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Simplified Mathematical Modeling of Uncertainty: Cost-Effectiveness of COVID-19 Vaccines in Spain

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Abstract: When exceptional situations, such as the COVID-19 pandemic, arise and reliable data is not available at decision-making times, estimation using mathematical models can provide a reasonable reckoning for health planning. We present a simplified model (static but with two-time references) for estimating the cost-effectiveness of the COVID-19 vaccine. A simplified model provides a quick assessment of the upper bound of cost-effectiveness, as we illustrate with data from Spain, and allows for easy comparisons between countries. It may also provide useful comparisons among different vaccines at the marketplace, from the perspective of the buyer. From the analysis of this information, key epidemiological figures, and costs of the disease for Spain have been estimated, based on mortality. The fatality rate is robust data that can alternatively be obtained from death registers, funeral homes, cemeteries, and crematoria. Our model estimates the incremental cost-effectiveness ratio (ICER) to be 5132 € (4926–5276) as of 17 February 2021, based on the following assumptions/inputs: An estimated cost of 30 euros per dose (plus transport, storing, and administration), two doses per person, efficacy of 70% and coverage of 70% of the population. Even considering the possibility of some bias, this simplified model provides confirmation that vaccination against COVID-19 is highly cost-effective.

Keywords: COVID-19 vaccination; mathematical modelling; health economics modelling; Best Adjustment of Related Values (BARV); Cost-Effectiveness Analysis (CEA); coronavirus; healthcare expenditures; Quality Adjusted Life Years (QALY); Incremental Cost Effectiveness Ratio (ICER); collective choice; discount rate

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1. Introduction

Since the first publications of efficacy data on COVID-19 vaccines [1,2], a growing number of other products have been developed in different countries by a number of pharmaceutical companies. However, it is crucial that a steady and adequate supply is available to the population within a short period of time. The COVID-19 pandemic has already imposed significant costs on national economies, causing increasing pressures on health budgets. Despite the effort it represents, it is essential that sufficient financial resources are guaranteed to carry out the vaccination plans. In this study, a mathematical model for cost-effectiveness analysis of COVID-19 vaccination is presented to provide policymakers with the evidence of the economic value of this health intervention. It is worth noting that the absence of reliable data, and even more so, data in constant progression, make this estimation very difficult, especially in the context of a pandemic, when the time available for producing complex forecasts is limited, and health managers may not have sophisticated mathematical technology at their disposal. Simple mathematical modeling could provide an approach and throw some light on this issue [3], and the method and conclusions of this study can help facilitate setting priorities in the decision-making process and the allocation of the health care budget.

In addition to the proposal for the mathematical procedure, this document has three purposes. Firstly, to present some figures on the impact of COVID-19 on health, in support of the concept of serious disease, the control of which still requires additional economic efforts. To this end, the number of quality-adjusted life-years (QALYs) lost to the pandemic has been calculated; secondly, to establish an estimate of the cost of health care due to COVID-19 in Spain; and thirdly, to present data on the cost-effectiveness of the vaccine.

2. Materials and Methods

Data for Spain related to the situation of the COVID-19 pandemic on 27 October 2020 and on 17 February 2021 have been calculated using the Best Adjustment of Related Values (BARV) method, which attempts to adjust reliable figures within a range and calculate other less reliable but related values by means of an iterative adjustment, so that the possible errors of all the variables are minimized by minimizing all deviations [4]. Although a more complex computerized procedure may be used, results may also be obtained using a simple spreadsheet, with the possibility of adding weighting to more reliable data and by an iteration process obtaining the results for the less known variables that minimize all errors.

For mortality, the procedure already used in previous work [4] was followed, collecting the unexpected increase in mortality (excess deaths) registered in four periods from the Spanish Mortality Database (MoMo) [5], assuming (*ceteris paribus*) the increase to be due to COVID-19.

The QALY, $Q(x_A)$, representing the number of years (adjusted for quality) for each group of median age (A) lost as a result of morbidity/mortality due to COVID-19, have been calculated, based on the estimate of years of life expectancy (LE = x) for age A, using the formula [6,7]:

$$Q_0 = QALY(x_A) = \sum_{j=1}^{x_A} U_j (1 - r)^{j-1}$$

Following Attema et al. [8], the utility U for each year obtained from the life table is discounted for the successive years (constant QALY model). When compared with the standard discount rate used in business $[1/(1 + r)]^{j-1}$ this procedure provides similar values.

