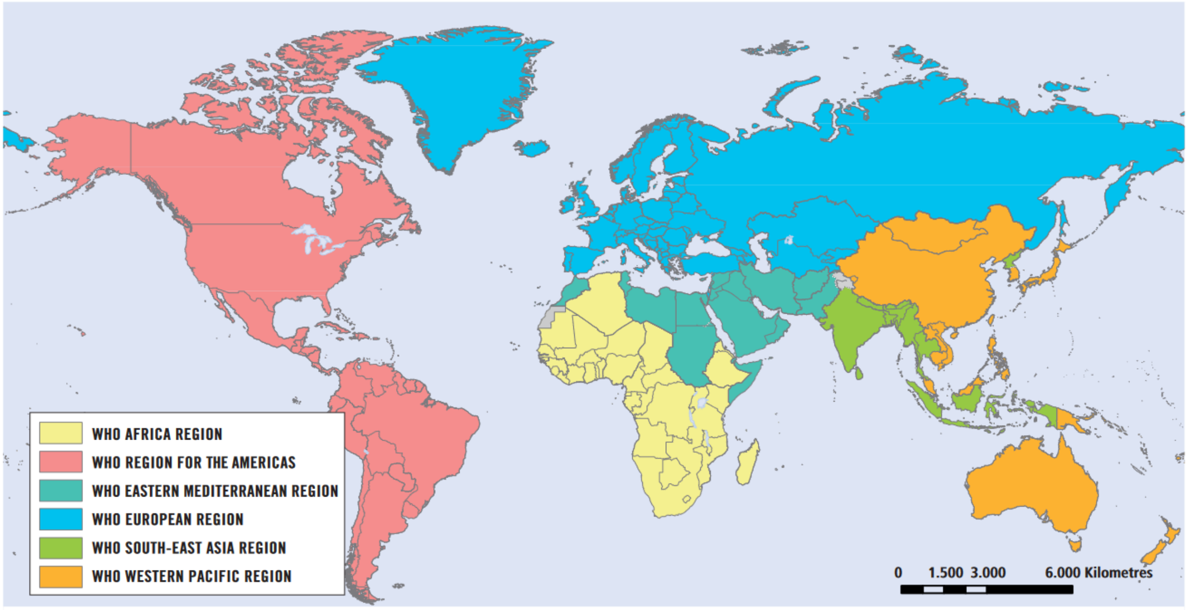
6. If this diffusion is verified in at least one other country in another WHO region, it means that a pandemic is ongoing and, therefore, phase six is announced.

7. When pandemic activity seems to be decreasing, a post-peak period is ongoing, but, on the other hand, there are chances of possible future waves.

8. Lastly, the post-pandemic period can be declared when the pandemic virus starts to produce the same effects on the population of the seasonal influenza[51].

The following figure maps the various WHO regions.

Figure 2.1: WHO regions



Source: WHO (2009)

This guidance document confirms the crucial role of WHO in assessing the pandemic response, since they state that it must supervise recommendations[52] for antiviral use both in terms of prophylaxis and treatment; in the meanwhile, it must oversee the global stockpile of antivirals, expand the availability and implement actions for their quick distribution in moments of need.

[51] The source for all pandemic phases is WHO (2009), which also specifies that the borders shown in the map do not imply any opinion on behalf of WHO itself on legal status of any territory.
[52] According to WHO (2009), the recommendations are clustered together based on the phases of the pandemic and the five components of preparedness and response, i.e. planning and coordination, situation monitoring and assessment, reducing the spread of disease, continuity of health care provision and communications.

In addition, even national governments must be involved in the management of antivirals, especially to evaluate safety and effectiveness of the drugs, as well as to cooperate with WHO in the stockpiling and allocation process.

All these articles and guidelines have been published prior to the outbreak of the 2009-2010 "Swine flu" A (H1N1), hence they have not incorporated the impact of this pandemic and the lessons that health care authorities have learnt.

So, for example, Bassetti et al. (2011) have studied the effects of the swine flu in North-western Italy, finding that age, lung and neurocognitive disorders are linked to a higher probability of the patient to be hospitalized in intensive care units[53]. At the same time, authors confirm the administration of the antiviral oseltamivir to 85% of the patients, mainly in a range of two days after the onset of symptoms.

Biggerstaff et al. (2014), instead, published a literature review of the values of the reproduction number across the pandemics of 1918-1919, 1957-1958, 1968-1969, 2009-2010 and the seasonal influenza. It is a very relevant article for the purpose of this study, because the reproduction number, i.e. the virus transmission magnitude, affects the intensity of the intervention strategies, so, for example, the amount of antivirals stockpiled in advance as a prevention for possible pandemics: since, as specified by Biggerstaff et al. (2014), a reproduction number greater than 1 results in a growth of the infection within the population, then a higher R can be connected with higher antiviral stockpiling needed to intervene[54].

Actually, according to this article, the reproduction number, described as the number of individuals that can be infected by a confirmed case in the absence of preventing mechanisms, is dependent on the amount of people that are susceptible to the virus. Moreover, authors also highlight two other concepts: the basic reproduction number R_0 and the effective reproduction number R_E. In the first case, the population taken into consideration is wholly susceptible to the virus, whereas in the second case a fraction of the population has obtained immunity, so the proportion of susceptible individuals is reduced.

The pandemics analysed by the authors assume different values of the reproduction number R: for the 1918-1919 "Spanish flu" the median estimate is 1.80, for the 1957-1958 pandemic it is 1.65, in the case of 1968-1969 "Hong Kong" flu it is 1.80 and, lastly, 2009-2010 swine influenza

[53] See Bassetti et al. (2011) for a broader description of the sample studied and the criteria for hospital admission.
[54] This correlation between antiviral stockpiling and the reproduction number is underlined by Germann et al. (2006) in the description of the impacts of each intervention strategy for different levels of virus transmissibility.

assume a median reproduction number of 1.46[55]. On the other hand, the seasonal influenza is estimated to have the lowest reproduction number, with a value of 1.27.

Hence, based on these data, considering the strategy of antiviral stockpiling and distribution alone to limit the pandemic diffusion through targeted prophylaxis or treatment is unfeasible, due to the huge amount of drugs that must be stockpiled[56].

For example, recalling the study of Germann et al. (2006) that simulates outbreaks of the 1957-1958 H2N2 pandemic, authors underline that a pandemic with a basic reproduction number R_0 equal to 1.7 requires ten million courses of oseltamivir by the United States.

So, cheaper alternative strategies, like specific purchase agreements among governments and drug companies, are needed to handle antiviral usage during pandemic outbreaks.

The salient role of virus transmissibility has been remarked even by the pandemic influenza risk management guidance issued by WHO in 2017, that updated the previous version of 2009 and incorporated the experience of the H1N1 2009-2010 pandemic. The beforementioned measure is one the three key indicators, together with virulence and impact of the disease, to be considered when implementing operating decisions like social distancing, vaccine production, antiviral stockpiling and distribution. Other new important components are included in this document, such as the appliance of principles of all-hazards Emergency Risk Management for Health (ERMH), the introduction of a risk-based attitude on pandemic influenza, a revised approach on global pandemic phases and the description of the Pandemic Influenza Preparedness (PIP) framework.

The objective of the ERMH is to agglomerate common elements of preparedness and response, as warning and surveillance of virus activity, across various sectors, promoting a multisectoral and multidisciplinary approach to various threats and increasing the presence of emergency programmes for health in national and international policies[57].

Secondly, the risk-based approach incentivizes national governments to create and implement flexible plans to cope with changing nature of pandemics, focusing on a continuous risk assessment.

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[55] See Biggerstaff et al. (2014) for the computation method, the length of the serial interval used to calculate all R values and whether the articles analysed by the authors considered basic or effective reproduction numbers.

[56] Even Germann et al. (2006), in fact, highlights that the stockpiling of antiviral agents may be the main implementation issue of targeted prophylaxis or treatment of infectious individuals, because of large quantities required.

[57] The other principles of ERMH indicated in WHO (2017) "Pandemic influenza risk management. A guide to inform & harmonize national and international pandemic preparedness and response." are comprehensive risk management, community resilience, sustainable development, and ethical basis.

Furthermore, global pandemic phases are presented as a continuum, characterized by four parts: interpandemic phase, alert phase, pandemic phase and transition phase.

Whereas during the first stage no frightening signals are observed, in the second phase surveillance activity discovers a new subtype of influenza in humans, that may or may not spread globally, causing a pandemic phase.

A transition phase, instead, occurs when response actions decrease[58].

Lastly, the PIP framework described in the 2017 updated guidance encourages countries to share both knowledge about potential virus threats and resources like antivirals or vaccines, as well as clarifying roles of WHO and single countries in developing interventions.

In the same year, WHO issued a strategic framework that delineates the features of different types of emergencies, including biological threats with pandemic potential, and also identifies overarching principles and elements to improve emergency preparedness, which is defined as "the knowledge and capacities and organizational systems developed by governments, response and recovery organizations, communities and individuals to effectively anticipate, respond to, and recover from the impacts of likely, imminent, emerging, or current emergencies."[59]

The process of plan implementation must follow an iterative cycle, in which main principles taken into account are the all-hazard and whole-of-society approach, a consistent funding and risk management attitude, whereas some key elements are logistical structures for essential supplies, quick access to diagnostic services, surveillance, early warning and information management systems[60].

Moreover, two interesting strategic objectives presented are the operational readiness, explained as quick and effective application of actions highlighted in preparedness plan, and the One Health approach, which involves the cooperation among human and health services in order to detect possible epidemic outbursts, especially in more fragile cases where human-animal connection is stronger[61].

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[58] WHO (2017) "Pandemic influenza risk management. A guide to inform & harmonize national and international pandemic preparedness and response." specifies that WHO is responsible for the communication of a Public Health Emergency of International Concern and declaration of a pandemic, so the passage among different phases.

[59] The source is WHO (2017) "A strategic framework for emergency preparedness".

[60] Elements of emergency preparedness are grouped by the levels at which they must be implemented. See WHO (2017) "A strategic framework for emergency preparedness" for a deeper description of these elements, as well as of all principles.

[61] This last concept is even discussed by Amuasi and Winkler (2020) and "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023".

The coordination of health care services has shown to be decisive to face, for example, the outbreak of the 2014 Ebola virus disease in West Africa, a vulnerable area owing to the shortage of essential health care activities and the lower level of boundaries among animals and humans; within this framework, that emergency underscored the surging relevance, in the eyes of healthcare institutions, of simulation exercises to address whether high-priority, non-affected countries set up appropriate emergency response systems to manage the importation of such virus[62].

So, the issuance of the "Simulation exercise manual" by WHO in 2017 had the intent of creating a common methodology in the realization and examination of exercise programs themselves. This manual defines exercises as "a form of practice, training, monitoring or evaluation of capabilities, involving the description or simulation of an emergency to which a described or simulated response is made", while it even classifies them into the two categories of "discussion-based exercises" and "operations-based exercises", according to the level of reality and stress simulated in the environment, that tests all seven factors of the emergency preparedness cycle, i.e. planning, organizing, training, equipping, exercising, evaluating, and taking corrective action[63].

The first category is only composed by tabletop exercises, i.e. discussions led by a facilitator on specific threats in a low-stress and informal setting, while in the second one closeness to reality and level of stress are higher. Drills, functional exercises and full-scale exercises characterize the operations-based exercises. These more complex types can test from single functions of a plan, like in the drills, to multiple departments, as in the functional exercises or in the full-scale exercises. Whether emergency personnel is involved in the simulation, the manual talks about full-scale exercises, whereas, without such involvement, the document speaks of functional exercises. Planning timeframe of each type of simulation, as well as required resources, are contingent on the level of complexity and realism[64].

At the end of this flourishing period, in 2018, WHO published other two relevant guidance: "A checklist for pandemic influenza risk and impact management" and "Essential steps for

[62] The source is WHO (2017) "Simulation exercise manual".
[63] See WHO (2017) "Simulation exercise manual" for both a description of the responsibilities of exercise director, exercise controller, exercises evaluators, facilitators, actors, technical experts, local advisors, admin and logistics staff, and to identify which emergency preparedness component are analysed in each exercise type.
[64] See WHO (2017) "Simulation exercise manual" for a broader explanation of all aspects of each process, in terms of location, target audience, planning timeframe, exercise timeframe, required resources and purpose of the simulation.

developing or updating a national pandemic influenza preparedness plan", that should be used jointly for preparedness planning.

The first guideline incorporates the lessons from the H1N1 2009-2010 pandemic, substitutes the 2005 WHO checklist, while having the intention of assisting national governments in managing pandemic influenza preparedness and response plans. This checklist includes the ERMH approach presented in the 2017 WHO pandemic influenza risk management guidance and splits the planning activities into essential and desirable ones, based on necessary resources and specific priorities of the country[65].

Regarding antiviral usage, the document focalizes on the aspects of drug resistance and prophylaxis.

About the first problem, desirable actions highlighted are the expansion of laboratory capacity and implementation of protocols to check the effectiveness of antivirals. The main focus, instead, is on the second aspect. Since health care activities and other crucial services[66] must be maintained even during a pandemic, an essential action suggested is the administration of doses of antiviral, with the aim of preventing infection, to health-care workers and other employees at risk of contagion. Besides, according to this guidance, in order to have a proper supply of these medicines in moments of need, a prudent action that should be taken is the creation of national stockpiling of antivirals.

At the same time, this agenda points out that "advance purchase agreements" can be implemented in parallel with stockpiling activities, to ensure stable supply of all types of essential medicines necessary during a pandemic.

"Essential steps for developing or updating a national pandemic influenza preparedness plan", instead, directs the attention on the evolution of national systems for preparedness planning, specifies their objectives and helps governments to create a clear procedure to implement them. The three phases of the process described in this report are "preparation and situation analysis", "developing or updating a plan" and "evaluating, finalizing & disseminating the plan".

In the first step, the main goals involve various sectors in the planning activity, like in the whole-of-society approach, then also the identification of countries' financial and technical needs in

[65] WHO (2018) "A checklist for pandemic influenza risk and impact management" itself indicates that the activities must not be considered as standard operating procedures. See the document for a deeper view on the other updates presented, as the incorporation of risk and severity assessment by governments.

[66] See WHO (2018) "A checklist for pandemic influenza risk and impact management" for the whole list of essential services.

the case of outbreak and the definition of responsibilities of all parts engaged, as, for example, single communities, governments or the health sector.

Creating a draft of the plan and modifying it according to the various recommendations of the parts represented are the key purposes of the second stage of the procedure.

In the third step, the major challenges to be addressed are analysing and revising the plan through simulation exercises, gaining its approval from government authorities and, lastly, finding the most effective methods to distribute it to the public[67].

So far, all the reports and articles presented have been published prior to outburst of the SARS-COV-2 pandemic, that has dramatically changed the worldwide perception of pandemic risk.

Amuasi and Winkler (2020) suggest a multidisciplinary approach on climate change and environmental sustainability problems which can take into account majority of factors, like risk of cross-species transmission or humans-animals level of interaction, that affect spillover of zoonotic viruses with pandemic potential.

The Italian pandemic preparedness and response plan 2021-2023, based on the two beforementioned documents issued by WHO in 2018, updates the previous version of 2006, defines the law framework within which the plan can be realized, clarifies the responsibilities and the roles of relevant actors such as the Italian national Ministry of Health or WHO itself, remarks that a "one health approach" should be contemplated, attempts to explain the reasons of the failure of surveillance and containment measures for the SARS-COV-2 pandemic and tries to create operational protocols to be followed in each pandemic phase to respond to alarming signals of epidemic threats.

It is valid for three years and, in accordance with its dynamic nature, it must be revised for the first time after one year of the beginning of its execution.

It also includes the principles of the ERMH[68], indexes the intervention needed to two different scenarios of either moderate or high clinical severity and transmissibility, as for example the amount of necessary intensive care units to cope with both situations, indicates the importance of continuous tests or exercises that should be conducted in the interpandemic time span to verify the suitability of the plan, and internalizes the concepts of preparedness and readiness.

[67] See WHO (2018) ""Essential steps for developing or updating a national pandemic influenza preparedness plan" for a deeper explanation of all required actions and specific considerations of each phase of the plan.

[68] For example, an entire paragraph of the "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023" is dedicated to the ethical aspects of the implementation of emergency measures by relevant authorities.

Furthermore, it distinguishes how financial resources should by funded by both national and regional authorities.

The plan considers epidemics with R_0 around 1.7 and high clinical severity as the most probable ones, even though it does not exclude the possibility of higher transmissibility. Regarding this scenario, providing one course of antiviral drugs within one day from symptom onset for both treatment of the infected people and prophylaxis of their contacts, without additional actions such as social distancing or school closures, may decrease by 70% the probability of transmission to others given infection for both groups.

Likewise, it may be even more beneficial for close contacts of infected individuals, reducing by 30% the probability of infection given exposure and by 60% the risk of symptom onset given infection[69].

These measures should be taken into account when authorities face decisions concerning the amount of necessary intensive care units because, in accordance with report estimates, antivirals usage may reduce the human resources needed to face the pandemic, hence creating, through less crowded hospitals, a safer environment for health care workers themselves.

Albeit Italian Ministry of Health directly oversee antiviral stockpiling during the interpandemic phase, aspects of supervision and monitoring are not treated in this document, because such operation must align with international instructions.

About antiviral prophylaxis, instead, the plan underlines that Ministry of Health, together with regional governments and Italian medicines agency, must recognize priority target groups of people that require quicker drug administration and modify the distribution strategy following the evolution of the pandemic[70].

However, authorities like universities or the National Institute of Health must focus on the effectiveness of these treatments on the alarming viruses detected, with special attention on antiviral drug resistance.

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[69] See "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023" for the data on clinical attack rate observed, necessary hospitalizations and intensive care units given various scenarios and intervention strategies.

[70] For example, "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023" specifies that a delivering strategy should change whether pandemic vaccine production has started or not.

