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Quantifying the Societal Impact of Delayed Access to Innovative Medicines: A Mathematical Framework for Health Policy Decision-Making

Foteini Theiakou [1], Catherine Kastanioti [1], Dimitris Zavras [2], Dimitris Rekkas [3] and Nikolaos Kontodimopoulos [4,*]

[1] Department of Business Administration and Organizations, University of Peloponnese, Kalamata, GREECE
[2] Department of Public Health Policy, University of West Attica, Athens, GREECE
[3] Department of Pharmacy, University of Athens, Athens, GREECE
[4] Department of Economics and Sustainable Development, Harokopio University, Athens, Greece
* Correspondence: nkontodi@hua.gr.

Abstract: This study presents a novel mathematical framework to quantify the societal and economic impacts of delays in the reimbursement and distribution of innovative medicines. Utilizing the concept of Years of Life Lost (YLL) as a measure of premature mortality, the framework calculates the impact of delay on YLL, Years of Potential Productive Life Lost (YPPLL), and Cost Per Life (CPL). The proposed model incorporates mortality probabilities through the Heligman-Pollard (HP) model, examining how delays influence health outcomes, particularly for patients awaiting treatments like Icosapent Ethyl. The findings reveal that extended delays significantly increase mortality and economic losses, emphasizing the need for timely access to high-value therapies. This framework not only highlights the adverse effects of delayed reimbursement on vulnerable populations but also advocates for equitable healthcare access. By integrating various factors such as health policy influences and willingness to pay for Quality-Adjusted Life Years (QALYs), the model serves as a comprehensive decision-making tool for policymakers. Ultimately, this research underscores the importance of efficient pharmaceutical policymaking in maximizing the societal benefits of innovative treatments, ensuring that both health outcomes and economic sustainability are prioritized in healthcare systems.

Keywords: pharmaceutical policy; innovative medicines; social loss; reimbursement delays; mathematical model; quality-adjusted life years (QALYs)

1. Introduction

Pharmaceutical policy refers to the set of laws, regulations, and strategies designed to manage the development, distribution, and use of medicines within a healthcare system. Its primary objective is to ensure that the population has access to safe, effective, and affordable medicines, while also promoting rational drug use and ensuring sustainability in healthcare costs. Pharmaceutical policy supports decision making as to how society can use its available resources to improve health and reduce inequalities.

A well-structured pharmaceutical policy typically includes several key components such as regulation of drug approval and safety - a regulatory framework that ensures that all drugs meet established standards and are safe for public consumption through regulatory agencies [1] and pricing and reimbursement policies to manage drug costs and ensure equitable access to essential medicines [2]. However, formulating pharmaceutical policy for innovative medicines presents significant challenges, particularly in balancing the introduction of new, high-cost treatments with maintaining fair competition and ensuring equitable access to novel treatments as these treatments often represent significant advancements over existing therapies, offering more effective, safer, or personalized options for managing diseases [3,4]. According to a study by the World Health Organization [5], the introduction of new medications has significantly reduced mortality rates for

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conditions such as cardiovascular diseases and cancers, highlighting their importance in extending life expectancy.

Furthermore, by preventing disability and premature death [6], innovative medicines help preserve human capital [7]. A recent study demonstrated that early intervention with innovative treatments in diseases such as rheumatoid arthritis and multiple sclerosis can prevent long-term disability, allowing individuals to maintain active and fulfilling lives [8]. This indicates that innovative medicines are not only vital for individual health but also for economic productivity. A report by the European Federation of Pharmaceutical Industries and Associations (EFPIA) found that employees with access to effective treatments for conditions like diabetes and depression showed improved productivity and reduced sick leave [9]. A study by Claxton et al. [10] examined the impact of delayed access to innovative medicines in the United Kingdom, demonstrating how even modest delays can lead to significant losses in quality adjusted life years (QALYs), thereby impacting overall societal welfare.

However, an approval of a treatment does not necessarily translate into immediate availability of a novel therapy for all patients as delays in reimbursement decisions can significantly hinder access, particularly in publicly funded healthcare systems [11]. Such delays can prolong patient suffering, lead to worsening health conditions, and widen health inequalities, especially for those who cannot afford to pay out-of-pocket for expensive therapies [6]. On the other hand, innovative medicines are not associated with a confirmed clinical benefit [12] so reimbursement procedures require a series of time-consuming steps by the HTA authorities [9].