Each group of current median age A has a life expectancy x_A and a yearly variable U_j utility. Summing over all the discounted remaining years of life (1 to x_A) will provide the adjusted life years lost due to COVID-19. Thus, U_j is the utility ratio for each year in the rank $|A, A + x|$; r is a constant discount rate of 3.5%, selected according to the income of Spain [7,8]. Sensitivity analyses have been done for r = 3% and 4%. Some of the U_j values, not found in the references, have been computed by linear extrapolation of neighboring values. Table 1 summarizes the five-year values of the life table used, although we have computed and used year-by-year values from 50 to 95 years of age, extrapolating missing data.

Table 1. Summary by five-year values of the life table used for the calculation of quality-adjusted life-years (QALYs).

	Men			Women		
Age	**Life Expectancy (LE)**	***U***	**LE Good Health**	**Life Expectancy (LE)**	***U***	**LE Good Health**
0	80.48	0.793623	63.87	85.9	0.79350	68.13
50	31.85	0.687555	21.90	36.8	0.60030	22.10
55	27.42	0.674419	18.49	32.2	0.56993	18.32
60	23.20	0.599138	13.90	27.6	0.53354	14.71
65	19.21	0.589744	11.33	23.1	0.48085	11.10
70	15.43	0.556034	8.58	18.7	0.47353	8.85
75	11.91	0.522736	6.23	14.5	0.46622	6.75
80	8.80	0.489438	4.31	10.6	0.37504	3.99
85	6.25	0.456140	2.85	7.40	0.28387	2.11
90	4.39	0.383721	1.68	5.00	0.11491	0.58

Source: Authors' computation based on data from Spanish National Institute of Statistics [9] and Eurostat [10]. Data corresponding to 2017. Data of years not included in tables have been calculated by linear extrapolation of the nearest values.

The table highlights the so-called male-female mortality paradox: Females live longer but in a worse state of health [11].

To calculate the QALYs lost due to the pandemic in Spain, not only the total number of deaths has been considered, but also, for those patients discharged from hospital alive, a weight of morbidity considering their future QALYs (as expected by age and gender) to be reduced an average of 10% ($Q\mathrm{w} = 0.9Q_0$) forward discharges and 20% ($Q\mathrm{w} = 0.8Q_0$) for ICU discharges, following weights of a Markov model used for other chronic diseases [12–14].

Additional data such as population statistics, figures related to influenza, and other values or ratios used in the text, have been obtained from the corresponding published institutional statistics [15–18].

3. Results

3.1. Magnitude of the Healthcare Problem: COVID-19 Outbreak versus Influenza

As of 27 October 2020, the estimated prevalence of COVID-19 in Spain was not very different from that of AH1N1 influenza, although it must be noted that there was an active outbreak of the former with about 20,000 new daily notifications at that time (accumulated incidence of about 500 per 100,000 habitants in 14 days) [16–23]. Table 2 comparatively presents the information together with Case Fatality Ratio (CFR) and Infectious Fatality Ratio (IFR) estimations up to that moment.

Table 2. Comparison of COVID-19 and A-Influenza data in Spain as of 27 October 2020.

Population	**47,431,688 [1]**			
	COVID-19	**×100,000‡**	**Influenza**	**×100,000‡**
Prevalence [2]	7,010,340	14,780	6,521,798	13,750
Confirmed [3]	1,116,738	2354	619,000	1305
Hospitalized	170,789	360	27,657	58
ICU	15,278	32	1800	4
Fatalities	59,422		3900	
Mortality (over [1])	0.13%	125.3	0.01%	8.2
CFR (over [3])	5.32%		0.63%	
IFR (over [2])	0.85%		0.06%	

Source: Authors' computation with data from sources [20–23]. ICU, intensive care unit. ‡ Inhabitants.

As evidenced by the figures, the prevalence in both cases was about 15%, but COVID-19 is causing about six times more hospitalizations, over eight times more admissions in ICU, and fifteen times more fatalities. To facilitate comparison of these data with those in influenza reports, the alternative method suggested for reporting CFR in ongoing outbreaks has not been followed [24].