At the end, the last salient document on the antiviral therapy is an ICER report conducted by Yeung et al. (2023) that analysed the impact of three specific drugs, but it will be largely discussed in the next chapter.

2.2. Review of articles on real options theory in the health sector

Derivatives can be described as financial contracts whose value is dependent on the value of underlying assets, and are categorized by some characteristics, as the type of underlying, the market in which are traded or their payoff profiles. They exist to fulfil different investors' needs, like hedging, i.e. trying to immunize the risk exposure stemming from a specific position in the underlying, or speculation, i.e. the aim of the investor to make a profit if the underlying asset moves in an expected way[71].

Various kinds of underlying asset are present, like stocks, futures, currencies, indexes or even non-financial instruments, that are considered in the case of real options, which will be discussed later in this paragraph. Among all the different types of derivatives, options are non-linearly dependent on the underlying asset[72], they are traded either on exchanges or on over-the-counter (OTC) markets, and they give their holders the right, but not the obligation, to do something. They're different from other financial instruments like forwards or futures, because options' buyers can decide whether or not to exercise the right[73].

Moreover, entering into a financial option requires an up-front payment, the option premium or cost of the option, to the counterpart of the contract. The buyer, or holder, is the one that pays the up-front amount of money to the seller, or writer, of the option.

There are two main types of options, i.e. call and put options, that give different rights.

A call option gives the holder of the option the right, but not the obligation, to buy an underlying asset by a certain date for a certain price, whereas a put option gives the holder the right, but not the obligation, to sell an underlying asset by a certain date for a certain price.

Instead, sellers of the option must respect their obligations to complete the transaction whether option buyers decide to exercise their rights.

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[71] The source is Boyle and McDougall (2011), which has been consulted on Internet Archive on the 15th of February 2024.
[72] Options' payoffs are not linear functions of the value of the underlying.
[73] See Hull (2015) for the description of all possible underlying asset and for the differences among exchange-traded markets and OTC markets.

Call option writers are obliged to sell the underlying asset, whereas a put option seller must purchase the asset, at the predefined strike price[74].

The strike price, also called exercise price, is the price indicated in the contract at which the option's holder can either buy or sell the underlying stock, depending on the type of option chosen. As the strike price increases, put option's price increases because the payoff on exercise, i.e. cash-flow given by the derivative and defined as a function of the underlying's value, is the amount by which the strike price exceeds the price of the underlying asset in the market. Vice versa, the price of a call decreases whether the strike price increases, since the payoff on exercise is the amount by which underlying asset price in the market exceeds the strike price.

At the same time, put price has a negative relationship with underlying stock value, because it is exercised whenever the strike price exceeds the aforementioned variable, whereas the call price has a positive relationship with the same measure.

Even the risk-free rate in the economy affects positively the call price and negatively the put price, since its increase creates a combined effect of increasing stockholders' expected return from the stock itself and decreasing option holders' present value of future cash flows.

The expiration date, or maturity, is the date indicated in the contract at which the option's holder can either buy or sell the underlying stock, depending on the type of option chosen.

European options, both calls and puts, can be exercised just at maturity, while American options, which are most of the ones traded on exchanges, can be exercised at any moment prior to maturity. However, optimal exercising time for American call options is at maturity, unless a dividend is paid by the underlying asset[75]. On the contrary, American put options may be exercised before maturity if the underlying value is extremely low.

Both calls and puts are more valuable whether their time to maturity increases (for this reason American options value more than European ones), because they have the possibility to become "in the money" (ITM), which means, for a call option, that the underlying stock price is above the exercise price specified by the contract, while for a put option the strike price exceeds the underlying asset price. Options that are ITM are usually exercised by the holder. When, instead, in a call option, the exercise price exceeds the underlying stock price, such call is "out of the money" (OTM) and it is usually not exercised. A put option is "out the money" if the strike

[74] The sources for the definitions of call and put options are Boyle and McDougall (2011), consulted on Internet Archive on the 15th of February 2024, and Hull (2015).
[75] See Copeland and Antikarov (2003) for an example of the effect of a dividend payout on the value of American call options.

price is below the underlying asset price. If exercise price equals underlying stock price, then options, both calls and puts, are “at the money” (ATM)[76].

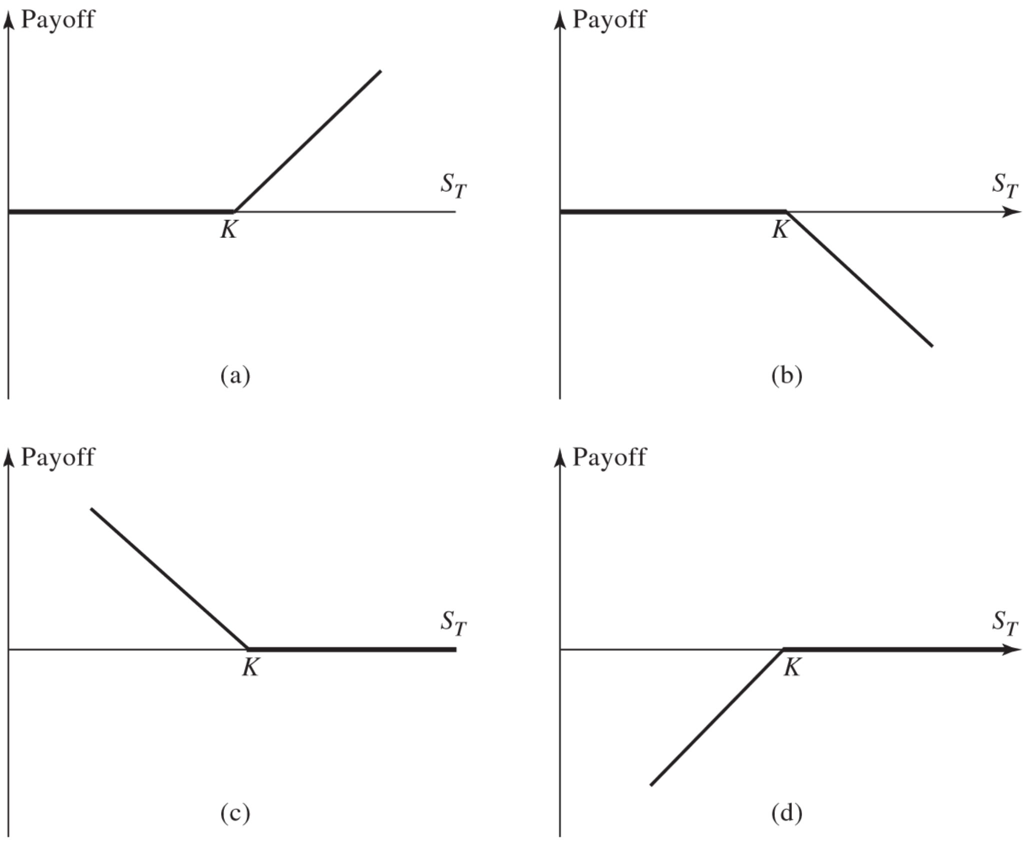
As already underlined, an option financial contract has two different counterparts, that enter into different positions regarding such transaction: the buyer takes a long position in the option, and the seller takes a short position.

Therefore, simple options can result in four combinations that mimic the possible positions assumed by investors: long call, long put, short call and short put. These cases represent, respectively, the position of a call option holder, put option holder, call option writer and put option writer. Putting exercise price equal to K and price of underlying asset at maturity equal to S_T, it is possible to show through some graphs retrieved from Hull (2015) the payoffs at maturity for each position. So, European options are the ones considered below.

In the graph (a) a long call position is drawn, while a short call is visible in the graph (b). Instead, the third and fourth quadrants show, respectively, a long and a short put position.

[76] See Hull (2015) for the definitions of strike price, maturity, risk-free rate, European options, American options, ITM options, ATM options and OTM options.

Figure 2.2: Payoffs from different option positions



Source: Hull (2015)

Analytically, the payoff of a long call position is Max(S_T – K, 0), and a short call offers the opposite payoff, i.e. – Max(S_T – K, 0) = Min(K – S_T, 0). The investor that enters in a long call position hopes in an increase of the underlying asset value, has unlimited potential gains and the maximum loss is represented by the cost of the option, when the underlying stock value at maturity is not above the strike price. The gain of a short call investor, instead, has an upper bound indicated by the entire premium received, but, if the underlying asset value exceeds the exercise price at maturity, the potential losses are unlimited.

On the other hand, the payoff a long put position is Max(K – S_T, 0), and a short put offers an opposite payoff, i.e. – Max(K – S_T, 0) = Min(S_T – K, 0). The long put investor hopes for a decrease in the value of the underlying asset and obtains the maximum gain when the underlying falls to zero at maturity; the maximum loss, whenever the option is not exercised, is its cost. The put option seller has opposite expectations, with a maximum gain, that is the entire option premium received, in the case of an increasing or stable underlying asset value; the maximum loss, instead, occurs when the underlying stock value falls to zero[77].

Due to the asymmetrical payoff of options, it is worth mentioning that option holders benefit positively from the volatility of the underlying stock price, since it is more likely that options, either calls or puts, become ITM and, at the same time, option holders face bounded losses by simply not exercising the option when it has no value. The examples shown in the graph do not take into account the option premium, hence, the holder may sometimes exercise the right to buy or sell the underlying asset and, at the same time, lose money. This can happen when, for instance, a call option is ATM or even when it is ITM, but the underlying stock price do not exceed the sum of option cost and exercise price. Anyway, it is generally recommended to exercise call options whenever the underlying stock price is above the strike price at maturity, as well as it is wise to exercise put options if the strike price at maturity exceeds the underlying stock price.

The positions just described are the simplest ones, but a wide range of strategies exist, based on different combinations of option with or without other assets to mimic various investment profiles.

Furthermore, the derivatives so far analysed are the plain vanilla options, so the standard version, but even exotic options can be found, especially in OTC markets, and they involve more complex payoffs[78].

The potential of option pricing techniques has been used not only in financial markets to hedge risks on financial instruments, speculate or try to take advantage of possible arbitrage opportunities, but also in other fields of economic studies, like capital investment analysis, since those methods have proven to be useful in evaluating options embedded in investment opportunities. Traditional approaches like the net present value (NPV) consider, for instance, firm's investments as "now or never" decisions, in which project should be initiated whether expected discounted benefits exceed expected discounted costs of the project itself but fail to take into consideration the possibility to postpone an investment and wait for more information that may influence its timing or desirability[79].

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[77] The source for the explanation of the payoff in each position is Boyle and McDougall (2011), consulted on Internet Archive on the 20th of February 2024 for this part.

[78] See Hull (2015) for an analysis of the effect of volatility on option prices, for suggestions on optimal exercise timing for call and put options, and for a broader illustration of exotic options.

[79] See both Attema, Lugnér and Feenstra (2010) and Dixit and Pindyck (1994).

Li M. et al. (2022) specified that "the valuation of a current investment would also consider the value of the potential future investment opportunities made possible by the current investment".

Dixit and Pindyck (1994), instead, drew a connection among the situation of a firm that faces irreversible investments decisions and holding a financial option; more specifically, they indicated that "a firm with an investment opportunity likewise has the option to spend money (the exercise price), now or in the future, in return for an asset (e.g., a project) of some value".

Sometimes, the value of those options can influence the profitability of an investment so much that even projects with non-positive NPVs may be worthwhile, because the recognition of their value can increase the value of the expected discounted benefits of the expenditure. Hence, firms dealing with investment opportunities face a similar situation to a holder of a financial option, even though, in the latter case, the underlying asset on which the derivative is contingent is represented by, for instance, a stock, whereas in the case of a firm it is characterized by a real asset.

In the following chapters of this analysis, financial contracts with options characteristics related to the purchase of a real asset, like antiviral drugs, will be treated. Therefore, due to nature of the underlying asset, this kind of investment analysis method can be defined as "real options approach" (ROA).

In their guide to the application of real options, Copeland and Antikarov (2003) defined them as "the right, but not the obligation, to take an action (e.g. deferring, expanding, contracting or abandoning) at a predetermined cost called the exercise price, for a predetermined period of time", i.e. the life of the option. They identified six main variables which influenced real options value: exercise price, time to expiration of the option, value of the underlying asset, standard deviation of the underlying asset's value, risk-free rate of interest over the life of the option and, lastly, possible dividends paid by the underlying[80]. The majority of these variables affect in the same way financial and real options, although some differences are present. For example, holders of financial options cannot influence the underlying asset's value, whereas the real assets' values on which real options are contingent can be impacted by their owners[81]. The consequence of a different type of underlying is that, usually, in the case of real options, the assets on which the derivative is contingent are not traded, so their prices cannot be observed in the market.

[80] To stress the importance of this last factor, recall the case of American call options, since they should be always exercised at maturity, unless their underlying asset pays a dividend.
[81] This case has been retrieved from Copeland and Antikarov (2003), which, for this part, has been consulted on Internet Archive on the 12th of February 2024.

Hence, to overcome this obstacle an important assumption for the ROA, called Marketed Asset Disclaimer (MAD) should be carried out when evaluating projects or investments in which flexibility is included. MAD assumption suggests to employ the present value of a project without flexibility as the best estimate for the underlying risky asset, instead of trying to find proxies in the market, when such underlying is not traded.

Besides, another important assumption for the evaluation of investments with flexibility incorporated is that properly anticipated cash flows of the project itself follow a random walk process[82].

Starting from these assumptions, Copeland and Antikarov (2003) proposed a procedure, comprised of four steps, for the application of ROA in the evaluation of a generic investment or project:

1. Estimate the NPV of the project without flexibility.

2. Build an event tree, based on the set of combined uncertainties that drive the volatility of the project.

3. Put decision nodes into the event tree to convert it into a decision tree.

4. Value payoffs in the decision tree using the method of the replicating portfolio or risk-neutral probability approach[83].

Various types of options may be included in investments, as, for example, the possibility to sell or close it (abandonment option), the possibility to expand it (expansion option), to reduce its scale (contraction option) or to postpone it (option to defer). In addition, investments can incorporate multiple options, like an abandonment and an expansion one: in this context, the two options are generally not independent, since a project cannot be expanded if it has already been abandoned[84].

Real options have a common framework in which they are implemented and it is usually composed by three main characteristics: irreversibility and uncertainty of the investment, as well as the chance to defer it. The irreversibility component is linked to the high costs required

[82] The source for those two assumptions in the implementation of ROA is Copeland and Antikarov (2003), whereas, for the definition of random walk processes, see Hull (2015). The part of the study by Copeland and Antikarov (2003) related to the two assumptions has been consulted on Internet Archive on the 13th of February 2024.
[83] The source for the definitions of event tree, decision tree, replicating portfolio method and risk-neutral probability approach, as well as for a broader description of this process, is Copeland and Antikarov (2003). The related chapter of such book has been consulted on Internet Archive on the 14th of February 2024.
[84] See Hull (2015) for a precise illustration of all these types of real options and for the analysis of an example of multiple options embedded in a single investment.

to recover the expenditure for the investment, while uncertainty is connected with the riskiness embedded in the project itself, in a sense that benefits follow a stochastic process[85]; lastly, the deferral part relies on the opportunity for the investor to delay the investment to wait for better values of the uncertain benefits or for new information[86].

According to Dixit and Pindyck (1994), "various sources of uncertainty about future profits (fluctuations in product prices, input costs, exchange rates, tax and regulatory policies) have much more important effects on investment than does the overall level of interest rates", so the capacity of the ROA to cope with uncertain investment conditions seems pretty useful and valuable in such contexts.

Moreover, real options can be split into different categories contingent on the nature and the level of uncertainty faced by decision makers: for example, if there is high market uncertainty but low technological uncertainty, typically this is the framework of a scouting option. On the contrary, positioning options have low market uncertainty but high technological uncertainty; stepping-stone options, instead, have high market and technological uncertainty[87].

The application of ROA relates to a wide range of different segments of the economy in which uncertainty, irreversibility and possibility to defer are present, like investments in natural resources, real estate development, corporate strategy and so on[88].

A pretty new field of investigation is the implementation of ROA in the health sector, since a bibliometric study performed by de Cássia Rocha, Gonçalves and Lawryshyn and published in 2020 mentioned that the first research for this area developed through a ROA was carried out in 1996 for the decision whether to invest or not in a medical machinery. In fact, the health sector presents the characteristics aforementioned in various different decisions, as purchasing or not machineries, stockpiling drugs as a preventive measure or delaying treatments to a patient.

The last case, for example, has the three main characteristics embedded: the treatment is, at least partially, irreversible, with benefits on the patient that are not entirely certain, and the deferral preserves an option to start treatment in future moments[89]. Of course, some issues may arise from the implementation of ROA in such decisions, like the risk that patients worsen their

[85] See Dixit and Pindyck (1994) for the definition and the description of stochastic processes.
[86] Definitions of irreversibility, uncertainty and possibility to be deferred are taken from Attema, Lugnér and Feenstra (2010).
[87] To have a broader description of positioning options, scouting options and stepping-stone options, see Williams and Hammes (2007).
[88] See Zeng and Zhang (2011) for a review of various applications of the real options approach.
[89] This example is retrieved from the article of Driffield and Smith (2007).

conditions, but the value of such option is deemed to be so important that it has been declared in scientific literature that any health care decision which includes possibility of deferral may be evaluated through ROA[90].

Anyway, it is relevant to note that some differences among financial and real options exist and are difficult to handle in a field like the health sector. For instance, an option to defer treatments is influenced by multiple sources of uncertainty, whereas simple financial options have just one source, or also the requirement of specific data to be inserted in option pricing techniques, as well as the necessity of expressing patient's benefits in monetary terms[91].