The objective of the study is to outline a novel mathematical framework regarding delayed entry of novel medicines as an independent variable affecting (a) years of life loss (YLL) [13], and (b) years of potential productive life loss (YPPLL), where YPPLL refers to the productive years an individual would have lived in the absence of an event [14]. By factoring in the age at death, rather than just the occurrence of death, this calculation aims to provide a more accurate representation of the societal burden or impact of a particular cause of mortality. Its main purpose is to assess the relative significance of various causes of early death within a population, helping health planners prioritize prevention efforts. Additionally, the proposed mathematical framework offers a guidance tool for policymakers to evaluate the broader impact of new medicines.

2. Mathematical Model

The Years of Life Lost (YLL) is a widely used public health measure to assess premature mortality. YLL is a metric used to assess premature mortality by considering both how often deaths occur and the age at which they happen so it estimates the time a person would have lived if he hadn't died prematurely. YLL for a particular cause is calculated by multiplying the number of deaths (N) due to that cause by a Loss Function (LF) that defines the years lost based on the age of death.

The basic formula for YLL, for a specific cause (c), age (a), sex (s), and year (t), as reported by WHO is as follows [13]:

$$Years\ of\ life\ lost: \boldsymbol{YLL}(cause, sex, age, time\ period) = N(cause, sex, age, time\ period) * L(sex, age) \quad (1)$$

where:

N: number of deaths caused by the condition (c)
at a specific age (a) and sex (s) during year (t),
L: loss function

Brustugun expressed the YLL measure as follows [15]:

$$YLL = \sum_{x=0}^{X} (\#\ of\ deaths\ at\ age_x)(expected\ remaining\ life\ years\ at\ age_x) \quad (2)$$

To quantify the societal impact of delayed access to innovative medicines, it is necessary to express the number of deaths as a function of age, based on function (2). To achieve this, we must

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first calculate the probability (mortality rate) q_x, which represents the likelihood that a person aged x will die within a year.

$$q_x = \frac{d_x}{l_x} \tag{3}$$

where:

d_x: the number of deaths at age x and l_x is the number of people alive at age x.

It is important to note that d_x is the number of people who died before reaching age $x+1$, thus we can write that $d_x = l_x - l_{x+1}$ [16].

The Seligman-Pollard (HP) model [17] measures the probability q_x that a person of age x will die before age $x+1$.

After substituting the equation (3) into the eight-parameter HP model, d_x could then be calculated as follows:

$$q_x = [A^{(x+B)^C} + De^{(-E(lnx-lnF)^2} + \frac{GH^x}{1+GH^x}] = \frac{d_x}{l_x} \Longrightarrow d_x = l_x[A^{(x+B)^C} + De^{(-E(lnx-lnF)^2} + \frac{GH^x}{1+GH^x}] \tag{4}$$

where:

A, B, C, D, E ,F, G, H: parameters to be estimated.

The HP model illustrates the variation in mortality rates across different stages of life, from childhood and young adulthood to old age. The first term of equation (4) captures mortality trends in early life: parameter A represents the child mortality rate, B reflects the mortality rate at age one, and C indicates the decline in mortality over time (ages 0-9). The second term addresses the increase in mortality due to accidents in adulthood and maternal deaths among women of reproductive age (ages 10-40), with D representing the severity, E indicating the concentration, and F denoting the peak position of this "hump." The third term follows Gompertz's law, where G represents the baseline mortality level for older adults, and H indicates its rate of increase beyond age 40 [18–20].

We propose the following equation (5) where the dependent variable "q_x" depends on the variable "x" that is defined as follows:

$$x = age_{diagnosis} + delay \tag{5}$$

The following proposed mathematical model quantifies the number of deaths:

$$d_x = l_x[A^{[(age_{diagnosis}+delay)+B)]^C} + De^{(-E[\ln(age_{diagnosis}+delay)-lnF)]^2} + \frac{GH^{(age_{diagnosis}+del\quad)}}{1+GH^{(age_{diagnosis}+delay)}} \tag{6}$$

As it is illustrated at the equation (6) the variable "delay" affects the number of deaths that are included in the YLL measure. The variable "delay" refers to the number of days that elapse from the approval to the reimbursement of a novel medicine into the system. At this point, we assume that there is no delay on the day of diagnosis. However, for patients who were diagnosed and died within the same year, the delay is considered to be the same across all cases.