These data for COVID-19 incidence and prevalence in Spain as of that date were not very different from those in the UK, with about 20,000 new cases per day and over one million reported cases, as of 31 October [25]. The data correspond to moments of ongoing pandemic waves.

Table 3 provides the comparative figures between 27 October and 17 February, and includes the ratios used in our model based on the number of fatalities (n_f).

Table 3. COVID-19 data as of 17 February 2021 compared to data from 27 October 2020.

	27 October 2020	17 February 2021	Template
Prevalence [2]	7,010,340	9,814,476	Based on Pub.
Confirmed [3]	1,116,738	3,107,172	Reported
Hospitalized	170,789	306,727	3.45 n_f
ICU	15,278	26,477	0.3036 n_f
Fatalities (number)	59,422	84,150	n_f
Mortality (over [1])	0.13%	0.18%	
CFR (over [3])	5.32%	2.7%	
IFR (over [2])	0.85%	0.86%	

Source: Authors' computation with data from sources [19–26]. Population 47,431,688 inhabitants.

3.2. COVID-19 Related Expenditures

The «Framework for Estimating Health Spending in Response to COVID-19» report [27]—which includes 214 countries and territories, projecting volumes of people and costs between 8 March 2020, and 7 March 2021 (52 weeks)—has been published by the International Monetary Fund and models different scenarios, social distancing, lockdowns, and other variables. According to its conclusions, «effective social distancing and quarantine reduce the additional health spending from a range of US$0.6–1 trillion globally to US$ 130–231 billion, and the fatality rate from 1.2 to 0.2 percent, on average» (p. 2). As per this source, with satisfactory containment of the disease, increase in health expenditures due to COVID-19 would represent about 0.2–0.3% of the world's Gross Domestic Product (GDP) for 2019, «and fatality rate would be 0.1% of the population, on average, across countries» (p. 8).

The published costs that the disease is generating for healthcare systems, even when focused only on inpatient and outpatient care, are very variable, representing different health care approaches. Most of the reports are from the USA, where the healthcare provider is covered by a combination of payments by companies and users. In the most complicated cases, hospitalization due to COVID-19 rose to US$75,000 or even more. An average from US$9764 (for less severe cases) to about US$14,500 per person has been reported by the Kaiser foundation and other sources [28–31]. According to Avalere, COVID-19 hospitalizations could cost the U.S. healthcare system between US$9.6 billion and $ 16.9 billion in 2020 [32]. This represents between US$30 and US$50 per inhabitant. Reports from other countries with lower GDP, such as Mexico or Chile, show lower costs. There are also systematic reviews on the average length of stay for COVID-19 hospitalizations, which may be used for cost estimation [33].

Considering the available information and the reported costs for the Spanish Health Care System [34–38], the direct costs (to 17 February 2020) have been estimated and summarized in Table 4. Again, this information may not be exhaustive. The expenditure figure for asymptomatic cases is an estimate that includes over-the-counter medicines. It is not clear whether all hospitalizations in private centers have been included in these statistics but considering that most cases are financed by the public system, this uncertainty has not been very significant.

Table 4. Estimation of direct healthcare costs for COVID-19 in Spain as of 17 February 2021 (direct cost including medication).

HC Provision	Number of Cases	Cost per Unit	After Discharge	Total
50% of cases with few symptoms	4,935,398	20 €		98,707,960 €
PC and OP health assistance	2,639,250	190 €		501,457,500 €
Hospital ward standard	246,236	3700 €	200 €	911,073,200 €
Hospital ward w/comp.	18,534	10,000 €	300 €	185,340,000 €
ICU (including ARDS)	25,548	27,000 €	350 €	689,796,000 €
Total				2,386,374,660 €
Per inhabitant				50 €
Per% of GDP				0.21%

Source: Authors' computation based on References [26,34–38]. OP, outpatient. PC, primary care. ARDS, acute respiratory distress syndrome.