Those problems notwithstanding, the literature on such topic has grown in the last decades, and the impact is so high that, according to an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) report written by Lakdawalla et al. in 2018, real option value should be included as an additional element in the traditional Cost Effectiveness Analysis (CEA) to create a more comprehensive measure of what constitutes value in the healthcare area. CEA computed value from a health economic point of view through incremental costs and incremental benefits. Lakdawalla et al. (2018) explained this approach in the following way: "Future cost savings resulting from a treatment today should be subtracted from the direct treatment cost to yield the net incremental cost of treatment". Costs were considered from the perspective of decision makers, like governments or taxpayers, whereas benefits were considered from the perspective of patients. However, Lakdawalla et al. (2018) believed that CEA alone misreported value in the healthcare sector and suggested to include ROA in the evaluation system. They justified this argument with the idea that patients might profit from existing treatments whether those therapies gave the option to the individuals to prolong their lives until the arrival of medical innovations; hence, the value of a current treatment came from two different sources, i.e. the immediate effect on the patient and the possible benefits coming from progresses in the medical field[92].

So, in this context, the literature review on ROA in the health sector undertaken by de Cássia Rocha, Gonçalves and Lawryshyn in 2020 is relevant to distinguish the most important articles for the aim of this study.

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[90] More specifically, Driffield and Smith (2007) stated that "any health care decision that may potentially be deferred, whether treatment of an individual, developing and releasing a new pharmaceutical, or considering a society-wide initiative to promote a vaccination program, can theoretically be analysed using real options theory".
[91] See Driffield and Smith (2007) for a broader explanation of the differences between financial and real options, as well as the troubles that can be encountered when dealing with ROA implementation in the health sector. See instead Copeland and Antikarov (2003) for the consolidated approach, that combines multiple sources of uncertainty into one.
[92] Note that this aspect reconciled with the quotation of Li M. et al. (2022) on the valuation of an investment.

Firstly, Palmer and Smith (2000), through the concept of net social benefit and an option model, quantified the impact of uncertainty and irreversibility in cost-effectiveness frameworks that deal with economic decisions about health care technologies. They found that the presence of some degrees of uncertainty and irreversibility in health technology assessments is crucial to give value to options embedded in such decisions, hence increasing their cost-effectiveness ratio. Therefore, they suggested to adjust a health technology cost-effectiveness ratio for its implicit degrees of uncertainty and irreversibility before comparing it to a threshold value and take the decision to implement or not such technology.

Then, Maurer (2001) applied the ROA to perform a valuation of incentive arrangements in managed care contracts in which the provider faced conflicts of interest in a principal agent framework. The health plan acted as the principal and the provider as the agent. In particular, the author studied the case of a withhold arrangement[93] through a model that was able to account for the stochasticity of both the expected value of the terminal investment cost and the financial value of the incentive to invest in excess quality in such arrangement. The withhold arrangement was designed as a compound option comprised of a put option dependent on the value of a call option written on the total investment in the member panel. The analysis showed that changes in the expected health plan's investment cost influenced more the financial value of the incentive whether the contract was close to the end; moreover, it was demonstrated that higher-risk contracts provided more stable financial values of the incentive to avoid the investment in excess quality[94].

Afterwards, Driffield and Smith (2007) described analogies and differences among financial and real options and used ROA to analyse "watchful waiting"[95] of patients affected by slow progression diseases, with the aim of exploiting an option to defer a treatment to a moment in which more information about the evolution of the illness is gained. They underlined the analogies between financial options and this possibility of deferral, remarking the relevance of uncertainty and irreversibility in the decision, but they also emphasized some challenges that could be found in the implementation, like the requirement of a stochastic strike price, i.e. surgery costs, or monetary quantification of the treatment. At any point in time, they questioned whether benefits from the delay continued to surpass the costs, expressed in terms of both

[93] Maurer (2001) indicated that a withhold arrangement was present when "the health plan retains a portion of the promised compensation and makes the return of the funds in the withhold contingent on the plan's incurred service costs falling within the cost target".
[94] See Maurer (2001) for a broader description of the derivatives and for a wider illustration of the results.
[95] Driffield and Smith (2007) defined watchful waiting as a period of constant monitoring of the ill individual during which the patient itself did not receive any treatment. The specific disease employed in the pricing model was abdominal aortic aneurysm.

surveillance expenses and risk of clinical worsening of the individual, and they discovered that ROA, compared to traditional CEA, could account better for option value embedded in watchful waiting, so the deferral option should be included in medical decision making.

Then, Smith (2007) employed a survey on a sample of Australian respondents to examine whether option value and externality value could be mis-specified in contingent valuation in health care, so that studies focused only on use value of treatments. He defined use value as "valuing a health benefit accruing immediately and with certainty to the respondent", externality value as "valuing a health benefit accruing to a person other than the respondent through either caring or reduced risk of contagion" and, lastly, option value as "valuing a health benefit potentially accruing to the respondent but at some point in the future". The willingness-to-pay of respondents for a treatment in the case in which use value was combined with either externality value, option value, or both, was significantly higher than in the scenario in which use value alone was considered. So, even though the author recommended a replication of the survey on a larger sample, he suggested that these two additional sources of value should be analysed in contingent valuation studies in health care.

Attema, Lugnér and Feenstra (2010) wrote one of the most interesting papers for our analysis, directing attention to the use of ROA to evaluate government's decision of stockpiling antiviral drugs for the prevention of pandemic influenza. The numerical example taken into account was observed from the point of view of Dutch national government, with an investment time horizon of five years, whereas the antiviral considered was Tamiflu, that was regarded as effective regarding infectivity and recovery rate of a patient whether it was taken within 48 hours of symptoms onset. No specific strain for the research has been indicated. Such framework was in line with the requirements to apply ROA, since antivirals were not easily resalable in the market, uncertainty was present in the probability of pandemic outburst and in antiviral benefits on individuals in the case of pandemic occurrence, while the deferral component was related to the possibility for the government to wait for further information regarding pandemic strains or probability of outbreak. They also confirmed that embedded uncertainty of the investment led the option value of delaying to be worthwhile. The main costs of a pandemic described were drug purchase costs, stockpiling costs and prescription costs, even though those last ones were treated as negative benefits; the main benefits, instead, were discounted life years saved, savings in production losses and reduction of health care consumption due to influenza complications. Both benefits and costs were expressed in monetary terms. Even if they indicated that results could change according to the population considered and whether savings in production losses were neglected, authors found "strong evidence favouring investment in antivirals in

Netherlands" and remarked the relevance of ROA in addressing health care decisions, since the option value approach, with respect to the standard cost-benefit analysis, made the possibility of waiting more appealing.

Anyway, it is important to mention the relationship, scrutinized by Harrington and Hsu (2010), between the introduction of contracts with option features in programs of preventive antiviral stockpiling and the quantity of drugs supplied by manufacturers in case of pandemic outburst. Authors examined the Manufacturer Reserve Program (MRP) developed by Hoffman-La Roche and GlaxoSmithKline (manufacturers of Tamiflu and Relenza), that gave to its holders (mainly hospitals), for an annual reserve fee, the "right to buy a single course (of the antiviral) at the regular price with delivery within 24–48 h". Even though authors did not explicitly mention the ROA[96], the characteristics of such contract were similar to options, but the right was on the purchase of a real asset. The outcome of their research was that pre-pandemic antiviral stockpiling could increase with the introduction of an MRP only if production costs of the drug were high, otherwise, for low costs, manufacturers would have reduced the ex-ante inventory in order to give value to such option through the induced shortage of the antiviral[97].

Another article regarding this same field of investigation was a preprint non-peer reviewed paper of Koh and Paxson (2009). They evaluated, through five theoretical real R&D option models[98], the options embedded in the production of one antiviral, Tamiflu, and two vaccines, Sanofi-Aventis and GlaxoSmithKline (GSK) one, that could be useful to cope with possible outbreaks of influenza A (H5N1) pandemic. Authors found that the expansion option for Tamiflu was worthwhile, but also that possible under-supply of such antiviral could result in valuable investment opportunities in such therapy for even other drug manufacturers. Regarding vaccines, instead, conclusions were different for Sanofi-Aventis and GSK medications: project option values for the first firm were greater, probably because of a higher vaccine production rate in the case of Sanofi-Aventis, which, at that moment, was a leader in the production of therapies for infectious/bacterial diseases[99].

Moving forward, Pike et al. (2014) published another interesting article for our analysis, discussing strategies to handle Emerging Infectious Diseases (EIDs) of zoonotic origin, in particular avian influenza, that might result in pandemics. On the one side, they estimated

[96] Therefore, such article is not mentioned in the literature review on ROA in the health sector portraited by de Cássia Rocha, Gonçalves and Lawryshyn (2020).
[97] See Harrington and Hsu (2010) for the specific calculations that led to these findings.
[98] The manufacturers were Roche, Sanofi-Aventis, and GSK. See the preprint version of Koh and Paxson (2009) for the reasons behind the choice of those treatments and for the description of each option model.
[99] See the preprint version of Koh and Paxson (2009) for a broader explanation of empirical results.

through ROA the optimal timing for the implementation of worldwide adaptive strategies to face pandemic burst; on the other side, they compared adaptation policies, i.e. measures that reduced pandemic spread after its outbreak, with mitigation policies (like the "one health" approach), i.e. measures that aimed to target pandemic drivers[100], in terms of NPV of expected damages caused by the level of EIDs spread for each strategy. Regarding the first topic, they discussed some interventions that increased policy spending on adaptation plans and assumed different reduction rates of EIDs[101] for any of these procedures, finding that the optimal one multiplied policy spending at that moment by a factor of five, with a decrease in the number of EIDs of 50%. Besides, they discovered, using the ROA, that the time span to effectively create a global response to the pandemic threat was within 27 years from the publication of the study. About the second topic, outcomes showed that mitigation policies could be more cost-effective than adaptation policies in decreasing the amount of discounted expected damages that may occur, even though funding for such interventions was not precisely indicated by the authors, which only suggested some guidelines.

The last paper mentioned by de Cássia Rocha, Gonçalves and Lawryshyn (2020) and valuable for this study is the publication of Park (2016), which addressed vaccination strategy in the framework of a stochastic process for pandemic transmission. Its empirical analysis was derived from data on influenza A (H1N1) diffusion in South Korea. The author utilized the ROA to compare, in a herd immunity framework, the optimal levels of vaccine stockpile when accounting for economic benefits and costs of vaccination with the optimal levels obtained from a traditional epidemiological model[102] in which economic effects were neglected. ROA could be employed due to some features of the context in which vaccination strategy was implemented: irreversible damages stemming from pandemic burst, irreversibility of vaccination expenses and stochastic dispersion of the virus. It was discovered that the incorporation of economic effects in the analysis increased the level of vaccine stockpile required to face the pandemic outbreak, probably even influenced by the high transmission rates observable in a densely populated nation as South Korea.

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[100] Pike et al. (2014) indicated that the increasing number of EIDs over the last decades has been caused by a variety of factors, such as human population growth, land use change and international trade. See the paper for a broader description of each intervention strategy.

[101] Pike at al. (2014) discussed the case of US policy spending.

[102] The concept of herd immunity was described in the paper as "a form of threshold where the vaccination of a significant portion of a population provides immunity protection in society", whereas the epidemiological model employed was the stochastic susceptible-infected-susceptible (SIS) framework. See Park (2016) for further explanation of those concepts, for their implications in the article and for the illustration of economic benefits and costs of vaccination.

All these articles have been published prior to the experience of COVID-19, that revealed all the shortages of health care systems in handling such pandemic.

In this scenario, Roope et al. (2021) highlighted, through the case of occupied bed suitable for mechanical ventilators during the first wave of COVID-19 in the United Kingdom, the lack of long-term vision of countries in the resource allocation for the health sector. Underinvestment in information infrastructure meant, for the United Kingdom, a non-efficient distribution of patients around the entire nation, given that some hospitals became completely full, although bed occupancy never surpassed 62% at a national level. So, they underscored the importance of investing in public goods, because of an embedded option value related, for instance, to the possibility of speeding up the global recovery process through expenditures that aimed to fund investigation on the creation of effective vaccines[103], or to an efficient allocation of patients and resources when hospitals were under pressure. In line with the findings of Pike et al. (2014), mitigation strategies like ex-ante funding for information infrastructure, even if costly in the short-run, may be more cost-effective compared to ex-post interventions developed after a pandemic has broken out. Furthermore, Roope et al. (2021) recommended the creation of schemes capable of measuring option value of investments in the health sector.

At the end, it is definitely worth mentioning the article of Li M. et al. (2022), that actually created a guide to execute ROA in the health care field, using a theoretical structure for the description of various types of real option values and the issuance of a method for the application of such approach. Authors employed the example of the maximization of lifetime expected Quality-Adjusted Life Years (QALYs)[104] for an individual, affected by a chronic illness, who could live for a maximum of two time periods. They defined real option value as the difference between the expected QALYs computed accounting for the possible arrival of a new effective treatment among the two periods and the expected QALYs calculated in the traditional method that neglected the chance of arrival of innovative drugs[105]. Regarding medical treatments, they identified three not mutually exclusive types of option values in the health sector: life expectancy expansion, decrease of illness progression and direct influence on emerging technologies. All these categories were connected with the possibility for those sick individuals to take advantage of healthcare advancements occurring between the two time periods, either through a sufficient extension of patient's life, who could live long enough to try new medications, or through other mechanisms, like avoiding the worsening of patient's

[103] Roope et al. (2021) defined this case as "option value of research".
[104] The ISPOR report by Lakdawalla et al. (2018) defined QALYs as "the fraction of a perfectly healthy life-year that remains after accounting for the damaging effects of an illness or condition".
[105] See Li M. et al. (2022) for the specific calculations linked to this case.

physical condition. More interestingly, Li M. et al. (2022) even developed a guidance, comprised of six steps, to carry out ROA in the aforementioned field:

1. Understand if the option value is significant, as, for example, when medical advancements may arrive in a close time considered beneficial for the patient.

2. Define how future medical advancements enter treatment pathways.

3. Estimate incremental QALYs in a conventional CEA model that ignores real option value.

4. Forecast future improvements in health, either through a trend approach or a pipeline approach.

5. Calculate the real option value using forecasted future improvements in health.

6. Measure the uncertainty of the real option and present it in a separate way from the conventional value[106].

Their conclusion was that considering the real option value "may require adding an option premium to the value-based price for many, in particular, life-extending treatments", so valuations in healthcare should not ignore such value, because its neglection may end up in underinvestment in worthwhile treatments. This is in line with the findings of Smith (2007), who underscored that option value could augment the use value of treatments.

So far, this study has described main features of financial options, their linkages with real assets, the characteristics of the ROA and a literature review of the main articles about this method's implementation in the health sector.

In the subsequent parts, following suggestions and conclusions of previous authors in this field of research, it will be described a numerical application of financial contracts on a real asset, in particular option contracts on a specific treatment for COVID-19 that will be discussed in the next chapter.

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[106] See Li M. et al. (2022) for a broader description of these steps, as well as for the definitions of trend and pipeline approach.

3. Use of antivirals to treat Covid-19 pandemic and the Paxlovid case

3.1. Improving preparedness and readiness of the Italian National Health Care System as indicated by the National Pandemic Plan 2021-2023

The overall idea behind this chapter is justifying the use of Paxlovid, both from a clinical and economic perspective, as underlying of the financial contract, while explaining how it may impact on the relationship between governments and producer, as well as its potential benefits for the society.

Firstly, to achieve this outcome, let's focus on the framework in which the financial contract can enter as an economic measure. In order to have a standard approach to possible future pandemics, the Institute for Clinical and Economic Review (ICER) report by Yeung et al. (2023) has issued a series of policy recommendations to suggest to governments[107] how they can behave and improve their response towards pandemics' bursts. Aspects like higher transparency of price negotiation among drug companies and governments, as well as more equal distribution of medicines' supply across different nations[108] and within all areas of the same countries, are stressed out in this report, that explicitly asks for the inclusion of "protection clauses in future price negotiations"[109] to let the cost of the drug be in line with clinical benefits for the potential patients.

Such provisions help us to introduce the relevance for the national governments, particularly in the Italian case, of improving two aspects of the response to a pandemic, according to the national pandemic plan: preparedness and readiness. Both terms are retrieved from the document "Pandemic influenza preparedness and response: a WHO guidance document" of 2009, used as a guideline for national pandemic plans in the subsequent years.

The first characteristic is defined as a dynamic cycle of specific activities, like creating softwares as "Go Data" for data collection on pandemic spread, that must be adopted by national governments both in preparation and during the response towards a pandemic, while the second one is linked to the capacity of responding effectively and quickly to a pandemic outbreak following the passages specified in the preparedness[110].

[107] Yeung et al. (2023) not only gave suggestions for the federal government, but also for guideline developers, manufacturers, payers, and researchers. Further analysis, which is beyond the scope of this thesis, of these additional aspects can be found in the version of the ICER report updated on the 14th of June 2023.

[108] For example, Ye (2022) expressed that China is not obtaining a sufficient supply of the oral antiviral Paxlovid to treat Covid-19, hence they needed to create their own antiviral treatment.

[109] For more information on the provisions, see chapter 8 of Yeung et al. (2023).

[110] To have a broader view on those two definitions and look at more examples of preparedness' activities, see also "Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu) 2021-2023".

The issuance by insurance firms of financial contracts, that can give the right for the buyer (in this case national governments or other healthcare institutions) to obtain at a fixed price a predetermined stock of medicines just in case of need, may help to stabilize the price and the supply of medical treatments, giving more space to the national authorities to organize the allocation in a more efficient way, in accordance with an improvement of the principle of preparedness. Moreover, this tool can act as an "ex-ante protection clause" in the relationship between drug companies and governments during a pandemic: in this context, a publicly available financial contract with a fixed and predetermined strike price can increase the transparency and public awareness of price negotiation dynamics, in accordance with the policy recommendations of the ICER report.

Furthermore, those contracts whose underlying is, in fact, a real asset like a medicine capable of reducing hospitalizations and deaths among individuals infected by Sars-Cov-2, reconcile with the suggestion of the 2018 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) report to add the idea of Real Options to the standard Cost-Effectiveness Analysis (CEA), in order to give value to uncertain future benefits due to improvements in the medical research[111], like, for example, the creation of a vaccine.