Thus, after substituting $x = age_{diagnosis} + delay$ into equation (2), YLL is expressed as a function of variable "delay":

$$YLL = \sum_{x=0}^{X}\left(l_x[A^{[(age_{diagnosis}+de\quad)+B)]^C} + De^{(-E[\ln(age_{diagnosis}+delay)-lnF)]^2} + \frac{GH^{(age_{diagnosis}+dela\ )}}{1+GH^{(age_{diagnosis}+de\quad)}}\right)(expected\ remaining\ life\ years\ at\ age_x) \tag{7}$$

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Since health policy affects the variable "delay" as a health policy factor, we express the variable "delay" as a function of "Health Policy":

$$delay = f(health\ policy) = \begin{cases} delay, & when\ health\ policy = 1, meaning\ that\ a\ health\ policy\ does\ not\ exist \\ 0, & health\ policy = 0, meaning\ that\ a\ health\ policy\ exists \end{cases}$$

Then, equation 7 can be revised as follows:

$$YLL = \sum_{x=0}^{X} \left(l_x [A^{[(age_{diagnosis} + f(policy) + B)]^C} + De^{(-E[\ln(age_{diagnosis} + f(policy) - lnF)]^2} + \frac{GH^{(age_{diagnosis} + f(policy))}}{1 + GH^{(age_{diagnosis} + f(policy))}} \right) (expected\ remaining\ life\ years\ at\ age_x) \quad (8)$$

According to the proposed mathematical framework the variable "delay" affects the YLL measure and therefore has a societal impact. Apart from YLL, we consider that the delayed access of novel medicines also affects productivity in terms of YPPLL [14]. It is worth noting that the human capital approach should be employed to compute permanent and temporary losses that are due to premature mortality and absenteeism, respectively [14]. YPPLL projects the economic and social impacts of an event due to premature death that are public health priorities for policymaking. The basic formula for YPPLL is written as follows:

$$Years\ of\ Potential\ Productive\ Life\ Lost\ YPPLL = \sum_{x=1}^{X} (l_x w_x d), \quad (9)$$

where:

x: age cohorts = 1, 2, …

w_x:productive years remaining at age of death

d: discount rate for the value of life,

After substituting the number of deaths in the equation 9, it could be written as follows:

$$YPPLL = \sum_{x=0}^{X} \left(l_x [A^{[(age_{diagnosis} + f(health\ policy) + B)]^C} + De^{(-E[\ln(age_{diagnosis} + f(health\ policy) - lnF)]^2} + \frac{GH^{(age_{diagnosis} + f(health\ policy))}}{1 + GH^{(age_{diagnosis} + f(healt\ \ policy))}} \right) w_x d \quad (10)$$

Productivity loss is a measure of the resources lost when employees work at suboptimal levels or are absent from work. A societal perspective aims at maximizing the welfare gains to society, commonly incorporates all relevant costs to society, including the losses due to the reduced productivity of patients [21]. The general formula for the cost of productivity loss (CPL) is as follows:

$$CPL = \sum_{x=0}^{X} YPPLL_x GDP\ per\ capita\ P \quad (11)$$

where: P: proportion of the working population in cohort x.

The impact of variable "delay" to CPL is defined after substituting the formula YPPLL to equation 11.

Next, we applied the proposed mathematical model to an existing dataset for a specific novel drug, Icosapent Ethyl, to predict Years of Life Lost (YLL), Years of Potential Productive Life Lost (YPPLL), and Cost Per Life (CPL) as functions of the variable "delay." Icosapent Ethyl is a highly purified and stable ethyl ester of EPA (eicosapentaenoic acid), shown to reduce triglyceride levels. It is used as an adjunct to diet in adult patients with triglyceride levels of at least 500 mg/dL [22,23]. According to the results of the REDUCE-IT trial [24], the risk of cardiovascular events was lower with Icosapent Ethyl therapy compared to placebo in patients with elevated triglyceride levels, despite

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concurrent statin therapy [25]. Patients were eligible for enrollment if they were 45 years or older with established cardiovascular disease, or 50 years or older with diabetes mellitus and at least one additional risk factor. Eligible patients also had a triglyceride level of at least 135 mg/dL. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, measured in a time-to-event analysis. The secondary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

We input the cardiovascular death probabilities for a 45-year-old patient with elevated triglyceride levels, who lacked access to the novel medicine, into the *MortalityLaws* mathematical package in R to estimate the eight parameters of the HP model [26]. The *MortalityLaws* function is a parametric model that describes the mortality process of individuals over a substantial portion of their lifespan. This function can be fitted using maximum likelihood estimation or by selecting an appropriate loss function for optimization. In our case the Loss Function [27] is applied as follows:

$$LF = \ln\left(\frac{estimated\ value}{observed\ value}\right)^2$$

Then, we estimated the parameters of A, B, C, D, E, F, G, H from the HP model as follows: A = 0.0001, B = 0.0040, C = 16.7891, D = 0.0010, E = 11.6349 ,F = 12.7702, G = 0.0024, H = 1.0662

The empirical analysis revealed that as the age of diagnosis increases, the observed values align closely with the fitted ones. Additionally, the results indicate that cardiovascular mortality in the patient group with delayed access to the novel medicine, Icosapent Ethyl (placebo group), rises as the independent variable "x" (representing delayed access) increases.