According to our estimations, an average (cases in ward plus cases in ICU, excluding outpatient assistance) hospitalization costs about €5900 (US$7139). For Spain (2019), with a population of 47.3 million and a GDP of €1119,976M, COVID-19 health care (up to 17 February 2021) will represent about €50 per inhabitant, or around 0.21% of GDP, similar to the projection for all 2020 already commented on (0.2–0.3%) [27,30]. It must be taken into consideration that the disease is spreading rapidly, and this value only includes direct costs. The average, per day hospitalization cost was estimated at €369 (250–750), for an average length of stay of 15.9 days, obtained from a large series in France [33,39].

The pandemic has brought with it many other economic issues. Some of these are summarized in Table 5, in addition to the direct health care costs mentioned above (points 1–6).

Table 5. Summary of some relevant costs related to COVID-19.

Cost Directly Linked to Health Care	
1.	Primary care patients with minor symptoms.
2.	Primary care for patients later requiring hospitalization or during follow-up after discharge from hospital.
3.	Emergency assistance.
4.	Hospitalization and rehospitalization on ward.
5.	Use of mechanical ventilation devices.
6.	Intensive Care hospitalization and rehospitalization.
7.	Special treatments (monoclonal antibodies, convalescent plasma, etc.)
8.	Cost related to shrouding, storage, transfer, cremation or burial, and terminal cleaning of the rooms of the deceased.
9.	Operational costs, including staffing related to the increase of activity.
10.	Acquisition, training, consumption, and elimination of personal protective equipment for staff, including orderlies, maintenance personnel, security, cleaning, etc.
11.	Cost of the opportunity of delayed assistance to other diseases due to COVID-19.
12.	Outpatient drug costs, including pharmacy consultations and over-the-counter treatments.
13.	Transport (e.g., ambulances)
14.	Prescribed and over-the-counter medication.

	General population and business
1.	Protective measures, including panels, gloves, hydroalcoholic gels.
2.	Related to home lockdown for adults and children, including babysitting for workers with children remaining locked down at home.
3.	Related to labor reduction, readaptation, or loss.
	Governmental
1.	Reorganization and adaptation of public services, including police, port, and airport controls, quarantine compliance controls, military emergency services, their protective equipment, and cleaning agent's consumption.
2.	Relief plans, extra services, and supports for vulnerable people (unemployed, elderly, etc.)

3.3. Cost-Effectiveness of Vaccination

According to data reported as of 17 February 2021 [26], we have estimated that 554,539 QALYs (539,367–577,679) have been lost either directly due to mortality from COVID-19, or as a result of future morbidity, without taking into account additional losses, such as the opportunity costs of delayed treatments for other diseases as a result of the pandemic and other hidden costs [40]. Table 6 depicts a template for calculating the QALYSs referred to as the total number of fatalities, a data usually consistent in demographic statistics.

Table 6. Template for calculating COVID-19 adjusted and discounted years (QALYs) resulting from direct mortality and expected morbidity, based on the total number of fatalities (n_f).

n_f = **Total Number of Fatalities**	**Number**	**Average Age**	**Life Expectancy**	**L/Free of Disease**	**QALY (Q_0)**		$Q_w = 0.2Q_0$	**Total Q**
Men alive after ICU	$0.10242n_f$	62.6	21.2	12.8	8.6	(8.2–9.0)	1.7	N*Q_w
Women alive after ICU	$0.11466n_f$	62.9	22.3	12.7	7.3	(7–7.6)	1.5	N*Q_w
							$Q_w = 0.1Q_0$	
Men alive after ward hospitalization	$1.25436n_f$	66.5	18.3	10.6	7.4	(7.1–7.7)	0.7	N*Q_w
Women alive after ward hospitalization	$1.40431n_f$	68.1	17.8	9.7	6.0	(5.8–6.3)	0.6	N*Q_w
Subtotal (morbidity)	Σ							
Men death by age (hospital and home)							$Q_w = Q_0$	
<65	$0.03702n_f$	52	30.1	20.2	11.3	(11.2–11.4)	11.3	N*Q_w
65–74	$0.06664n_f$	70	15.5	8.6	6.3	(6.3–6.4)	6.3	N*Q_w
>74	$0.42459n_f$	80	12.3	6.4	3.7	(3.6–3.9)	3.7	N*Q_w
Women death by age (hospital and home)							$Q_w = Q_0$	
<65	$0.03306n_f$	55.0	27.1	17.5	9.8	(9.7–9.9)	9.8	N*Q_w
65–74	$0.05951n_f$	70.0	15.5	8.6	5.6	(5.5–5.8)	5.6	N*Q_w
>74	$0.37918n_f$	80.0	12.3	6.4	3.7	(3.6–3.9)	3.7	N*Q_w
Subtotal (mortality)	**Σ**							

Source: Authors' computation with data from sources [12,13,26,41–43]. Discount rate (3%, 3.5%, 4%).