In this framework, the idea of using antivirals as underlying of those financial contracts is in line with the suggestion of Torneri et al. (2020), that, due to contact tracing imperfections, recommended to administer antivirals to control local outbreaks of Covid-19 reducing both final size of the epidemic and cases at peak. Since Torneri et al. (2020) was published prior to the mass distribution of vaccines, it is crucial to remark that the use of antivirals remain helpful even in the context of vaccinated population, because of the inability of the vaccines to protect individuals from infections related to Covid-19 variants, whereas antivirals have proven to be effective against them[112].

3.2. Antivirals' approval and therapies' efficacy to treat patients affected by coronavirus pandemic

The intention of this paragraph is identifying, through a review of various possible Covid-19 therapies, the target drug that can be used as underlying of the financial contract.

For example, in November 2022, the monoclonal antibody sotrovimab and the antiviral remdesivir are both authorized therapies against Covid-19[113]. The latter one is an antiviral agent

[111] See Lakdawalla et al. (2018) for further details.
[112] The source is Vangeel et al. (2022).
[113] The source is European Medicine Agency (2022), List of critical medicines for COVID-19 public health emergency (PHE) under Regulation (EU) 2022/123.

developed for the treatment of Ebola virus infections and it has proven to be effective against various RNA viruses[114]. Remdesivir, which requires a therapy of daily intravenous injection for five days, shows, in a study on a population of Chinese hospitalized patients with moderate COVID-19, that initiating this antiviral therapy within two days after hospital admission results in shorter time to clinical improvements based on WHO clinical progression scale, less risk of in-hospital death and less days of hospitalisation compared to the control group[115]. Regarding remdesivir, the main issue is the administration method, which is more expensive compared to other orally taken antivirals[116], as well as more difficult to be complied with its schedule.

The same argument fits also for cases of treatment with monoclonal antibodies like sotrovimab, that need intravenous injection as well[117]. Furthermore, monoclonal antibodies struggle to be effective against the Omicron variant[118], because they are directed to the spike protein to block the virus before entering into the human cell, and majority of the mutations of Omicron are located around the receptor binding domain of the spike protein[119].

Therefore, the choice of oral antivirals (or existing drugs with possible antiviral effects) as underlying rather than other therapies is connected with more availability, since some already existing treatments like, for example, fluvoxamine can be repurposed as drugs to heal Covid-19 infections, as well as more efficacy against Omicron variant, easier compliance with treatment schedule for the patients and, lastly, practicality, because these treatments can be administered by the patient itself after a medical prescription, in comparison to more expensive administration methods, as injections in medical settings in the case of monoclonal antibodies[120] .

Hence, all these advantages and, in particular, the reduction in administration costs can be considered by governments and health care institutes that have to deal with budget's constraints, especially in cases of extreme emergency like during a pandemic.

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[114] The source is Torneri et al. (2020).

[115] The source for remdesivir characteristics, unit costs of the drug, treatment schedule and related outcomes is Wong et al. (2022 b). See this article for deeper explanation on study population, data analysis and possible adverse events associated with remdesivir.

[116] While Saravolatz, Depcinski and Sharma (2023) suggested further research on other additional therapies with respect to remdesivir, Vangeel et al. (2022) drew a comparison on the effectiveness between the various treatments for Covid-19.

[117] For further details about treatment with sotrovimab against Covid-19 see Gupta et al. (2021).

[118] Hammond et al. (2022) raised doubts about the effectiveness of monoclonal antibodies against variants.

[119] The source is Li P. et al. (2022).

[120] Reis et al. (2022), Jayk Bernal et al. (2022) and Hammond et al. (2022), while focusing on evaluating the antivirals' efficacy of, respectively, fluvoxamine, molnupiravir and nirmatrelvir plus ritonavir against Covid-19, highlighted the higher cost-effectiveness of these drugs compared to monoclonal antibodies.

For these reasons, the focus of this dissertation is now shifted towards orally administered antivirals.

The ICER report is helpful in our analysis to look at the outcomes, in terms of absolute and relative risk reduction of hospitalizations and deaths with respect to placebos, of three different therapies (fluvoxamine, molnupiravir and nirmatrelvir-ritonavir) to prevent further disease development among patients with mild-to-moderate Covid-19 infection, but at high risk for more severe progression due to several possible pathologies, like diabetes, cardiovascular diseases or obesity[121].

The fluvoxamine is an already available drug, approved by the Food and Drug Administration (FDA) as antidepressant, whose efficacy to reduce hospitalizations and deaths among individuals infected by Covid-19 has been shown in several studies. It is a selective serotonin reuptake inhibitor (SSRI) and a σ-1 receptor (S1R) agonist that can have both anti-inflammatory and possible antiviral effects[122]. The recommended therapy against Covid-19 in mild to moderate infected patients at risk of progression to severe disease is an oral administration of a dose of 100 mg twice daily for 10 days in individuals over 18 years of age[123]. Sukhatme et al. (2021) drew a literature review about fluvoxamine possible mechanisms of action against SARS-COV-2 and highlighted seven possible ways, mainly related to the multiple roles of S1R. Since those mechanisms are uncertain, it is preferrable to indicate three theories that are remarked even by Reis et al. (2022): its anti-inflammatory action through activation of the S1R, its antiplatelet activity and the capacity of increasing plasma levels of melatonin.

On the other hand, both molnupiravir[124] and nirmatrelvir-ritonavir[125] have obtained Emergency Use Authorization (EUA) by the FDA for the treatment of Covid-19 infections.

Molnupiravir is a small-molecule ribonucleoside prodrug of N-hydroxycytidine (NHC), which has activity against SARS-CoV-2 and other RNA viruses and a high barrier to development of resistance[126]. The recommended therapy, for individuals over 18 years of age, is an oral administration of a dose of 800 mg every 12 hours with or without food for five days, but repeat

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[121] See the supplementary material of Yeung et al. (2023) for all the inclusion and exclusion criteria of each of the trials.
[122] The source is Sukhatme et al. (2021).
[123] See Reis et al. (2022) for fluvoxamine pharmacokinetics.
[124] For the molnupiravir, the first EUA for oral use was given by the FDA on December 23rd 2021, and then revised in July 2023. See Fact sheet for healthcare providers: emergency use authorization for Molnupiravir (2021) for further details about limitations, warnings and adverse reactions of the therapy.
[125] For the nirmatrelvir plus ritonavir tablets (Paxlovid), the first EUA for oral use was given by the FDA in December 2021. See Fact sheet for healthcare providers: emergency use authorization for Paxlovid (2021) for further details about limitations, warnings and adverse reactions of the therapy, especially in the case of drug-drug interactions among Paxlovid and certain anticoagulants and immunosuppressants.
[126] See Yeung et al. (2023).

or extended courses of the therapy are not allowed under the EUA[127]. Its mechanism of action against Covid-19 infection can be defined as the accumulation of deleterious errors throughout the viral genome that ultimately render the virus non-infectious and unable to replicate[128].

Nirmatrelvir, instead, is an orally administered antiviral agent targeting the SARSCoV-2 3-chymotrypsin–like cysteine protease enzyme. Ritonavir is an HIV-1 protease inhibitor, which has no activity against SARS-CoV-2, administered to boost the level of nirmatrelvir[129]. The recommended therapy, for individuals over 12 years of age and weighting more than 40 kg, is an oral administration of a combination of this treatment (300 mg) plus ritonavir (100 mg), a protease enzyme inhibitor, twice daily with or without food for five days; as for molnupiravir, repeat or extended courses of therapy are not allowed under the EUA[130]. The mechanism of action of this combination, whose brand name is Paxlovid, is the limitation of the viral replication cycle[131].

Albeit Yeung et al. (2023) have found significant effectiveness of therapies in comparison to placebos to prevent further progression, i.e. hospitalization or death, of Covid-19 infected patients, in the case of fluvoxamine's therapy, the adherence to treatment is less than 75% of the treated sample because of drug intolerability, whereas the discontinuation rate of the treatment due to adverse events is lower for molnupiravir and Paxlovid.

The following table retrieved from Yeung et al. (2023) recaps the quantities of adverse events and discontinuation rates for all therapies.

[127] The source for the pharmacokinetics is Saravolatz, Depcinski and Sharma (2023).
[128] See Jayk Bernal et al. (2022) for further explanation of molnupiravir's mechanism of action against Covid-19.
[129] See both Hammond et al. (2022) and Yeung et al. (2023).
[130] The source for the pharmacokinetics is Saravolatz, Depcinski and Sharma (2023).
[131] See Hammond et al. (2022) for further explanation of Paxlovid's mechanism of action against Covid-19.

Table 3.1: Adverse events and discontinuation of the therapy

Intervention (Trial)	Any Adverse Event, n/N (%)		Serious Adverse Events, n/N (%)		Discontinuation Due to Adverse Event, n/N (%)	
	Intervention	Placebo	Intervention	Placebo	Intervention	Placebo
Molnupiravir (MOVe-OUT)	216/710 (30)	231/701 (33)	49/710 (7)	67/701 (10)	10/710 (1)	20/701 (3)
Paxlovid (EPIC-HR)	255/1,109 (23)*	266/1,115 (24)*	18/1,109 (2)	74/1,115 (7)	23/1,109 (2)	47/1,115 (4)
Fluvoxamine (TOGETHER)	169/741 (23)†	188/756 (25)†	59/741 (8)	70/756 (9)	84/741 (26)	64/756 (18)‡

n: number, N: total number
*Treatment-emergent adverse event.
†Summed treatment-emergent adverse events of various severities.
‡Discontinuation due to side effects.

Source: Yeung et al. (2023)

Regarding adverse events, the most frequent ones for all these three therapies are nausea, diarrhoea and headache[132] and the risk of incurring in them is higher in the placebo groups when compared to molnupiravir and Paxlovid, whereas it is similar between placebo and fluvoxamine groups.

The relative risk reduction of retention in an emergency setting due to Covid-19 is 32% for patients treated with fluvoxamine, whereas the relative risk reduction of hospitalizations and deaths is 30% for molnupiravir and 88% for Paxlovid. The absolute risk reductions are, respectively, 5%, 3% and 5,62%[133].

In order to choose the target antiviral among those three, it is relevant to understand the advantages and the disadvantages of each therapy.

The following tables, taken from the ICER report, summarize costs, inpatient hospitalizations, Quality-Adjusted Life Years (QALYs), life years and equal value of Life Years (evLYs) in the base-case scenario under health care sector perspective, the cost-effectiveness for each drug in the same context and the changes in the previous variables resulted from four different scenario analyses. The first scenario analysis is related to the inclusion of societal costs and outcomes associated with productivity gains/losses and intensive care unit capacity, the second case restricts the analysis to the unvaccinated population, the third one halved the probability of hospitalisation among usual care up to 2% and, lastly, the fourth scenario analysis excludes unrelated health care costs, that are linked to life years gained.

[132] The source is Wen et al. (2023).
[133] The sources are Reis et al. (2022) for the absolute risk reduction in fluvoxamine, while Yeung et al. (2023) has been used for retrieving all other treatments' efficacies.

These tables allow to see how various parameters affect the outcomes for each treatment: not surprisingly, analysing the outcomes for a subgroup of unvaccinated individuals results in a drop of the cost per QALY gained of each drug, as does the exclusion of future health costs, whereas restricting the analysis to a subgroup of lower risk individuals means less cost-effectiveness of each therapy.

The authors advise against a comparison between each therapy in terms of cost effectiveness because of the systematic differences in the trial population and design.

Table 3.2: Results for the base case, health care sector perspective

Treatment*	Treatment Cost	Total Cost	Inpatient Hospitalizations	QALYs	Life Years	evLYs
Molnupiravir	$707	$298,500	2.49%	15.9380	19.4739	15.9386
Paxlovid	$529	$298,500	0.43%	15.9637	19.5046	15.9654
Fluvoxamine	$12	$297,800	2.42%	15.9389	19.4750	15.9395
Usual Care	--	$297,700	3.56%	15.9247	19.4580	15.9247

evLY: equal-value life year, QALY: quality-adjusted life year

Table 3.3: Incremental cost-effectiveness ratios for the base case, health care sector perspective

Treatment*	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Inpatient Hospitalization Averted
Molnupiravir	Usual care	$61,000	$51,000	$58,000	$76,000
Paxlovid	Usual care	$21,000	$18,000	$20,000	$26,000
Fluvoxamine	Usual care	$8,000	$7,000	$8,000	$10,000

evLY: equal-value life year, QALY: quality-adjusted life year

Table 3.4: Model outcomes under a modified societal perspective

Treatment*	Treatment Cost	Total Cost‡	ICU Admissions	QALYs†	Life Years†	evLYs†
Molnupiravir	$707	$301,400	0.97%	15.9524	19.4916	15.9537
Paxlovid	$529	$302,300	0.17%	16.0059	19.5566	16.0097
Fluvoxamine	$12	$300,800	0.95%	15.9543	19.4939	15.9556
Usual Care	--	$300,200	1.39%	15.9247	19.4580	15.9247

evLY: equal-value life year, ICU: intensive care unit, QALY: quality-adjusted life year

*We advise against comparing the cost effectiveness between interventions given the systematic differences in the trial populations and design.

†Includes costs/outcomes for the treated patient and any excess death averted as a societal benefit.

Table 3.5: Incremental cost-effectiveness ratios for unvaccinated only subpopulation

Treatment*	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Inpatient Hospitalization Averted
Molnupiravir	Usual care	$48,000	$41,000	$46,000	$51,000
Paxlovid	Usual care	$15,000	$12,000	$14,000	$15,000
Fluvoxamine	Usual care	$4,000	$3,000	$3,800	$4,000

evLY: equal-value life year, QALY: quality-adjusted life year

Table 3.6: Incremental cost-effectiveness ratios for lower risk subpopulation

Treatment*	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Inpatient Hospitalization Averted
Molnupiravir	Usual care	$74,000	$61,000	$71,000	$181,000
Paxlovid	Usual care	$34,000	$27,000	$32,000	$82,000
Fluvoxamine	Usual care	$21,000	$17,000	$20,000	$50,000

evLY: equal-value life year, QALY: quality-adjusted life year

Table 3.7: Incremental cost-effectiveness ratios excluding future unrelated health care costs

Treatment*	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Inpatient Hospitalization Averted
Molnupiravir	Usual care	$30,000	$25,000	$29,000	$37,000
Paxlovid	Usual care	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Fluvoxamine	Usual care	Cost-saving	Cost-saving	Cost-saving	Cost-saving

evLY: equal-value life year, QALY: quality-adjusted life year

Source for all tables: Yeung et al. (2023)

It is relevant to note that fluvoxamine is the cheapest treatment considering base-case results and all scenario analyses[134] because it is a repurposed drug, which means that price and the costs per various numbers of QALY gained are usually lower with respect to the other therapies, since the therapy is already available in the market, but for other applications. Therefore, at first glance, it seems appealing to take into consideration the fluvoxamine in our analysis, even if the absolute and relative risk reduction of hospitalizations and deaths are lower compared to the treatment with Paxlovid.

On the contrary, some issues are raised by the ICER report about the real comparability of those trials, because, in fact, the primary outcome is not equal across all trials: in the cases of molnupiravir and Paxlovid rates of reduction in hospitalization and death are assessed, whereas

[134] Fluvoxamine is the cheapest treatment even considering the threshold and sensitivity analyses of Yeung et al. (2023).

for the fluvoxamine the definition of hospitalization is slightly different, since it is described as the retention in an emergency setting for Covid-19 or being transferred to an hospital; in addition, considering a proxy of the hospitalization stand-alone, the effectiveness of the therapy is lacking.

Considering these factors, the uncertain mechanisms of action of fluvoxamine and the high discontinuation rates in patients that opt for this therapy, although the idea of repurposing this drug for Covid-19 therapy is inviting, the choice of the underlying for the financial instrument can better fall on either Paxlovid or molnupiravir.

An updated version of a network meta-analysis conducted by Siemieniuk et al. (2020) confirms a probable reduction in hospital admission and risk of death for patients with non-severe forms of Covid-19 treated with molnupiravir and nirmatrelvir-ritonavir; in addition, the article highlights that molnupiravir, with moderate certainty, probably decreases the amount of time needed to heal symptoms.

Paxlovid shows the highest level of risk reduction, even though some contraindications for people with renal impairment and for drug-drug interactions are present, whereas the studies on molnupiravir raise some doubts about an increase in the viral mutation rate compared to placebo, advise against its use for pregnant women and expose the risk of affecting bone and cartilage growth in people under 18 years of age[135].

Due to these reasons, molnupiravir should be prescribed as a residual medication, according to the EUA issued by the FDA, only to individuals unable to follow other therapies for Covid-19[136] . In fact, the guidelines of the National Institutes of Health (NIH) of the United States give the highest priority for the administration of Paxlovid in mild to moderate Covid-19 infected patients at high risk for progression to severe forms, under supply constraints[137].