3. Discussion

The proposed mathematical framework focuses on the parameter "DELAY," which is influenced by pharmaceutical policymaking. This framework quantifies the societal impact of delay in terms of Years of Life Lost (YLL), deaths, Cost Per Life (CPL), and Years of Potential Productive Life Lost (YPPLL). The model indicates that a potentially highly innovative drug requires swift handling and minimal delays in the reimbursement process to avoid significant losses in deaths, YLL, YPPLL, and CPL. Conversely, when the variable "DELAY" is high, only therapies with limited clinical benefits should be affected.

However, future research could incorporate another controllable parameter, such as the loss of well-being due to illness. This loss includes discomfort, incapacity, pain limitations, mobility difficulties, emotional stress, and any challenges patients face in daily activities as a result of their illness. It is important to note that the most common approach in the literature [28] for measuring social preference in avoiding illness is through willingness-to-pay (WTP) for a Quality-Adjusted Life Year (QALY). The QALY is calculated by multiplying the patient's life expectancy by the average quality of life experienced, which is measured on a scale from 0 to 1. A value of 0 typically represents the worst possible health state (i.e., death), while a value of 1 represents perfect health. The relative product then determines the QALYs. For instance, if a patient has a life expectancy of 10 years (Life Years - LY) and a quality of life of 70% (Q = 0.7), this health state would generate 10 * 0.7 = 7 QALYs, which can be considered equivalent to years of full health.

The literature presents extensive theoretical discussion regarding the "correct" level of WTP, specifically in terms of the financial resources society should invest—through the approval and reimbursement of innovative therapies—to provide patients with an additional QALY. This value often varies based on a country's economic capabilities, the disease in question, the patient's age, the disease stage, and the aggressiveness or rarity of the disease. The World Health Organization suggests that the level of WTP should be approximately three times the per capita income, with €50,000 per year considered an acceptable threshold [28].

It should also be noted that factors indicating the marginal willingness to pay for a QALY are typically considered independent of the diffusion of innovation in the literature and are usually determined as a fixed amount. However, in certain cases, the differences in outcomes such as survival or prognosis between innovative therapies and existing standard therapies—like overall survival rate

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(OSR) and progression-free survival (PFS)—can be incorporated into the framework. Furthermore, QALYs do not account for productivity, which should be estimated separately as a distinct variable.

The implications of this mathematical framework extend beyond immediate health and economic outcomes, addressing broader issues of healthcare equity. Delays in access to innovative medicines disproportionately affect vulnerable populations, especially those in lower-income brackets or regions with limited healthcare infrastructure [29]. These groups often depend more on public healthcare systems and may lack the financial means to afford high-cost therapies out-of-pocket. As the model highlights, delays in reimbursement exacerbate health inequalities, allowing wealthier individuals to access treatments sooner, while disadvantaged populations face longer wait times. By quantifying the social losses associated with these delays, the framework makes a compelling case for prioritizing equitable access to innovative medicines, ensuring that all patients, regardless of socioeconomic status, can benefit from the latest advancements in medical care.

Additionally, the model emphasizes the need for a balanced approach to pharmaceutical policy—one that values both innovation and sustainability. While introducing innovative medicines is crucial for improving patient outcomes and advancing public health, it is equally important to manage healthcare spending to ensure the long-term viability of health system [30]. The framework encourages policymakers to carefully weigh the trade-offs between rapid access and economic constraints. By understanding the full scope of productivity losses, social well-being, and cost savings associated with new treatments, healthcare decision-makers can better navigate these challenges, promoting policies that maximize societal benefits without compromising the financial stability of health systems [31].

This model lays the groundwork for future research in health economics and policy analysis. It invites further exploration of how different variables, such as willingness to pay for QALYs or the coefficient of labor substitution, may vary across different healthcare contexts or evolve over time. Additionally, the framework could be refined to incorporate emerging data on real-world outcomes of innovative therapies, enhancing its predictive power. In the rapidly changing landscape of medical innovation, where breakthroughs in personalized medicine, gene therapy, and biotechnology are becoming increasingly common, this model provides a timely and relevant tool for navigating the complexities of pharmaceutical policy, ensuring that both patients and society benefit from timely access to the latest medical advancements.