The question of age and morbi-mortality for COVID-19 will give rise to issues, such as whether the patients that have died with the disease represent a subset of ill persons with less QALY than the average for the age, or for which population it would be more cost-effective to program early vaccinations [44]. At an estimated cost of €30 per shot (vaccine plus transport, storing, and administration) [45,46], the following table (Table 7) offers the cost-effectiveness analysis for different percentages of vaccine efficacy and discount rates (r = 3%, 3.5%, 4%), and different percentages of the population included in a vaccine program of two shots.

Table 7. Incremental cost-effectiveness ratio (ICER) for COVID-19 vaccine adjusted by different percentages of efficacy and population vaccinated in Spain with data as of 17 February 2021.

100% Population	**%Vaccine Efficacy▶**	**50**	**60**	**70**	**80**	**90**
Overall QALY ($r = 3\%$)	539,367	10,553	8794	7538	6595	5863
Overall QALY ($r = 3.5\%$)	554,539	10,264	8553	7331	6415	5702
Overall QALY ($r = 4\%$)	577,679	9853	8211	7038	6158	5474
80% Population	**%Vaccine Efficacy▶**	**50**	**60**	**70**	**80**	**90**
Overall QALY ($r = 3\%$)	539,367	8442	7035	6030	5276	4690
Overall QALY ($r = 3.5\%$)	554,539	8211	6843	5865	5132	4562
Overall QALY ($r = 4\%$)	577,679	7882	6569	5630	4926	4379
70% Population	**%Vaccine Efficacy▶**	**50**	**60**	**70**	**80**	**90**
Overall QALY ($r = 3\%$)	539,367	7387	6156	5276	4617	4104
Overall QALY ($r = 3.5\%$)	554,539	7185	5987	5132	4491	3992
Overall QALY ($r = 4\%$)	577,679	6897	5748	4926	4311	3832

Source. Authors' calculation. Cost per two shots, vaccine plus inoculation (30 € each).

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental cost resulting from vaccination by the measure of health outcome (incremental effect in QALYs) to provide a ratio of 'extra cost per extra unit of health effect' [47]. ICERs may be compared across disease areas and are evaluated with a pre-determined cost-effectiveness threshold.

Vaccination of about 70% of the Spanish population, with a conservative 70% ratio of efficacy and two shots, will result in €5132 (4926–5276) per QALY gained.

For comparison, the cost-effectiveness threshold, or basal-case ICER, was set between €22–33,000. NICE (National Institute for Health and Care Excellence) aims to spend less than £25,000 (€27,500) per QALY. A similar value (CAN$40,000 = €27,200) was set for other vaccination program by Brisson et al. [48].

It must be considered that the ICER threshold depends on a willingness to pay, and in consequence, on GDP. The World Health Organization suggests referring cost-effectiveness to GDP [49]. Although US$50,000 has been considered for a long time in the USA as the limit for the cost-effective threshold, this value has been criticized as being low [50]. The US threshold (2017 data) for very cost-effective (considered as less than one times GDP) has been reported to be < US$59,532; for cost-effective (between 1–3 times GDP) <= US$178,596; and considered not to be cost-effective (greater than three times GDP) when > US$178,596 [51]. Neumann et al. [50] suggest as a rule US$50, 100, and 200 thousand, for each range, matching very roughly with less than one times GDP per capita, between one- and three-times GDP, and over three times GDP. In any case, the prediction of our model for COVID-19 vaccine cost-effectiveness is well under the threshold; the vaccine is highly cost-effective [52,53]. Table 8 overviews the ICER of some vaccination reports in the last two decades:

Table 8. Incremental cost-effectiveness ratio (ICER) of some vaccination plans reported in the literature for the last two decades with conversion to EUR at the corresponding date for the year.