3.3. Specific effectiveness of Paxlovid to reduce hospitalizations and deaths

Following the reasoning at the end of the last paragraph, the analysis of antiviral's efficacy against Covid-19 infection will be, from now on, focused on the specific therapy with Paxlovid, due to: the benefits of its oral administration method, its relative safety, the NIH indications and the higher absolute and relative risk reduction of hospitalizations and deaths compared to the other treatments. Hence, for these reasons, Paxlovid will be the drug evaluated to account for

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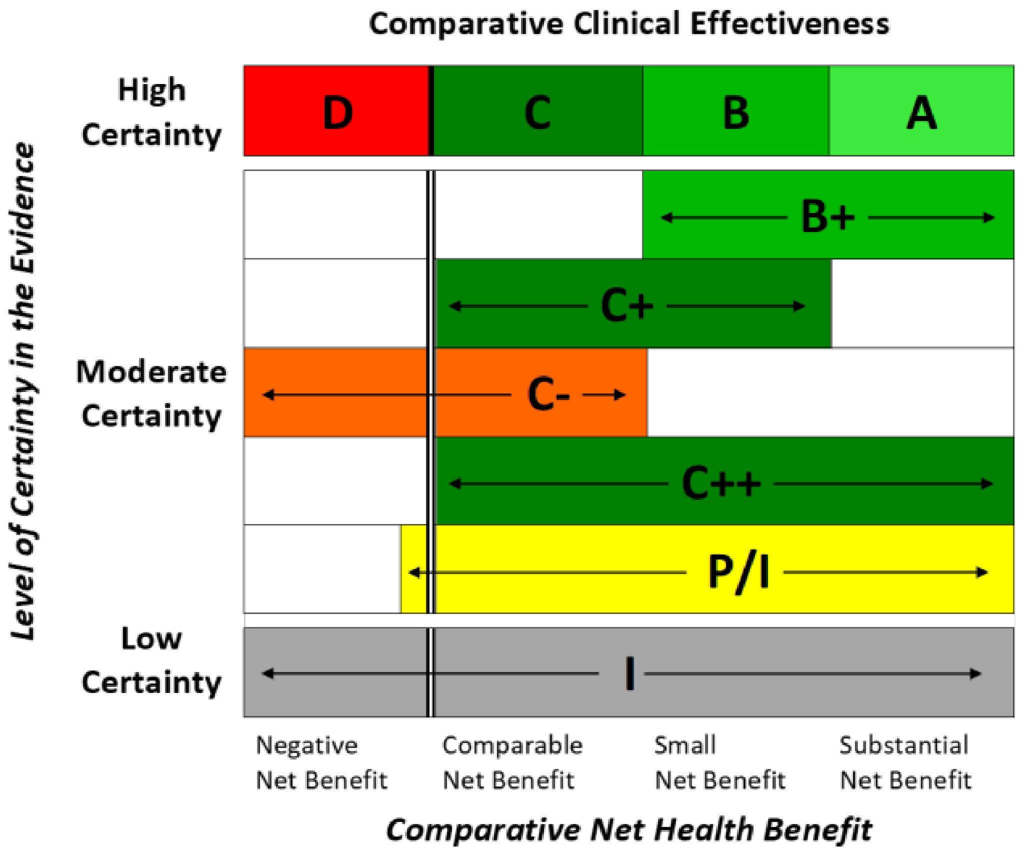
[135] The sources are Saravolatz, Depcinski and Sharma (2023) and Yeung et al. (2023).
[136] The source is Arbel et al. (2022).
[137] See Saravolatz, Depcinski and Sharma (2023) for a deeper view on the NIH guidelines and on the drawbacks of various treatments. This prioritisation is also remarked in Arbel et al. (2022).

the effect of the use of financial contracts in the supply and the price of antivirals in case of a pandemic outbreak. Its efficacy has been demonstrated in several studies, it is well-tolerated and the discontinuation rates are lower, for example, with respect to fluvoxamine.

The ICER report reviews articles on this therapy and it gives a measure to Paxlovid in terms of comparative clinical effectiveness, according to the ICER evidence rating matrix, of "incremental or better", which means that, due to the good tolerability and effectiveness, there is fair certainty of small or notable net health benefits of this treatment with respect to placebos.

Figure 3.1: ICER evidence rating matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D= "Negative"- High certainty of an inferior net health benefit
B+= "Incremental or Better" – Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Incremental" - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit
C- = "Comparable or Inferior" – Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit
C++ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" – Any situation in which the level of certainty in the evidence is low

Source: ICER report by Yeung et al. (2023)

This is the highest value, compared to the other two therapies, which both obtained a score of "comparable or incremental", which means that, for fluvoxamine, the degree of uncertainty of the net health benefits is high and, for molnupiravir, the risks associated with the therapy do not justify the clinical benefits on a population basis.

Since the trials have been performed before Omicron wave, these results are not comprehensive of possible effects on hospitalization and death linked to the outbreak of this variant. But it has been shown, through an in vitro analysis[138], that Paxlovid remains effective towards all coronavirus' variants, including Omicron, because this antiviral does not target the spike[139]. This characteristic is pointed out even in Wong et al. (2022 a), which remarks the prioritisation of Paxlovid over other antivirals and assesses the clinical effectiveness of this drug during an Omicron's dominated wave of the pandemic in Hong Kong for non-hospitalized individuals with mild to moderate Covid-19 at risk of progression to severe disease. This last study finds, after the recommended treatment schedule, a decrease of need for oxygen therapy, overall less risks of all-cause mortality and higher percentage of people that recovered from the disease and are dismissed alive, after a follow-up period of 28 days, in comparison to their control groups. Lastly, in this case, the analysis shows a faster viral burden reduction, but the achievements are conditioned by the age of the patient, the vaccination status and the presence of pre-existing comorbidities[140].

These results are in line with the outcomes of Arbel et al. (2022) regarding hospitalizations and death of Covid-19 infected patients treated with Paxlovid during an Omicron wave in Israel.

3.4. Analysis of the cost-effectiveness of Paxlovid and the necessity of ex-ante contracts of antivirals to prevent pandemics

The dissertation on Paxlovid will now shift from its efficacy to the cost-effectiveness of the implementation of this therapy, in order to have a more economic perspective on this health care sector's decision.

Through the measures of Disability Adjusted Life Years (DALYs) and Net Monetary Benefit[141] (NMB), the antiviral cost-effectiveness is studied in a sample of 10 million Chinese patients of different age groups (all patients aged over 18 years), including both vaccinated and unvaccinated individuals, with mild to moderate Covid-19 and at high risk of progression to severe disease.

Zhang et al. (2023) finds that, considering a setting where Omicron is the dominant variant and under the price available for Paxlovid at that moment, which do not give to the Chinese government the possibility to include that treatment in the National Reimbursement Drug List

[138] Study conducted by Vangeel et al. (2022), that assessed the effectiveness of Paxlovid, molnupiravir and remdesivir against all variants of concern.
[139] The source is Li P. et al. (2022), that analyzed the effect on Omicron of Paxlovid, molnupiravir and of a combination of the two antivirals.
[140] See Wong et al. (2022 a), for the eligibility and exclusion criteria of the study population, as well as for a deeper explanation of the clinical evidence across all subgroups of patients.
[141] DALY is a composite value of disease burden, while NMB addresses the relative cost-effectiveness among two different therapies. See Zhang et al. (2023) for a broader view of these two concepts, for the description of the data and the Markov model used to assess this cost-effectiveness analysis.

(NRDL), the drug's prescription is cost-effective only in patients over 80 years old, regardless their vaccination status.

The following table shows the subgroup analysis for the NMBs retrieved from that article.

Table 3.8: Net Monetary Benefits estimated for cohort with/without Paxlovid prescription

Subgroups	Cohort	Cost (RMB in 10 millions)		DALY		NMB (RMB in 10 millions)	Cost-effectiveness intervention
		Total	Difference	Total	Difference		
Vaccinated_18–39 years old	Non-Paxlovid	13,385		3,900		−13,352	√
	Paxlovid	15,275	1,890	3,900	0	−15,242	
Vaccinated_40–59 years old	Non-Paxlovid	13,459		4,149		−13,424	√
	Paxlovid	15,312	1,853	4,024	−124	−15,278	
Vaccinated_60–79 years old	Non-Paxlovid	9,895		5,227		−9,850	√
	Paxlovid	11,594	1,699	4,564	−664	−11,555	
Vaccinated_ > 80 years old	Non-Paxlovid	13,593		18,086		−13,438	
	Paxlovid	13,443	−150	10,993	−7,093	−13,349	√
Unvaccinated_18–39 years old	Non-Paxlovid	13,508		4,315		−13,471	√
	Paxlovid	15,337	1,828	4,107	−207	−15,302	
Unvaccinated_40–59 years old	Non-Paxlovid	14,247		6,804		−14,189	√
	Paxlovid	15,706	1,459	5,352	−1,452	−15,661	
Unvaccinated_60–79 years old	Non-Paxlovid	12,972		15,929		−12,836	√
	Paxlovid	13,133	160	9,915	−6,015	−13,048	
Unvaccinated_ > 80 years old	Non-Paxlovid	28,051		68,360		−27,465	
	Paxlovid	20,672	−7,379	36,130	−32,230	−20,362	√

RMB, Renminbi; DALY, disability adjusted life-years; NMB, net monetary benefit.

Source: Zhang et al. (2023)

On the other hand, they point out that some aspects, like long-term effects of Covid-19 on human body and a societal point of view of costs linked to Omicron variant's outbreak, are lacking in their analysis. Those aspects can increase the population study for which the antiviral prescription may become cost-effective.

Furthermore, authors show, working on model's parameters through a sensitivity analysis, that a reduction up to 98% of Paxlovid price[142] at that moment could end up in more age group with higher NMB's in the case of medical prescription of the treatment, i.e. including unvaccinated individuals aged 18-39 years, and all individuals older than 40 years of age.

This argument can be very helpful from an economic perspective, because it demonstrates that, through a price reduction, the medical intervention with Paxlovid's prescription is crucial in freeing a vast part of the workforce from the Covid-19 burden, ending up in a faster recovery

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[142] In Zhang et al. (2023) the price is expressed in Renminbi Yuan, whereas our analysis will use the Euro.

of the economies, since the oral administration of antivirals can be more easily adopted in comparison, for example, to monoclonal antibodies[143].

Unfortunately, negotiations among governments and drug companies cannot reach such agreement in price decrease because firms are not willing to accept such reduction, so the cost-effectiveness of the treatment may remain limited.

Hence, in this context, the idea of financial contracts on Paxlovid as underlying, with a predefined cost-effective price for the therapy, can help, under the ex-ante payment of a premium to the issuer, to stabilize the antiviral supply, align it with its clinical value, assisting governments or other healthcare institutions in hedging the risk of price fluctuations and abstaining from incurring in problems of price negotiations in case of extreme need of the drug, when the demand for the treatment is high, as during a pandemic wave.

Moreover, this kind of reasoning can further help countries that have lower access to vaccines to increase the set of possible interventions. Option issuers may be interested in this type of investment, which, in fact, is a short call position on a real asset, because they hope that these events, like a pandemic, will not occur before option's maturity, besides they can obtain the gain from the payment premium.

On the other hand, if a pandemic occurs, the option issuer is obliged to sell the antivirals at a prespecified price, which may be lower than the affordable price of the drug in the market at that moment, ending up in a loss.

In this context, governments and healthcare institutions cover themselves from the risk of price fluctuations through a long call position, with a gain equal to the difference between the drug's market price and strike price predetermined, based on some country-specific characteristics like risk of contagion for that nation and healthcare system efficiency, minus the ex-ante paid premium.

This occurs because the risk of overpayment is shifted from the government or healthcare institution towards the option issuer, that has to respect the obligation through the purchase of the antiviral at the affordable price in the market, when probably the demand is high and the price is pushed upwards. From the subscriber's perspective, there is a huge incentive to enter in this contract, but, since the option is a financial contract, it is also important to find the counterpart of the agreement, i.e. the potential option issuer.

[143] However, in various articles like Jayk Bernal et al. (2022) and Najjar-Debbiny et al. (2023) it has been remarked that complete vaccination remains the most relevant medical intervention against Covid-19.

Looking at an article from Lupkin (2022), that reveals how nations, in that case the United States, have already asked for some clauses in contracts with Pfizer, the Paxlovid producer, may help in the research. For example, the author highlighted two specific conditions: a buyback clause and a price match guarantee. In the first case, Pfizer is obliged to take back stocks of Paxlovid if the FDA removes the EUA for the therapy, hence, some part of risk is borne by the drug company as well: this clause has some implications on the financial option, because the insurance firm will now have this additional risk and it will withdraw the stocks of antivirals whether the government exercises the option but the FDA removes the authorization. So, the potential presence of this clause changes the characteristics of the financial option, giving an incentive for the option's issuer to ask for a higher premium, i.e. an amount of money that cannot be withdrawn by the government, and at the same time for a low strike price, i.e. the amount of money that can be lost whether the issuer repurchases the antivirals, because the insurance company wants both to maximize its gains through a higher up-front payment that can't be given back to the option buyer and to minimize losses from the risk of authorization removal. In the second case (the most interesting for our analysis), i.e. the price match guarantee, Pfizer is obliged to ensure a minimum charge for the treatment, since it has to align the price of Paxlovid for the USA to the minimum one among a list of six wealthy countries[144].

Hence, in this context, it is very difficult to earn from spatial price discrimination, because Pfizer must maintain, for a subscriber of this clause, the minimum price offered across a predetermined number of countries, otherwise the treatment cost for all nations will be pushed down by the newest bottom price. In presence of such condition, drug companies, i.e. Pfizer in the case of Paxlovid, cannot be interested in issuing financial options with such underlying, since this clause limits the exploitation of the gain from offering contracts with different strike prices to several nations according to their specific level of risk.

Therefore, insurance companies may be, even in presence of the two last provisions, the economic agents more interested in the issuance of those financial options, hoping that the outbreak of the pandemic will never happen and gaining from the payment premium, whereas potential subscribers can correspond to emerging economies, for example China[145], with lower access to all Covid-19 therapies, as well as countries, like Italy, that do not have same bargaining power as the USA to enforce favourable clauses as the ones beforementioned.

[144] Lupkin (2022) mentioned Canada, France, Germany, Italy, United Kingdom, and Japan as the ones included in the list. The most favoured nations clause said that if Pfizer offered a lower price of Paxlovid to one of these countries, it must match the same price for the USA.

[145] Recall the shortage of Paxlovid's supply for the Chinese nation presented by Ye (2022).

Those two categories of countries should benefit most from those financial contracts for the reason that they are more vulnerable and less capable of enforcing price reductions while negotiating with drug companies when antiviral demand increases.

Lastly, as previously pointed out, the only parameter that can be changed and that affects the cost-effectiveness of Paxlovid is its price[146], so in the next chapter, the focus will shift on the dynamics of the option price and its determinants, basing the arguments on the Paxlovid cost per treatment, to build a model that simulates the financial contract.

[146] Zhang et al. (2023) indicated the hazard ratio of severe Covid-19 and mortality, the risk of severe diseases upon infection and the medical costs for severe Covid-19 as the other three model parameters that influence the cost-effectiveness of the treatment but cannot be modified through policy interventions.

4. Modelling ex-ante contracts of the antiviral Paxlovid through options to have access in the case of Pandemic outbreak

4.1. Characteristics of the contract

So far, this research has focused on the description of pandemics, tools, like Paxlovid, employed to handle this burden and various examples of different applications of the ROA in the health sector.

The intent of this chapter is to formulate a financial contract for the purchase of Paxlovid, showing how to obtain a pricing of this one using exactly option techniques and studying the variables embedded in this contract through simulations and parameters' variations.

Let us describe the characteristics of such financial contract. It is an American call option written on the price of the antiviral Paxlovid, with a maturity of two months and a strike price equal to the current price of the drug. The seller of this contract is an insurance company, whereas the buyer is a European community healthcare institution[147]. This type of option does not already exist in an exchange traded market, it is non-tradable and it can be considered as an Over-the-counter (OTC) derivative, which is traded directly in a bilateral transaction between the two entities involved. Both the insurance firm and the healthcare institution must decide how to construct this financial derivative and they must agree on the terms of the contract[148].

For all these reasons, an analysis of the characteristics of this derivative is important to highlight its potential and its limits.

If these contracts are created in a European market, they can unlikely be signed by national healthcare entities, whereas it is more likely that they are signed by European community level institutions, which have more bargaining power and are usually the authorities that negotiate with pharmaceutical enterprises for the supply of the aforementioned therapies. Otherwise, they can be signed by national healthcare institutions, but more likely in countries, like the United States, that have a greater bargaining power and that are more prone to those types of insurance contracts[149]. Consequently, since this study takes a European point of view, the buyer of the option is considered to be a European community healthcare institution[150].

[147] If, at maturity, this option is not exercised, it expires. Then, the two parties involved in the contract can decide or not to sign new financial contracts.
[148] See both Hull (2015) and Boyle and McDougall (2011) for the definition of OTC derivative. This last source has been consulted on Internet Archive on the 24th of April 2024.
[149] In this context, it is relevant to remark that the United States already asked for some covenants, like buyback clause and price match guarantee, to Pfizer. See Lupkin (2022) for a broader description of these deals.
[150] One example can be the European Medicines Agency (EMA).

Several are the advantages of such contracts for the institutions that decide to enter in resembling transactions. Firstly, these entities have more flexibility of intervention when dealing with pandemic outbursts, since they have at their disposal a predetermined number of antivirals that can be utilized either to curb virus diffusion or to, at least, limit the negative outcomes of pandemic spread during a peak of a wave, limiting the number of infected individuals, deaths and economic losses. Secondly, they have the capacity of adjusting policies, since they are not obliged to exercise their option and they can choose the optimal timing of intervention, that can be coordinated with other measures like quarantines or curfews. Thirdly, these ex-ante contracts help to stabilize the price of the therapy, because institutions have insured themselves from the risk of overpayment of the drug caused by an increase in the demand of the antiviral[151].

The aim is to let holders exercise such option whether the existence of a pandemic is confirmed and obtain the stock of antiviral exactly when a peak of a pandemic wave occurs. The financial tool suited for this task is an American call option, that can be exercised at any moment prior to expiration. Given this early exercise possibility, such financial derivatives do not have an analytical solution and an approximation method is required to give them a value.

Among all the different procedures, the quadratic approximation described by Barone-Adesi and Whaley (1987) can fit this model, due to some reasons. Firstly, it works efficiently when the maturity of the option is less than one year, and this will be the case, as later explained. Secondly, it is computationally cheaper compared to finite-difference, binomial or other methods, that require the simulation of the possible paths of the underlying option price during the time span considered. Lastly, it will be useful for further study of the contract since it "is amenable to comparative-statics analysis" according to Barone-Adesi and Whaley (1987).

4.2. Analytical approximation of the financial contract

The Barone-Adesi and Whaley (1987) approximation method splits the value of an American call option in two parts, i.e. a European call option with the same maturity of the American one and an early exercise premium. Furthermore, the value of such option is given for two different ranges of values of the underlying: when the underlying is equal or above a critical commodity price S^*, and when it is below such threshold. This second scenario is the one that best fits this study.