Using the mathematical model based on age of diagnosis and delay can significantly enhance decision-making regarding a specific drug or class of drugs, particularly in areas such as risk-benefit analysis, treatment guidelines, and drug approval processes. By incorporating these variables, healthcare decision-makers can refine drug treatment strategies, ensuring they target the most appropriate patient groups and optimize the benefit-risk ratio for each group. This approach leads to more precise decision-making, ultimately improving patient outcomes while managing healthcare resources more efficiently. For instance, in patients diagnosed at age 45, the model may predict a significant reduction in long-term cardiovascular mortality through early intervention. Given the substantial predicted decrease in mortality, clinicians may prioritize aggressive treatment with the novel medicine for this age group (40+ years). The model suggests that early intervention yields the greatest long-term benefits, highlighting the importance of timely access to innovative treatments.

Quantifying the societal impact of delayed access to innovative medicines challenges traditional cost-benefit analyses (CBA) by expanding the scope beyond direct healthcare costs and immediate patient outcomes. Traditional CBA often focuses on short-term health gains, such as improvements in quality-adjusted life years (QALYs) or direct cost savings from reduced hospitalizations, while largely overlooking the broader economic and social consequences of delayed treatment. This framework integrates indirect costs, such as productivity losses from prolonged illness, increased caregiving burdens, and broader economic impacts like reduced workforce participation or increased social security dependency. By considering these extended societal costs, the framework provides a more comprehensive view of the true economic and social value of earlier access to innovative therapies.

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Moreover, this approach emphasizes the long-term, dynamic effects of delayed access that traditional models may miss. Delayed treatment can lead to irreversible health deterioration, potentially increasing future healthcare costs and making conditions more challenging or impossible to treat effectively. It also underscores the importance of innovation itself, recognizing that earlier access not only benefits current patients but also accelerates future medical breakthroughs and enhances long-term efficiencies within the healthcare system. By factoring in these extended consequences, the framework presents a more robust analysis for policymakers, urging them to value the long-term societal and economic impacts of innovation alongside immediate healthcare outcomes [32,33].

There are some limitations to this study that should be considered. Some complex healthcare variables may be oversimplified, potentially overlooking variations in real-world applications. The model assumes constant values for factors like the marginal willingness to pay for QALYs, which can vary over time and across contexts. Additionally, the model might not adequately account for external influences on healthcare access. A further limitation is the absence of a dataset estimating l_x (the number of individuals alive at age x). Without this data, we are unable to quantify Years of Life Lost (YLL), Years of Potential Productive Life Lost (YPPLL), and Cost Per Life (CPL) at age x for patients with elevated triglyceride levels who lack access to the novel medicine Icosapent Ethyl. Future research could address this limitation by collecting or utilizing such datasets to enhance the analysis of cardiovascular mortality in this patient population. Furthermore, the findings may not be universally applicable due to variations in healthcare systems, and the static nature of the model does not account for dynamic changes in medical technology and policy. Finally, it may not fully capture the long-term consequences of delayed access on health systems or address ethical considerations surrounding equitable access to innovative medicines.

4. Conclusions

This study introduces an innovative mathematical framework aimed at quantifying the societal and economic repercussions of delays in the reimbursement and distribution of novel medicines. By integrating key variables such as Years of Life Lost (YLL), Years of Potential Productive Life Lost (YPPLL), and the broader implications of productivity loss, the model offers a comprehensive perspective on the societal costs tied to delayed access to innovative treatments. The findings underscore the substantial social losses incurred due to these delays, particularly when novel therapies demonstrate significant enhancements in both life expectancy and quality of life.

The results highlight the critical importance of timely pharmaceutical policymaking, especially for innovative medications that exhibit high clinical value. Policymakers are strongly encouraged to streamline reimbursement processes to alleviate the adverse effects on individual patients and society at large. Delays not only diminish the therapeutic benefits available to patients but also exacerbate economic repercussions through reduced productivity and heightened healthcare expenditures. Moreover, the framework's adaptability—allowing for the incorporation of various factors such as health policy influences, market dynamics, and willingness to pay for quality-adjusted life years (QALYs)—positions it as a versatile tool applicable across different healthcare environments and economic conditions.

Ultimately, this model serves as a vital decision-making instrument for policymakers, aiding in the balancing act between the urgent need for rapid access to innovative therapies and the imperative of sustainable healthcare spending. By adopting a more holistic societal perspective, the framework facilitates a thorough evaluation of new treatments, ensuring that the benefits of medical innovation are maximized for patients, healthcare systems, and society as a whole. Future research endeavors should build upon this framework, incorporating real-world data to further refine its predictive capabilities and broaden its application in health economics and policy analysis.

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