Vaccination	Target Population	ICER	Currency Rate (1€→)		ICER (€)	d/Rate	Article	Year	First Author
Pneumoco	Adults 65 and over	11–33,000	€		11–33,000	0–5%	Bibliometric	2000	Ament
Lyme disease	Resident endemic areas	62,300	$US	(2001 = 0.89)	70,000	3%	Modeling	2001	Shadick
Influenza	Adults 50–64 y/o	10,766	£	(2005 = 0.67)	16,069	NA	Modeling	2005	Turner
Influenza	Children 6m–4 y/o	<25,000	$US	(2006 = 1.25)	≤19,925	NA	Modeling	2006	Prosser
H Papilloma (HPV)	12–24 y/o females	3000	$US	(2007 = 1.37)	2190	3%	Modeling	2007	Insinga
Papilloma (HPV)	12–24 y/o females+ males	16,000	$US	(2007 = 1.37)	11,679	3%	Modeling	2007	Insinga
H Papilloma (HPV)	12 y/o females	21–31,000	$CAN	(2007 = 1.46)	30,666–45,260	3%	Modeling	2007	Brison
A Hepatitis	Travellers	26,046	$US	(2008 = 1.46)	17,840	5%	Bibliometric	2008	Anonychuk
A Hepatitis	Health care workers	129,046	$US	(2008 =1.46)	88,388	NA	Bibliometric	2008	Anonychuk
A Hepatitis	Military	16,332	$US	(2008 = 1.46)	11,186	NA	Bibliometric	2008	Anonychuk
A + B Hepatitis	Children	<35,000	$US	(2008 =1.46)	<23,972	NA	Bibliometric	2008	Anonychuk
H Papilloma (HPV)	NA	32,884	€		32,884	NA	Modeling	2008	Bergeron
Herpres Zoster	Adults 60 and over	20,400	£	(2009 = 0.89)	22,921	6%	Modeling	2009	Van Hoek
pH1N1 Influenza	6m–64 y/o	8000–52,000	$US	(2009 = 1.39)	5755–37,410	3%	Modeling	2009	Prosser
Rotavirus	Children < 5 y/o	23,298	£	(2009 = 0.89)	26,178	3.5%	Modeling	2009	Martin
Rotavirus	Children < 5 y/o	61,000	£	(2009 = 0.89)	68,539	3.5–3%	Modeling	2009	Jit
H1N1v Influenza	Age groups	2733–3215	£	(2010 = 0.86)	2733–3215	3.5%	Modeling	2010	Baguelin
H Papilloma (HPV)	12 y/o females	1917	€		1917	3%	Modeling	2010	Olsen
H Papilloma (HPV)	Girls 12 y/o	3583	€		3583	3–5%	Modeling	2015	Olsen
Influenza (IIV3)	Adults 65 and over	3690	$US	(2016 = 1.11)	3324	3%	Modeling	2016	Raviotta
Influenza (TIV)	Adults 65 and over	10,750	€		10,750	0%	Modeling	2018	Capri

Source: Authors' compilation.

The numerator of the cost/quality ratio (i.e., the cost of vaccination in Spain) is not expected to increase, as the cost per dose may even be reduced by competition between vaccines, and the Spanish population will not experience appreciable changes in the short term. However, the denominator (years lost) continues to grow with a significant number of new deaths each day, so the ICER will progressively decrease as the pandemic continues to spread.

In other words, for every day of active illness, there will be a reduction in the ICER, as this represents a continuous increase in the loss of QALYs (denominator). However, if the number of patients alive after contracting COVID-19 (and consequently having immunity, assuming this lasts a reasonable time) increases substantially, it would also impact on reducing the cost-effectiveness of the vaccine.

In addition, vaccination will generate savings in health expenses and alleviate the economic consequences of the pandemic in both the health insurance sector and private hospital centers, which, as a result of COVID-19, are currently suffering wage cuts, lay-offs, and risk of financial unfeasibility [54]. This is just one of the economic issues related to COVID-19.