[151] Lastly, recalling the study of Zhang et al. (2023), this tool can extend the cost-effectiveness of Paxlovid for countries in which this therapy is extremely expensive.

The usual representation of the formula is the following one:

$C(S,T) = c(S,T) + A_2(S/S^*)^{q_2}$ when $S < S^*$

The term c(S, T) indicates the value of the European call option written on the same underlying of the American call, with both the same maturity and strike price. To obtain the value of the European call, it's sufficient to apply the Black, Scholes and Merton model:

$$c(S,T) = Se^{(b-r)T}N(d_1) - Xe^{-rT}N(d_2)$$

where $d_1 = [ln(S/X) + (b + 0.5\sigma^2)T]/\sigma\sqrt{T}$, $d_2 = d_1 - \sigma\sqrt{T}$, $N(d_1)$ is the cumulative univariate normal distribution for d_1 and $N(d_2)$ is the cumulative univariate normal distribution for d_2[152].

The variables S, X, T, σ, r and b are required to calculate the price of this derivative. S is the current price of the underlying. In Barone-Adesi and Whaley (1987), the partial differential equation $\frac{1}{2}\sigma^2S^2V_{SS} + bSV_S - rV + V_t = 0$ describes the process of S through time, with V as the commodity option price. Then, X is the strike price of the derivative, T is the time to maturity of the option, the standard deviation of the price of the underlying is indicated by σ and, lastly, r and b are, respectively, the short-term riskless interest rate and the cost of carrying the commodity, so the opportunity cost of the investment.

Barone-Adesi and Whaley (1987) assume r and b to be constant and proportional, while it is also imposed that $b < r$[153].

The second term of the sum, $A_2(S/S^*)^{q_2}$, represents the early exercise premium of the American call, and it is described by a perpetual option, i.e. a financial option without a fixed maturity, written on the same underlying and with same strike price of the European call[154]. The term A_2 is the amount paid by the perpetual derivative when S equals S^* for the first time and q_2 is a root of the second-order ordinary differential equation that represents the approximation of the early exercise premium[155].

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152 See Barone-Adesi and Whaley (1987) for the application of the Black, Scholes and Merton formula inside of this approximation method. See instead Hull (2015) for a broader theoretical description of this option pricing technique.

153 This assumption implies that the American option can be exercised prior to maturity. See Barone-Adesi and Whaley (1987) for the explanation.

154 See Hull (2015) for the description of perpetual options.

155 The approximation of the early exercise premium differential equation is given by $S^2f_{SS} + NSf_S - (M/K)f = 0$ in Barone-Adesi and Whaley (1987).

To calculate the early exercise premium the values of A_2, q_2 and S^* are required[156]:

$$A_2 = (S^*/q_2)\{1 - e^{(b-r)T} N[d_1(S^*)]\}$$

where $N[d_1(S^*)]$ is the cumulative univariate normal distribution of

$$d_1(S^*) = [ln(S^*/X) + (b + 0.5\sigma^2)T]/\sigma\sqrt{T}$$

and

$$q_2 = [-(N - 1) + \sqrt{(N - 1)^2 + 4M/K}]/2$$

where $N = 2b / \sigma^2$ and $M = 2r/\sigma^2$ are two notational substitutions used by Barone-Adesi and Whaley (1987). The term K, instead, is obtained through $K(T) = 1 - e^{-rT}$ and it helps to give less weight to the perpetual call in the whole approximation formula, since T is less than +∞. If $T = +\infty$, then $K = 1$.

Lastly, the critical commodity price S^* is an increasing function of time to maturity of the option. Barone-Adesi and Whaley (1987) approximate analytically S^* through the following equation:

$$S^* = X + [S^*(\infty) - X][1 - e^{h_2}]$$

in which $h_2 = -(bT + 2\sigma\sqrt{T})\{X/[S^*(\infty) - X]\}$ and $S^*(\infty) = X/[1 - 1/q_2(\infty)]$. The term h_2 is an adjustment required to compute S^*, given that the function of S^* is not anymore computed on an infinite interval, whereas the last equation is the upper bound, when $T = +\infty$, of the function of S^*[157]. Its lower bound, when $T = 0$, is instead the strike price X.

To compute $S^*(\infty)$, $q_2(\infty)$ is required, and it is computed as follows:

$$q_2(\infty) = [-(N - 1) + \sqrt{(N - 1)^2 + 4M}]/2$$

where $N = 2b / \sigma^2$ and $M = 2r/\sigma^2$ are two notational substitutions. The value $q_2(\infty)$ is a root of the second-order ordinary differential equation of the approximation of the early exercise premium when T approaches +∞.

[156] The article of Barone-Adesi and Whaley (1987) underlines that $A_2 > 0$ since S^*, q_2 and $1 - e^{(b-r)T}N[d_1(S^*)]$ are positive when $b < r$.

[157] Barone-Adesi and Whaley (1987) indicate that S^* should match the following equation: $S^* - X = c(S^*, T) + \{1 - e^{(b-r)T} N[d_1(S^*)]\} S^*/q_2$. The term $S^*(\infty)$ is the upper bound of this function.

4.3. Data and results

In order to employ the Barone-Adesi and Whaley (1987) approximation of an American call option in the described context of antiviral purchasing, it is necessary to indicate the value of specific variables. In the first place, the price of Paxlovid, S, is assumed to be equal to 489.41 €[158]. This is the current underlying commodity price, i.e. the starting value for the analysis of this financial contract.

Secondly, the riskless interest rate r is required to obtain the process that illustrates the underlying commodity price-change movements. The value of this variable is assumed to be 0.03, which is in line with last short-term government bond issuances in the euro area. Subsequently, to respect the assumptions of constant proportional rates and $b < r$, b has been imposed equal to 0.015, so half of the riskless interest rate, as it is set by Barone-Adesi and Whaley (1987).

Since, according to Swain, Lin and Wallentin (2024), the overall length of the first pandemic wave of Covid-19 in Italy and Europe was 48 days, it is reasonable to assume a short maturity for the financial derivative, in order to give the possibility to healthcare institutions to either exercise the option if they anticipate an upward trend of contagion, or let it expire otherwise. Recall also that this approximation works well for expiration dates that are less than one year far away. Hence, in this context, it is realistic to assume a time to maturity, T, of the option of two months ($T = 1/6$).

Afterwards, to provide an approximation for the standard deviation σ of the prices of Paxlovid, it has been hypothesised to employ the daily observations of Pfizer's prices, i.e. Paxlovid producer, over a time series of sixteen years. This condition has been imposed since time series of Paxlovid's prices were not available. So, daily observations of Paxlovid adjusted closing prices in the Frankfurt Stock Exchange from December 28th, 2007, until May 8th, 2024 have been retrieved from Yahoo Finance[159]. Then, an average of the adjusted closing prices has been

[158] The price in euro is computed adjusting the treatment cost of 529 $, indicated by Yeung et al. (2023), for the exchange rate between euro and dollar on the 14th of June 2023, which is the moment of the last update of the Institute for Clinical and Economic Review (ICER) report. The exchange rate for that day is obtained through the Bank of Italy, at the following link, consulted on May 17th, 2024: https://www.bancaditalia.it/compiti/operazioni-cambi/cambio/cambi_rif_20230614/.

[159] The data has been taken from the Frankfurt Stock Exchange to obtain daily observations in euro currency. The time series has been retrieved by the following link, which has been consulted on May 8th, 2024: https://it.finance.yahoo.com/quote/PFE.DE/history?period1=1198800000&period2=1715212800&interval=1d&filter=history&frequency=1d&includeAdjustedClose=true.

calculated for all the years between 2008 and 2023[160]. Later, growth rates have been computed for subsequent years in the following way:

$$Growth\ rate_{2009} = \frac{(average\ adjusted\ closing\ value_{2009} - average\ adjusted\ closing\ value_{2008})}{average\ adjusted\ closing\ value_{2008}}$$

and so on. Lastly, a standard deviation of all the growth rates from 2009 to 2023 is calculated, giving a value of $\sigma = 0.1673$[161].

To define a value for the last important variable involved, i.e. the strike price X, it is relevant to remark the effects of the buyback clause described by Lupkin (2022). The existence of such condition entails that the insurance firm bears the risk of repurchasing back the treatments whenever FDA removes the authorization for the therapy. Therefore, to maximize its profit, the insurance company may charge a high premium, i.e. cost of the option for the buyer, that cannot be given back to the healthcare institution, and, at the same time, a low strike price, because this is the amount of money that has to be spent whether it must repurchase the drug. So, the strike price X is set equal to the Paxlovid's price, 489.41 €, suggesting that the option contract is issued "at-the-money" (ATM), i.e. the exercise price equals the underlying price S.

Assuming that all the hypotheses needed to apply this method hold, now all the data required to compute the value of the financial derivative are available and the Barone-Adesi and Whaley (1987) approximation results in a financial value of the American call option C(S,T), written on the price of Paxlovid, equal to 13.95882 €, given the prespecified values of S, X, T, σ, r and b[162].

However, the price of this option is linked to a probability of pandemic outbreak because it is written on an underlying whose value depends on the pandemic threat[163]. Therefore, the cost of the financial contract must be multiplied by the risk of pandemic burst p to obtain an option price that is aligned with pandemic expectations. Two probabilities of pandemic outbreak are retrieved by the articles of Attema, Lugnér and Feenstra (2010) and Marani et al. (2021): the first article indicates a probability of 0.0075 per quarter, whereas the second one gives a risk of

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[160] Closing prices adjusted for stock splits, dividend distributions and capital gains have been used because these measures allow to better compare prices across time.
See the following link of Borsa Italiana for a broader explanation:
https://www.borsaitaliana.it/notizie/sotto-la-lente/risultato-esercizio-rettificato-normalizzato172.htm
This website has been consulted on May 20th 2024.
[161] The comparative statics analysis in chapter 4.4 simulates the change in the value of the derivative with respect to different standard deviations.
[162] See the appendix of this research for all the computations needed for this American call option.
[163] For example, a higher risk of the pandemic burst can imply an increase in the demand of the antiviral.

pandemic outburst of 0.44 in a century[164], which result, respectively, in $p_{Attema} = 0.005$ and $p_{Marani} = 0.000958$ for a two-months period[165].

Hence, considering each probability, the price of one option written on the value of the antiviral Paxlovid can either be evaluated at 0.0698 € or at 0.0134€ whether the probability of Attema, Lugnér and Feenstra (2010) or Marani et al. (2021) is chosen in an agreement.

4.4. Comparative statics analysis

A comparative statics analysis has been performed to understand how option price changes with respect to changes in the maturity of the derivative and the volatility of the underlying. All the options are issued ATM, while outcomes are presented for the two different pandemic outbreak probabilities p_{Attema} and p_{Marani}.

Firstly, let us examine how the option price is influenced by changes in the expiration date of the derivative T.

To choose the maturities for this part of the comparative statics analysis, a graph retrieved from a study of Zirilli, Limonti and Alibrandi (2022) on the trend of the Covid-19 infection rate in Italy[166] from February 2020 to December 2021 is presented and scrutinized.

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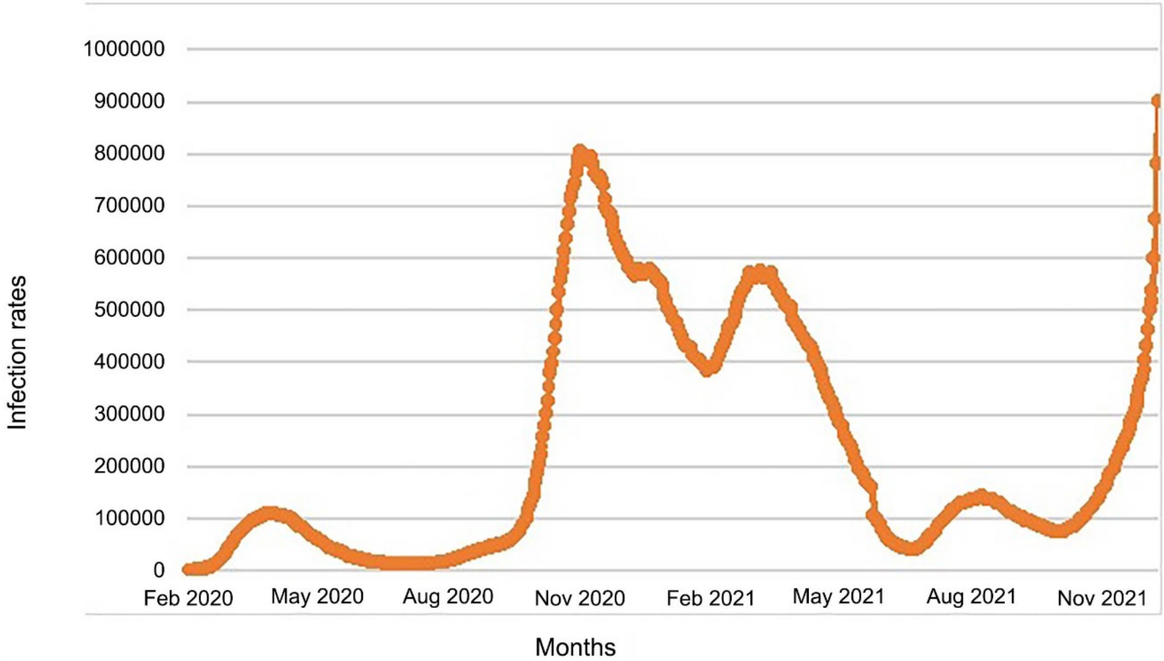
[164] See Attema, Lugnér and Feenstra (2010) and Marani et al. (2021) for all the calculations.

[165] This last probability has been obtained through the same formula presented by Marani et al. (2021), substituting 100 years with two months, so $P_{2m} = 1 - (1 - 3/523)^{\frac{1}{6}} = 0.000958$ instead of $P_{100y} = 1 - (1 - 3/523)^{100} = 0.44$.

[166] Zirilli, Limonti and Alibrandi (2022) calculated this value as the ratio among infected individuals and total population in Italy.

Graph 4.1: SARS-COV-2 infection rate in Italy



Source: Zirilli, Limonti and Alibrandi (2022)

It is noteworthy to analyse the distribution of the peaks for different pandemic waves. For example, the peak of the infection rate during the first wave is visible around April 2020, whereas the second wave, considered as biphasic by Zirilli, Limonti and Alibrandi (2022), exhibited a significant infection rate growth in the autumn months of 2020, with two diverse peaks around December 2020 and early spring 2021. Then, the vaccination campaign led to a consistent decrease of infections during spring 2021. Finally, the trend revealed a new, but smaller, peak in August 2021 and a last substantial infection rate growth linked to the outbreak of the Omicron variant, that resulted in lower hospitalization rates compared to previous waves[167].

Therefore, a set of option contracts with different maturities can help to either limit the initial growth of the infection rate during a pandemic wave, which may be extremely quick as, for instance, in autumn 2020, or to limit the effects of its peak, both in terms of deaths and hospitalizations, as in April 2020, December 2020 or early spring 2021. For this reason, the option price is calculated for the expiration dates of 2 months, 6 months, 9 months, 12 months, 18 months and 24 months, maintaining equal the other variables involved, i.e. r, b and σ.

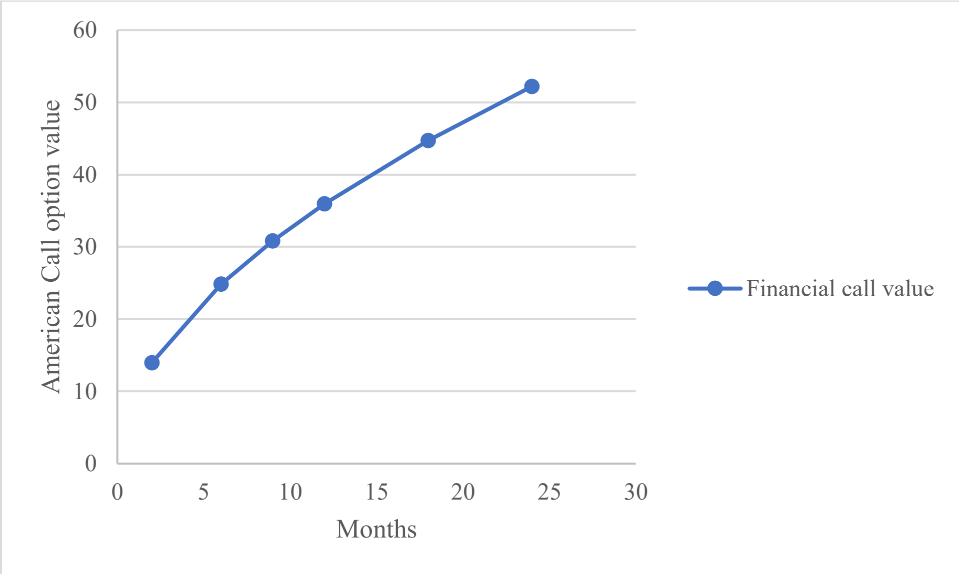
It is relevant to note that a longer T of the contract implies an increase in the probabilities of pandemic outbreak. In this context, the option price is influenced twice by the change of the

[167] See Zirilli, Limonti and Alibrandi (2022) for a broader analysis of the effects of each pandemic wave in Italy.

maturity through an expansion of the American call option C(S, T) value due to an higher T, that consequently cause an increase in either p_{Attema} or p_{Marani} because of a longer time span considered.

The next graph helps to appreciate how T influences C(S, T).