4. Discussion

In situations of uncertainty, when reliable data are either not available or arrive late, or the pressure on care is so great that statistics cannot be relied upon, the use of simple mathematical estimation models can provide information reliable enough for health planning, since in this case a highly accurate numerical assessment is not required, but rather a range. The consideration of COVID-19 as a serious issue must be easily deduced, not only from the data in tables above, but also from the social and political movements and urgent plans for action issued by national and international authorities, EU included [55]. The data in this paper refer to a disease with morbidity and mortality in progression, but what is important is that the model allows easy recalculation with the updating of information.

The procedure followed, including how CFR and IFR were computed, may have some limitations: Firstly, the method may estimate data that could not be fully accurate. Secondly, it is better to compute CFR during an active outbreak by the ratio death/(death + recovered) [56]. However, they have been considered as one-day 'snapshots' analyses and carried out, in the case of October values, homogeneously with data related to influence for easy comparisons. The importance and impact of our approach are further emphasized by the constant interest in the costs of the pandemic by the media [57], with estimations of values not far from our own results. Although, considering a relatively wide range for imprecision, the values serve as a proxy for the severity of the pandemic as compared to influenza and the economic benefits of vaccination.

A further constraint comes from the fact that economic evaluations of infectious disease interventions are often based on predictions from systems of ordinary differential equations (ODEs) or Markov models, either static or, more typically, dynamic ones that consider herd immunity, which is crucial to avoid overestimation of infection prevalence [58–60], although other approaches are possible [61]. Our simplified model may be criticized for not following that trend. However, studies of herd immunity on COVID-19 are already available [62], with seroprevalence rates very low (about 5%). There is also the issue of changing age, as the dynamic model could predict an increase in the average age at infection after immunization, which could impact the estimate of the cost-effectiveness of the program, particularly in this case of serious disease as a function of age. According to our model, about 80% of fatalities already correspond to subjects aged over 74. A multinational meta-analysis, with a total of 611,583 subjects, showed that 82.9% of the fatalities were for those 70 and over, very close to our model considering the four years (70–74) range difference and regional variations [63]. The fourth series of mortality data from MoMo [5] do not show significant changes in mortality ratios among waves by age, but it is true that the vaccination effect is not included, as the number of cases vaccinated up to 17 February that could be included in the mortality figure is to be considered nearly zero. Additionally, this limitation may result in less relevant, considering that constant models tend to underestimate the cost-effectiveness of the immunization program [59]. This papers presents a simplified mathematical model to establish a range for the cost-effectiveness of COVID-19 vaccination, rather than the procurement of a totally accurate computation, which in any case does not seem essential as long as the values obtained are well below the cost-effectiveness threshold.

If SARS-CoV-2 behaves as A(H1N1) influenza with periodic outbreaks—something not improbable as both are RNA viruses—even with measures of social distancing and periodic lockdowns (each time less popular among citizens), Spain should expect, in the next 10 years, between 7 and 12 million of confirmed cases, and over 400,000 deaths (at decreasing ratio of about 45,000 per year), a value consistent with estimations in the UK by Sandmann et al. [64]. Following this reference—assuming 75% efficacy, 10 years protection and 10% of revaccination, discount rate of 3.5% and monetized health impact at £20,000 (€22,000)—vaccination (plus physical distancing) versus no vaccination will represent between €6.11 and €21.95 million economic gain or Net Monetary Benefit (NMB) per million population (i.e., €288.9–€1038.5 million for Spain in ten years) [64]. Values are consistent after sensitivity analyses and the proportion of mortality in the UK. Simulations studies advocate efficacies of at least 60% [65]. This brings up the issue of the unknown duration of immunoprotection. If a periodic COVID-19 vaccination schedule were to be established, i.e., a schedule similar to that for other viral processes, such as influenza, the cost-effectiveness of vaccination could change appreciably.

The method of cost-effectiveness has been chosen because among the main indicators used in the economic analysis of healthcare planning, (cost-benefit, cost-effectiveness, and cost-utility), the effectiveness perspective is useful for decision-making on how best to allocate resources, while the cost-benefit ratio analysis helps decision-making on overall resource allocation. Quality-adjusted life year analysis allows direct comparison of a wide range of health interventions [66,67]. For QALYs, the use of utility scores from a life table (Table 1) eases the calculation of the adjusted number of years lost for the average age in each of the groups studied. The median age of about 70 for patients admitted in Spanish hospitals for COVID-19 [21] is not far from data from another report, also from a country with a National Health System, reviewing 16,749 cases [68].