Graph 4.2: American call option evolution with respect to different maturities

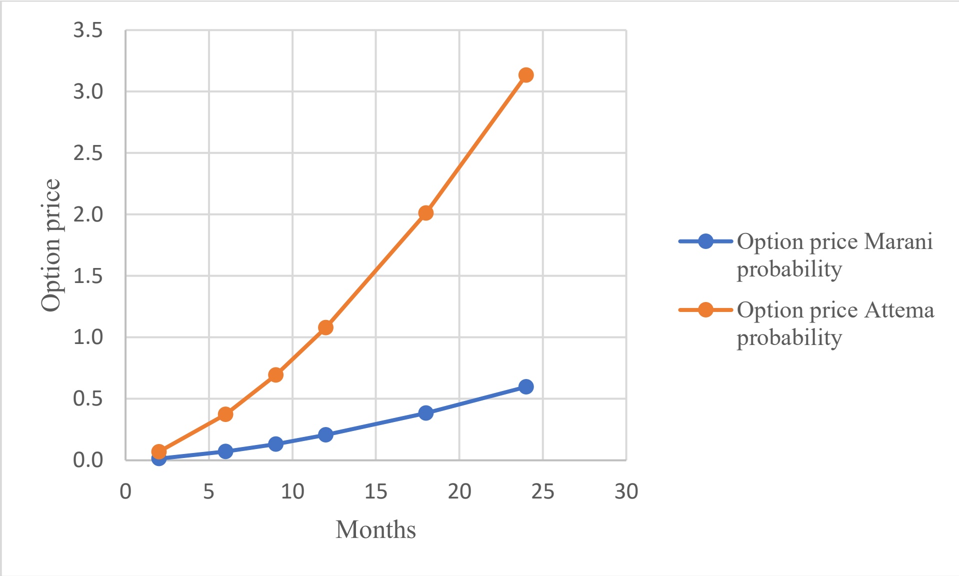


Source: Own elaboration in excel

As expected, the value of C(S, T) rises for longer maturities, so the buyer encounters a trade-off between purchasing cheap short-term maturity options, facing a higher risk of not exercising them if the pandemic evolution is slower than expected, and purchasing expensive long-term options, that instead offer a greater coverage against the pandemic risk.

The following graph shows instead the different evolutions of the option price for various maturities, when C(S, T) is multiplied by either p_{Attema} or p_{Marani}.

Graph 4.3: Option price evolution with respect to different maturities



Source: Own elaboration in excel

It is observable that, for the same T, multiplying C(S, T) by p_{Attema} implies an option price more than five times higher than the cost of the derivative when C(S,T) is multiplied by p_{Marani}. Moreover, this graph illustrates a slow, but visible, increase in the ratio between the two option prices as T grows: option prices for 2 months maturities are respectively 0.0698 € for p_{Attema} and 0.0134 € for p_{Marani}, which is 5.209 times lower, while, for an expiration date of 12 months, the option price for the Attema's probability is 1.0783 €, but the other option costs only 0.2062 €, that is 5.229 times lower. Instead, when considering a maturity of 24 months, the Attema's probability option is worth 3.1327 €, while the Marani's probability option costs only 0.5973€, that is 5.245 times lower.

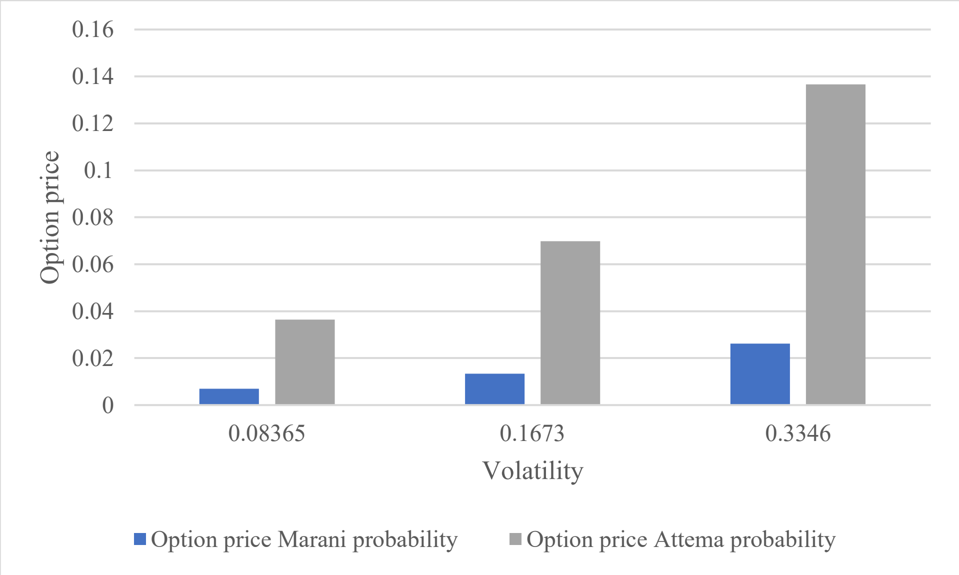
So far, this part of the comparative statics analysis tried to recreate a set of opportunities for European community healthcare institutions (or single governments) to ensure themselves from a pandemic risk through various purchase possibilities: they can either buy short maturity options whether they expect a rapid increase in the pandemic alarm, or longer maturity options whenever they anticipate that the pandemic evolution is slow.

However, this decision seems to be truly influenced by the probability p embedded in the calculation of the option price and not just by the maturity T, since the effect of the choice of p on the derivative appears to be quite remarkable. Consequently, option buyers and issuers should carefully take into account the probability of pandemic outbreak when they decide the terms of the contract.

Secondly, it is relevant to visualize how the derivative is influenced by doubling or halving the volatility of the underlying, resulting in three different standard deviations: 0.08365, 0.1673 and 0.3346. All the other variables involved, i.e. T, r and b, remain, respectively, equal to two months, 0.03 and 0.015.

The following graph helps to describe the effect of such change in the volatility of the price of Paxlovid.

Graph 4.4: Option price changes with respect to different volatilities of the underlying



Source: Own elaboration in excel

The values of original options already calculated in the previous paragraph are the ones presented in the two bars in the middle of the chart. As theory predicts[168] , a positive correlation between option price and the volatility of the underlying is noticeable: reducing by half the volatility of the Paxlovid price[169] decreases the option price calculated with p_{Attema} from 0.0698 € to 0.0365 € and the option price computed with p_{Marani} from 0.0134 € to 0.00699 €, almost halving their values. Instead, doubling the standard deviation of the underlying expands the value calculated with p_{Attema} to 0.1366 € and the one computed with p_{Marani} to 0.0262 €.

Those outcomes indicate that the option price grows as uncertainty regarding Paxlovid's price increases, and this is because the option derivative is exercised only if it is worth some value, so it benefits from the upside of the underlying without facing risks of its downside. Therefore, a contract created whenever the underlying price is stable, and no pandemic alarm is close to be announced is cheaper than a similar contract issued when pandemic threat is on the way. If

[168] See chapter 2.2 for the positive correlation among option price and volatility of the underlying.
[169] Let us recall that daily observations of Pfizer's prices are employed to approximate Paxlovid's prices.

some epidemiological factors signal a potential pandemic, the demand of the antiviral may increase and be conditioned by World Health Organization (WHO) announcements on the progress of the situation. In this circumstance, the price of Paxlovid is subject to a larger volatility that implies a more expensive option price and, consequently, creating a derivative contract in such scenario results in a greater cost for the buyer.

4.5. Economic analysis

This chapter has priced one option contract for the purchase of antivirals as a preventive measure to counteract the risk of pandemic outbreak, considering a scenario in which the antiviral was available and neither pandemic threat nor any signals were on the horizon. Hence, this study simulates the creation of such derivative whenever healthcare institutions want to ensure populations from an uncertain pandemic threat that is still not visible at the moment of contract signing.

So, a healthcare institution (or a national government) would have to pay either 0.0698 € or 0.0134 € (contingent on the choice between p_{Attema} and p_{Marani}) to an insurance company to acquire the right, but not the obligation, to purchase one treatment of Paxlovid, that contains the recommended therapy for five days[170] , at the predefined strike price of 489.41 € in any moment between $T = 0$ (contract signing) and $T = 2$ *months* (maturity of the option). If the pandemic occurs within two months, the buyer exercises the option, obliging the insurance firm to purchase the antiviral from Pfizer at the market price and reselling it to the healthcare institution at the predefined price[171].

It is now noteworthy to analyse economic implications derived from the employment of option contracts in the purchase of Paxlovid and compare it to other strategies adopted. For example, at the beginning of the year 2022 the Italian government bought 600000 doses of Paxlovid[172] , of which a large stock has been unused. Instead, American options help governments to purchase antivirals just in case of need and for the necessary quantity, avoiding wastes of therapies and public spending.

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[170] The source is the package leaflet of Paxlovid released by Agenzia Italiana del Farmaco (AIFA), viewed at the following link:
https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004849_049853_FI.pdf&retry=0&sys=m0b1l3.
This website has been consulted on June 11th, 2024.

[171] On the other hand, if the pandemic does not occur within two months, the option expires, and the buyer has paid a price for this right without exercising it.

[172] See the following link: https://www.governo.it/it/dipartimenti/commissario-straordinario-lemergenza-covid-19/19084. This website has been consulted on June 10th, 2024.

So, the intention of this paragraph is to address which can be an optimal approach that the Italian government should follow to protect its population from the effects caused by a pandemic outbreak[173].

In this context, the study of Zirilli, Limonti and Alibrandi (2022) and the database offered by the Italian Ministry of Health, which gives the total number of infected individuals for each day from February 24th, 2020[174] , are relevant to understand how the pandemic evolved in Italy and the portion of the population to whom Paxlovid should be administered.

For instance, such database indicates that after 6 months of the pandemic, on August 24th, 2020, 260298 people in total have been infected, whereas after one year from the beginning, on February 24th, 2021, more than two million and 800000 people contracted the virus. As even remarked by the graph 4.1 taken from Zirilli, Limonti and Alibrandi (2022), the greater increase in the infections occurred in the late summer and autumn of 2020, during the second wave of the pandemic: on July 30th 2020, considered by Swain, Lin and Wallentin (2024) as the beginning of the second wave of the pandemic in Italy, just 247158 people in total have been infected while on November 30th 2020[175] , more than one million and 600000 people in total have contracted the virus, according to the database provided by the Italian Ministry of Health. Following such data, it is reasonable to assume that a government purchase of 600000 antiviral treatments may help to flatten out the pandemic trend, reducing hospitalizations and deaths, especially because option contracts give the flexibility to acquire doses of Paxlovid whenever the government expects new waves of contagion.

To discuss economic implications of these options, let us consider two scenarios in which it is assumed that the Italian government buys 600000 option contracts, but with different expiration dates. In the first one, the government purchases 250000 options for a maturity of 2 months, 200000 options for a maturity of 6 months, 100000 options for a maturity of 9 months and 50000 options for a maturity of 12 months.

Option prices for each maturity and probability of pandemic outbreak are the ones calculated in the comparative statics analysis and they are presented in table 4.1. The overall costs of this strategy, computed as the purchased number of contracts with each expiration date and

[173] For instance, one target may be a reduction of the hospitalization rate of infected individuals.
[174] See the following link:
https://opendatamds.maps.arcgis.com/apps/dashboards/0f1c9a02467b45a7b4ca12d8ba296596 .
This website has been consulted on June 11th, 2024.
[175] In fact, a peak in the infection rate is visible around late November 2020 in the graph 4.1 retrieved by Zirilli, Limonti and Alibrandi (2022).

multiplied by their correspondent option price, are, respectively, 41190.09 € for p_{Marani} and 215225.31 € for p_{Attema}, as summarized in table 4.2.

Table 4.1: Option price for different maturities and probabilities of pandemic outbreak

	Marani	Attema
2 months	0.0134	0.0698
6 months	0.0713	0.3726
9 months	0.1327	0.6934
12 months	0.2062	1.0783

Source: Own elaboration in excel

Table 4.2: Expenses of purchasing options with different maturities for 600000 contracts

doses	total cost Marani	total cost Attema
250000	3344.24	17448.52
200000	14269.31	74521.31
100000	13267.42	69338.75
50000	10309.13	53916.72
	41,190.09 €	**215,225.31 €**

Source: Own elaboration in excel

Instead, the second scenario consists of a government purchase of 600000 contracts with a maturity of 12 months, resulting in a cost of this second strategy of 123709.50 € for p_{Marani} and 647000.69 € for p_{Attema}.

However, it has been assumed so far an administration of Paxlovid to each infected individual, although it should only be administered to people at high risk of progression to severe disease, thus implying a lower amount of option contracts required to achieve a proper coverage of the population at risk. A research of Ruggeri et al. (2020) highlighted that 6.6% of the infected patients needed hospitalization but, since this study was published in December 2020 and it did not take into account the subsequent evolution of the pandemic during the vaccination campaign and the outbreak of the Omicron variant, it is reasonable to assume that an interval between 5% and 10% of the infected individuals required hospitalization over the course of the pandemic. These two values may be considered as upper and lower bounds of the range that can serve as an approximation of the fraction of patients at risk of progression to severe disease.

Let us now replicate the calculi in the two scenarios assuming that Paxlovid should be administered to a portion of either 5% or 10% of the total of infected patients. Given that, the lowest amount of option contracts purchased by the Italian government to cover the population at risk can be 30000, whereas the greatest amount may be 60000. Supposing that the first scenario is repeated for the lower bound implies that the government purchases 12500 options for a maturity of 2 months, 10000 options for a maturity of 6 months, 5000 options for a maturity of 9 months and 2500 options for a maturity of 12 months. The overall costs of this strategy are now 2059.50 € for p_{Marani} and 10761.27 € for p_{Attema}, as summarized in table 4.3.

Table 4.3: Expenses of purchasing options with different maturities for 30000 contracts

doses	total cost Marani	total cost Attema
12500	167.21	872.43
10000	713.47	3726.07
5000	663.37	3466.94
2500	515.46	2695.84
	2,059.50 €	**10,761.27 €**

Source: Own elaboration in excel

Instead, the second scenario consists of a government purchase of 30000 contracts with a maturity of 12 months, resulting in a cost of this second strategy of 6185.48 € for p_{Marani} and 32350.03 € for p_{Attema}.

Lastly, let us repeat the computations for the upper bound of 60000 contracts acquired. Within this framework, the government buys in the first scenario 25000 options for a maturity of 2 months, 20000 options for a maturity of 6 months, 10000 options for a maturity of 9 months and 5000 options for a maturity of 12 months. The overall costs of this strategy are now 4119.01 € for p_{Marani} and 21522.53 € for p_{Attema}, as summarized in table 4.4.

Table 4.4: Expenses of purchasing options with different maturities for 60000 contracts

doses	total cost Marani	total cost Attema
25000	334.42	1744.85
20000	1426.93	7452.13
10000	1326.74	6933.88
5000	1030.91	5391.67
	4,119.01 €	**21,522.53 €**

Source: Own elaboration in excel

The second scenario consists of a government purchase of 60000 contracts with a maturity of 12 months, resulting in a cost of this second strategy of 12370.95 € for p_{Marani} and 64700.07 € for p_{Attema}.

The following table synthesises all the purchasing strategies available when p_{Marani} is the probability of pandemic outbreak considered.

Table 4.5: Summary of all purchasing strategies when p_{Marani} is the probability assumed

	5% hospitalization rate	10% hospitalization rate
Different maturities	2,059.50 €	4,119.01 €
12 months only	6,185.48 €	12,370.95 €

Source: Own elaboration in excel

Assuming that p_{Marani} is the probability used for the evaluation, the effective cost of purchasing option contracts as a preventive measure to counteract against negative outcomes of a pandemic, like increasing hospitalizations and Intensive Care Units (ICU) admissions, ranges among 2059.50 € and 12370.95 €, depending on hospitalization rate and on the strategy selected.

If the government expects a 5% hospitalization rate of the infected patients, it will buy 30000 contracts, with expenses that are either 2059.50 € whether options with maturities of 2 months, 6 months, 9 months and 12 months are bought, or 6185.48 € whenever only options with one year maturity are purchased. On the other hand, if the government expects a 10% hospitalization rate of infected patients, it will buy 60000 contracts, with expenses that are either 4119.01 € for the various maturities strategy and 12370.95 € whether only options with one year expiration date are purchased.

Let us now present in the following table the relative expenditure obtained with p_{Attema}.

Table 4.6: Summary of all purchasing strategies when p_{Attema} is the probability assumed

	5% hospitalization rate	10% hospitalization rate
Different maturities	10,761.27 €	21,522.53 €
12 months only	32,350.03 €	64,700.07 €

Source: Own elaboration in excel

Assuming that p_{Attema} is the probability used for the evaluation, the effective cost of this preventive measure ranges between 10761.27 € and 64700.07 €, depending on the hospitalization rate and the strategy selected.

If the government expects a 5% hospitalization rate, it will buy 30000 contracts, with a cost either of 10761.27 € for the acquisition of option contracts with various maturities or of 32350.03 € to buy derivatives with only one year expiration date. On the contrary, if the government expects a 10% hospitalization rate of infected patients, it will buy 60000 contracts, with expenses that are either 21522.53 € for the various maturities strategy and 64700.07 € whether only options with one year expiration date are purchased.

After having presented all the possible strategies under diverse conditions, it is now appropriate to discuss advantages and disadvantages of each purchasing plan, in order to determine an efficient approach for the Italian government to handle the risk of pandemic outbreak and its negative consequences.

Firstly, defining an optimal quantity of option contracts required to curb the virus diffusion and limit hospitalizations is contingent on at least two factors: the probability of pandemic outbreak assumed and the hospitalization rate of people that contracted Covid-19.

Consequently, deciding which is the optimal quantity of option contracts to be purchased among all eight possibilities is quite difficult and not extremely useful in terms of economic policies, so, for this reason, it seems to be more meaningful to understand whether the government benefits more from purchasing American option contracts with both short and long maturities, or from acquiring solely American derivatives with long expiration dates.

Given that a relevant objective of government healthcare policies is expenditure minimization, one main advantage of purchasing options with various maturities is its cheapness compared to the other scenario. However, there is a higher risk of not exercising all the derivatives if pandemic virulence or transmissibility are low[176] , because, in these cases, hospitalizations and ICU admissions do not grow exponentially, the pressure on the healthcare system is limited and the quantity of options that should be exercised is minimal[177] .