Additional reduction for chronicity, mainly resulting from permanent inflammatory handicaps (e.g., pulmonary fibrosis) requiring extra healthcare resources, has been considered in survivors in an average of 10% [$Q_w = 0.9\ Q_0$] in cases of ward discharges, and 20% [$Q_w = 0.8\ Q_0$] after ICU discharge. Similar utility scores have been obtained with Markov model methodology in cases of other chronic diseases (e.g., in Diabetes Mellitus, a disease that also requires periodic visits and controls) [69,70]. Sensitivity analyses of this utility score at ±10% (i.e., 0.09–0.11, and 0.18–0.22, respectively) maintain significant QALY gains in all cases; Q_w could be additionally adjusted for protection length of time and annual revaccination rate. A weighted variation related to age could also be considered.

Except for some promising drugs currently in development, there is no effective treatment for COVID-19. The first option considered was to examine the role that herd immunity might have. We have already predicted that herd immunity would not play a major role as a barrier to COVID-19 [4], as confirmed by subsequent serological studies [71]. Moreover, data suggest transmission, even from asymptomatic patients, in many cases [72].

With the results of over 365,000 tests done in England showing that antibody response to SAR-CoV-2 wanes over time [73], and reinfection cases reported [74], the possibility of herd immunity as a barrier remains low, although it must be admitted that the expected severity of reinfected cases should, at least theoretically, be lower, due to the residual memory effect of the immune system, which is characteristic of infections [75–77]. Therefore, at present, there is only one rational, proactive measure to increase herd immunity and effectively reduce the number of cases of COVID-19, that being vaccination plans [78].

A cost of the vaccine of about £10 for the product, with another £10 for administration, as estimated by Sandmann et al. [64], which seems reasonable for a country with a National Health System. According to a governmental report in Spain, each dose for the vaccine of influenza costs the Spanish Health Care System an average of €4.3, and the shot about €6.0 [79].

Considering not only the cost of extra protection measures and time required for isolation of health professionals prior to COVID-19 vaccine administration, and the high demand for a new product, but also the massive acquisitions already announced—it must be remembered that the EU has made arrangement for buying 300 million doses of the Sanofi-GSK vaccine—a range between 20–30 Euros for each shot (vaccine plus administration) when bought at great volume seems reasonable [45,80–82].

According to Reuters, there is a plan to inoculate about 50 million US citizens for about US$40 per person (€34.5) [83]. Other elements that could influence price are the low-temperature condition for transport and storage, particularly in developing countries, where the role of interventions may differ [84–86]; the forecast of scenarios may change in each case [87]. It should be noted that our study refers to two doses of vaccine, but there is no evidence to indicate that COVID-19 will not require revaccination, even for life. A plan in this case, like that of influenza, will represent about 10 times the cost indicated [79].

Finally, there may also be factors not captured in the QALY formulas, including indirect costs, the value of returning to normal life, the effects on mental health (anxiety, depression, fears of losing jobs, and lockdown, production losses, etc., that will additionally increase the benefits of vaccination. In other words, that cost-effectiveness measured with the standard procedures may not be the only thing that matters [88,89].

5. Conclusions

Left alone, successive COVID-19 outbreaks could represent between 7 and 12 million confirmed cases and over 400,000 deaths in Spain in 10 years. Vaccination against SARS-CoV-2 is the only reasonable approach, and seems clearly indicated after analysis of the risks of getting vaccinated versus not getting vaccinated, together with the vaccine data available [1,2].

The cost estimates with our mathematical model are simple, easily reproducible, and fit well with other available data. Data of Table 6 may be used for other purposes, e.g., in case of shortage of vaccines, to compare different commercial products.

Data allows us to appraise an ICER of 5132 euros (4926–5276 euros)—even while using a conservative approach of vaccinating about 70% of the Spanish population with a vaccine efficacy of about 70% (two injections). This is a very cost-effective ratio as a result of a vaccination plan; furthermore, the ratio improves (i.e., the cost decreases) for each day of new cases reported after 17 February 2021.

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