Conversely, the main disadvantage of exclusively purchasing derivatives with longer maturities is their expensiveness, albeit this second approach offers a greater degree of coverage, since American options give the possibility to exercise the right at any time. In this context, the government can buy at any moment within a one year time span, at a predefined price, the necessary quantity of antiviral treatments to curb virus diffusion and limit consequences: if virulence or transmissibility are high, the government will opt for exercising the rights sooner, whereas if virulence or transmissibility are low, the government will either buy a lower amount of options or directly wait for an increase in the virus spread. Compared to the first strategy, this method bears a lower risk of unexercised expiration of option contracts, but, if this happens, the inefficient expenditure is greater than in the first strategy.

The research of Bai et al. (2024), which focused on the impact of Paxlovid treatments in the United States, estimated that “the optimal strategy is always the highest achievable treatment

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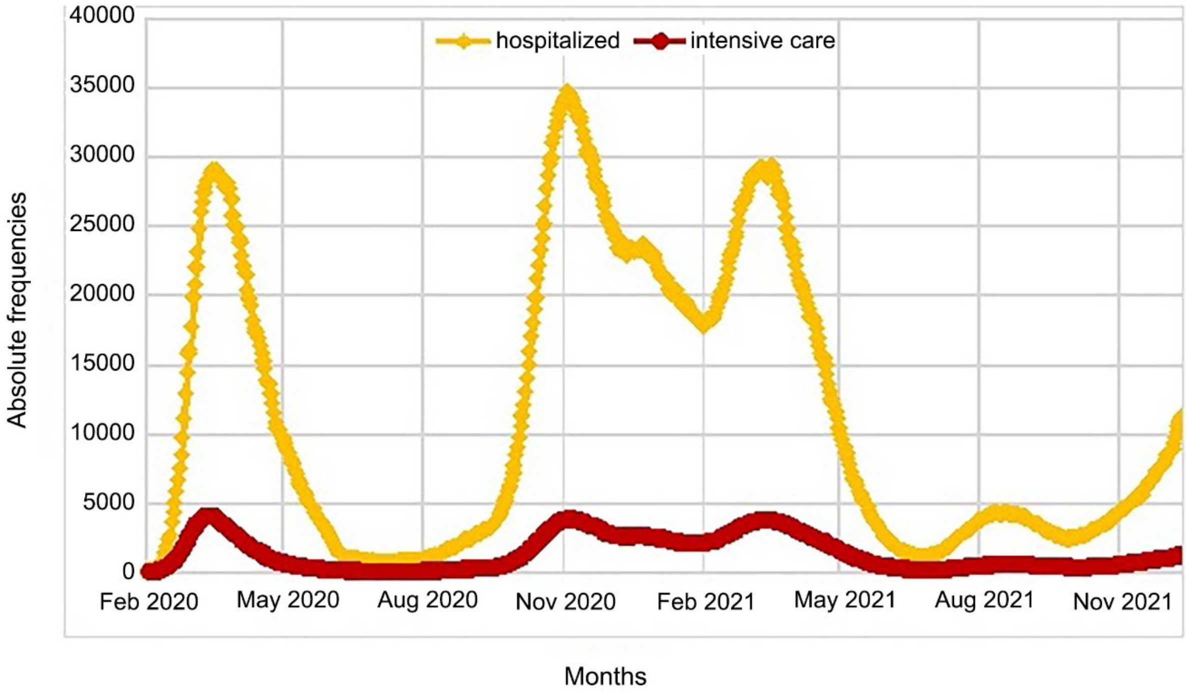
[176] Virulence and transmissibility of a virus with pandemic potential are described, respectively, by the case fatality ratio and the reproduction number. These two measures are illustrated in chapter 2.1.
[177] Of course, if the pandemic does not occur, option rights are not exercised.

rate" and, accordingly, it seems that the government should purchase 30000 or 60000 options with a 12 months maturity, provided that these rights offer to protect the population at risk for a longer time span.

However, in my opinion, the cost-saving strategy of buying contracts with various expiration dates is preferrable. To explain this argument, let us comment the graph taken by Zirilli, Limonti and Alibrandi (2022) on the trend of COVID-19 patients admitted to ICUs and hospitalized in Italy.

Graph 4.5: Trend of COVID-19 patients admitted to Intensive Care Unit and hospitalized in Italy



Source: Zirilli, Limonti and Alibrandi (2022)

Provided that the number of patients hospitalized and admitted to ICU has grown exponentially, the pressure on the healthcare system quickly expands at the beginning of the pandemic. If a pandemic like Covid-19 does not occur, the strategy with various maturities is, in any case, cheaper than the other one and the unused government expense is lower, whereas if such pandemic occurs, it is likely to exercise the rights and administer antivirals in the first months of the pandemic to individuals at risk. This will help to flatten out the curve of infections, to limit the amount of hospitalization and to give time to healthcare systems to properly adjust their needs to the changing situation, increasing for example ICU capacity. Hence, option contracts with short maturity can be enough to protect the necessary portion of the population at a way cheaper cost.

5. Conclusion

Growing literature over the last two decades on the use of option contracts in the healthcare sector suggests that derivatives are now becoming useful tools in this field to take decisions. An interesting case is the purchase of antivirals to prevent virus diffusion and avoid pandemic outbreaks.

So far, national governments have either faced risks of overpayments due to fluctuations derived from possible demand increases or, because of deals for large stocks of therapies, they wasted vast quantities of drugs.

In this context, option contracts can act as "ex-ante agreements" that help to stabilize the price of antivirals, while giving flexibility to national governments to buy and administer these treatments just in case of need. These derivatives allow national governments to obtain the right, but not the obligation, to buy courses of antivirals at any time prior to the expiration of the option. National governments can decide to exercise this right following information given by World Health Organization (WHO) whenever they believe it can be mostly efficient to curb virus diffusion or limit hospitalizations and deaths during a pandemic wave.

Therefore, this research discussed whether it could be possible to create a financial contract for the purchase of one course of the antiviral Paxlovid, that has proven to be effective against Covid-19.

European community healthcare institutions, like the European Medicines Agency (EMA), and insurance companies were indicated, respectively, as buyers and issuers of these contracts.

Moreover, this study scrutinized which variables mostly influenced the price of this derivative and presented an economic analysis of possible implementation strategies within the Italian context. American call option C(S, T) was the type of financial derivative suited for this analysis, which has been computed through the Barone-Adesi and Whaley (1987) approximation method. This approach divided the option into an European call c(S, T) with same strike price and maturity, plus a perpetual option.

Assumptions taken into consideration were the following: this call was issued At-The-Money (ATM), with underlying price S and strike price X equal to 489.41 €, a volatility σ of the price of the underlying equal to 16.73%, a maturity T of two months, a riskless interest rate r of 3% and a cost of carrying the commodity b equal to 1.5%. The value of C(S, T) obtained was 13.95882 €.

Two different probabilities of pandemic outbreak given by Attema, Lugnér and Feenstra (2010) and Marani et al. (2021) have been attached to the value of the American call, resulting in final option prices of either 0.0698 € or 0.0134 €.

The comparative statics analysis in paragraph 4.4 described the effects of changes in time to maturity T and standard deviation σ on the option price. It has been observed that T influenced the option price both increasing the value of C(S, T) and expanding the probabilities of pandemic outbreak p_{Attema} and p_{Marani}. Results have demonstrated that the choice between the two probabilities drastically modified the option price. Hence, national governments should carefully identify which probability of pandemic outbreak should be inserted in their contracts with insurance companies before deciding the maturity of the derivative. Furthermore, it has been confirmed that an increase in the volatility of the price of Paxlovid, i.e. the underlying, had a positive impact on the option value.

The economic analysis performed in paragraph 4.5 examined whether buyers should purchase option contracts with both short and long maturities or just buy derivatives with long expiration dates. Simulations on the purchase of Paxlovid treatment by the Italian government were presented. Since this therapy should be administered to individuals at risk of progression to severe forms of Covid-19, eight scenarios have been proposed.

Criteria respected to construct these different circumstances were the following ones: probability of pandemic outbreak considered, portion of hospitalized patients assumed and purchasing strategy adopted.

The first criterion relied on the distinction between p_{Attema} and p_{Marani}, whereas the second parameter followed a study of Ruggeri et al. (2020) that revealed a 6.6% hospitalization rate for Covid-19 infected individuals: a range with lower and upper bounds equal to 5% and 10% of hospitalized patients was supposed. This resulted in either 30000 or 60000 necessary options to fight pandemic threat. Lastly, the third criterion assumed that Italian government could either purchase all these contracts with a maturity of one year or opt for another approach in which some derivatives were bought with maturities of 2 months, others with 6 months, 9 months and one year.

Economic implications of the two strategies have been explored: on the one hand, buying only options with longer expiration dates provided a greater coverage to protect individual at risk, but this strategy was more expensive, while, on the other hand, options with shorter maturities were less likely to be exercised, unless a pandemic wave occurred within few months. Anyway, this cheaper alternative seemed to be preferable.

The trend in hospitalizations and Intensive Care Units (ICU) admissions, offered by Zirilli, Limonti and Alibrandi (2022), illustrated a consistent increase in hospitalized patients during the first months of the pandemic of Covid-19. Within this framework, options with 2 or 6 months maturities would be sufficient to limit clinical consequences of the first pandemic wave, that exercised great pressure on hospitals and found healthcare sectors worldwide almost unprepared. Remaining options could be exercised to mitigate the impact of subsequent waves.

Nevertheless, it is noteworthy to highlight that this study has some limitations that should be discussed in future research.

Firstly, Paxlovid's price assumed in the calculations was retrieved from the Institute for Clinical and Economic Review (ICER) report updated on June 14th, 2023. Future disclosure of the price of the contract signed by Italian government and Pfizer for the purchase of Paxlovid in 2022 should be inserted in computations to have a more accurate interpretation of the Italian case. Secondly, this research did not distinguish among proportions of antivirals that could be used either for treatment or for prophylaxis. Besides, no renewal possibility of the option contract was included. Investigation on this topic should be addressed to offer a greater set of alternatives to governments and healthcare institutions for the purchase of Paxlovid.

Lastly, this study focused on the creation of an agreement for a specific therapy that was effective against a specific virus: such narrow perspective should be expanded to provide more solutions in price negotiations in healthcare.

6. Appendix

The Barone-Adesi and Whaley (1987) approximation for American call option is obtained by the following formula when $S < S^*$:

$C(S,T) = c(S,T) + A_2(S/S^*)^{q_2}$.

Assuming that all the hypotheses needed to apply this method hold and provided that all the data required to compute the value of the financial derivative are available, it is possible to calculate the price of such American option.

Since the antiviral price S is equal to 489.41 € and the option is issued ATM, even the strike price X is equal to 489.41€. The riskless interest rate r is set equal to 0.03, whereas the cost of carrying b is equal to 0.015. The standard deviation σ of the Paxlovid's price is assumed to be 0.1673, while the maturity of the option is set at two months ($T = \frac{1}{6}$).

Firstly, it's important to quantify the critical commodity price S^*. Barone-Adesi and Whaley (1987) estimate S^* through the following equation:

$$S^* = X + [S^*(\infty) - X][1 - e^{h_2}]$$

in which $h_2 = -(bT + 2\sigma\sqrt{T})X/[S^*(\infty) - X]$

and $S^*(\infty) = X/[1 - 1/q_2(\infty)]$.

Authors remark in the appendix of their paper that S^* is an increasing function of time to maturity of the option, and this last equation is the upper bound, when $T = +\infty$, of this function.

Its lower bound, when $T = 0$, is instead the strike price X.[178]

To compute $S^*(\infty)$, $q_2(\infty)$[179] is required, and it is computed as follows:

$$q_2(\infty) = \left[-(N - 1) + \sqrt{(N - 1)^2 + 4M}\right]/2$$

where $N = 2b / \sigma^2$ and $M = 2r/\sigma^2$ are two notational substitutions used by the authors. Hence, the subsequent calculations give the value of S^*.

$$N = 2b/\sigma^2 = 0.03/(0.1673)^2 = 1.07183855$$
$$M = 2r/\sigma^2 = 0.06/(0.1673)^2 = 2.14367710$$

[178] See the appendix of Barone-Adesi and Whaley (1987) for the derivation of these formulas.
[179] The value $q_2(\infty)$ is a root of the second-order ordinary differential equation of the approximation of the early exercise premium when T approaches +∞.

$q_2(\infty) = \left[-(N-1) + \sqrt{(N\ -\ 1)^2 +\ 4M}\right]/2 =$

$= \left[-(1.07183855-1) + \sqrt{(1.07183855\ -\ 1)^2 + 8.5747084}\right]/2 =$

$= 1.4286514$

$S^*(\infty) = X/[1-1/q_2(\infty)] = 489.41/[1-1/1.4286514] = 1631.1536$

$h_2 = -\left(bT + 2\sigma\sqrt{T}\right)\{X/[S^*(\infty)-X]\} =$

$= -\left(0.015\frac{1}{6} + 0.3346\sqrt{\frac{1}{6}}\right)\{489.41/[1631.1536-489.41]\} =$

$= -0.059625359$

$S^* = X + [S^*(\infty)-X][1-e^{h_2}] = 489.41 + [1631.1536 - 489.41][1 - e^{-0.059625359}]$

$= 555.497$ €.

Since the underlying Paxlovid price assumed is 489.41€, below the critical antiviral price, recall that the American call option must be calculated as:

$C(S,T) = c(S,T) + A_2(S/S^*)^{q_2}.$

This formula decomposes an American call option into an European one written on the same underlying, with same expiration date and strike price, and the early exercise premium. To obtain the value of the European call, it's sufficient to apply the Black, Scholes and Merton model:

$$c(S,T) = Se^{(b-r)T}N(d_1) - Xe^{-rT}N(d_2)$$

where $d_1 = [ln(S/X) + (b + 0.5\sigma^2)T]/\sigma\sqrt{T}$, $d_2 = d_1 - \sigma\sqrt{T}$, N($d_1$) is the cumulative univariate normal distribution for d_1 and N(d_2) is the cumulative univariate normal distribution for d_2.[180]

Hence, the subsequent calculations give c(S, T).

$d_1 = [ln(S/X) + (b + 0.5\sigma^2)T]/\sigma\sqrt{T} =$

$= [ln(489.41/489.41) + (0.015 + \frac{0.1673^2}{2})\frac{1}{6}]/(0.1673\sqrt{\frac{1}{6}}) =$

$= 0.07075$

$d_2 = d_1 - \sigma\sqrt{T} = 0.07075 - 0.1673\sqrt{\frac{1}{6}} = 0.00245$

[180] See Barone-Adesi and Whaley (1987) for the application of the Black, Scholes and Merton formula inside of this approximation method. See instead Hull (2015) for a broader theoretical description of this option pricing technique.

$N(d_1) = 0.52820$

$N(d_2) = 0.50098$[181]

$c(S,T) = Se^{(b-r)T}N(d_1) - Xe^{-rT}N(d_2) =$

$$= 489.41e^{(0.015-0.03)\frac{1}{6}}0.52820 - 489.41e^{-0.03\frac{1}{6}}0.50098 = 13.9012 \text{ €}.$$

To calculate, instead, the early exercise premium $A_2(S/S^*)^{q_2}$, the values of A_2 and q_2 are required[182].

$$A_2 = (S^*/q_2)\{1 - e^{(b-r)T}N[d_1(S^*)]\}$$

where

$$d_1(S^*) = [ln(S^*/X) + (b + 0.5\sigma^2)T]/\sigma\sqrt{T}$$

and

$$q_2 = [-(N-1) + \sqrt{(N-1)^2 + 4M/K}]/2 .$$

Recall that $K(T) = 1 - e^{-rT}$.

Hence, the following calculations give the value of the early exercise premium.

$K = 1 - e^{-rT} = 1 - e^{-0.03\frac{1}{6}} = 0.0049875$

$q_2 = [-(N-1) + \sqrt{(N-1)^2 + 4M/K}]/2 =$

$$= [-(1.07183855 - 1) + \sqrt{(1.07183855 - 1)^2 + 4(2.14367710/0.0049875)}]/2 = 20.696$$

$d_1(S^*) = [ln(S^*/X) + (b + 0.5\sigma^2)T]/\sigma\sqrt{T} =$

$$= [ln(555.497/489.41) + (0.015 + 0.5(0.1673)^2)\frac{1}{6}]/(0.1673\sqrt{\frac{1}{6}})$$

$$= 1.92526$$

$N[d_1(S^*)] = 0.97290$[183]

$A_2 = (S^*/q_2)\{1 - e^{(b-r)T}N[d_1(S^*)]\} =$

$$= (555.497/20.696)\{1 - e^{(0.015-0.03)\frac{1}{6}}(0.97290)]\} = 0.7925$$

$A_2(S/S^*)^{q_2} = 0.7925(489.41/555.497)^{20.696} = 0.05762$ €.

[181]The values of $N(d_1)$ and $N(d_2)$ have been computed through excel, using the function "Norm.Dist", which returns the normal distribution for a specified mean and standard deviation, with values 0.07075 and 0.00245, mean "0", standard deviation "1" and cumulative distribution "true".

[182] The article of Barone-Adesi and Whaley (1987) underlines that $A_2 > 0$ since S^*, q_2 and $1 - e^{(b-r)T}N[d_1(S^*)]$ are positive when $b < r$. Recall that q_2 is a root of the second-order ordinary differential equation of the approximation of the early exercise premium.

[183] The value of $N[d_1(S^*)]$ has been computed through excel, using the function "Norm.Dist", which returns the normal distribution for a specified mean and standard deviation, with value 1.92526, mean "0", standard deviation "1" and cumulative distribution "true".

Having now computed both the value of the European call and the early exercise premium, we can finally price the American call option, when $S < S^*$, written on the value of a treatment course of the antiviral Paxlovid, using the Barone-Adesi and Whaley (1987) approximation method.

So, we simply have to sum the European call value and the early exercise premium:

$$C(S,T) = c(S,T) + A_2(S/S^*)^{q_2} = 13.9012 + 0.05762 = 13.95882 \text{ €}.$$

This is the financial value of the American call option.

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