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SPECIAL CONTRIBUTION

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PREDICTIONS OF THREE MATHEMATICAL MODELS IN RELATION TO COVID-19 VACCINATION STRATEGY IN SPAIN. JUNE 2021

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SUMMARY

The Ministry of Health has coordinated three studies that have estimated the impact of the COVID-19 Vaccination Strategy in Spain. The aim was for the models to help establish the priority population groups for vaccination, in an initial context of dose limitation. Based on the same epidemiological and vaccination information, three different mathematical models have been developed whose results point in the same direction: combined with physical distance, staggered vaccination, starting with the groups at highest risk of complications, would prevent 60% of infections, 42% of hospitalisations and 60% of mortality in the population. These models, which can be adapted to the new scientific evidence available, are dynamic and powerful tools for the evaluation and adjustment of vaccination programmes, driving the development of this field of research, and helping to achieve more efficient health outcomes.

Keywords: COVID-19, Mathematical models, Vaccination programmes.

ABSTRACT

Predictions of three mathematical models related with the COVID-19 Vaccination Strategy in Spain. June 2021

The Ministry of Health has coordinated three studies that have estimated the impact of the COVID-19 Vaccination Strategy in Spain. The models aim to help how to establish prio- rity population groups for vaccination, in an initial context of dose limitation. With the same epidemiological and vaccine informa- tion, the results of this three different mathe- matical models point in the same direction: combined with physical distancing, staggered vaccination, starting with the high risk groups, would prevent 60% of infections, 42% of hospitalizations and 60% of mortality in the population. These models, which can be adapted to the new available scientific evidence, are dynamic and powerful tools for the evaluation and adjustment of immunisation programs, promoting research on this field, and helping to achieve more efficient results in health.

Key words: COVID-19, Mathematical modeling, Immunization programmes.

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JUSTIFICATION

The COVID-19 pandemic is causing enormous human and economic costs in Spain and worldwide. The use of effective and safe vaccines in a population-based strategy is essential to reduce the impact of the pandemic and restore the normal functioning of our society.

Mathematical models make it possible, through the use of mathematical tools and knowledge of the disease and its vaccine, to represent and predict an epidemic situation, estimate future situations and evaluate actions already taken[1] . Since the beginning of the epidemic, not only the need for epidemiological information has become clear, but also the importance of using these models to help health authorities manage the crisis.

This interest was reinforced by the knowledge that numerous researchers in our country were developing models focused on predicting the behaviour of the pandemic in different scenarios, both epidemiological and vaccination against COVID-19.

In this context, the Ministry of Health contacted the Carlos III Health Institute to find out about the availability of projects that, through the *FONDO - COVID-19* programme *for the execution of SARS-CoV-2 and COVID-19 research projects within the* framework of *Royal Decree-Law 8/2020, of 17 March, on extraordinary urgent measures to address the economic and social impact of COVID-19*, were developing mathematical models to estimate the impact of SARS-CoV-2 infection in Spain.

Three projects were identified that could contribute to the work that was intended to be developed within the COVID-19 Vaccination Strategy in Spain[2] . In November 2020, the first meeting of the mathematical modelling group was held as part of the COVID-19 Vaccination Technical Working Group and the need to model different vaccination scenarios to enable decision-making was established. These models, with their ability to simulate different scenarios, are potentially capable of estimating the impact of different possible vaccination strategies on reducing infections, hospitalisations and deaths[3] .

The aim was therefore for the models to help, above all, to establish priority population groups for vaccination, in an initial context of dose limitation.

METHODS

All three models received the same epidemiological information from the National Epidemiology Centre, as well as vaccine efficacy and other parameters of interest. This information changed over time, as did the epidemiology and expectations of available vaccine doses.

Summary of the structure of the models:

Model 1: Universitat de Barcelona and Centre de Recerca Matemàtica. The proposed model is based on a *hidden* Markov *chain* whose hidden layer is a regenerative process with Poisson innovations, Po- INAR, together with a mechanism that allows the estimation of unreported cases in non-stationary time series. One of the contributions of the model is that the expectation of the innovations of the unobserved process is a time-dependent function defined in such a way that the dynamics of the evolution of the epidemic, including the impact of exogenous interventions such as non-pharmacological measures, can be estimated by the model.

The model could be generalised so that the underreporting intentionality parameter is time-dependent, so that it could accommodate possible seasonal trends or components present in the data. Additionally, the model could be generalised so that the parameter underreporting intention is time-dependent, thus accommodating possible seasonal trends or components present in the data. All model parameters can be estimated using numerical approximations of the maximum likelihood method, and details can be found at[4] .

Model 2: Carlos III University, Madrid. *Barcelona Supercomputing Center* and ISCIII. This is an agent-based model that models the spread of the virus, including its variants, and considers the characteristics and interaction patterns of individuals, as well as vaccination and other non-pharmacological interventions. The simulator (*Epigraph*) has different components that allow the simulation of different epidemiological and social patterns[5] . These components are:

– Social model: the use of social networks allows the inclusion in the model of social interaction patterns (number of individual contacts, social habits of different groups such as students, workers, people who stay at home most of the time, as well as older adults). In addition, subgroups are made according to the type of work and retirement activities. It also includes occasional social gatherings, such as celebrations.

– Epidemiological model: This is a stochastic compartmental SEIR-type model to which compartments of latent infection, asymptomatic, hospitalisation or death are added. Duration and transitions between compartments are randomly estimated based on epidemiological data. Each infectious state has an R_0 (basic reproductive number). The probability of hospitalisation and lethality is age-dependent.

– Transport model: Models people's movements between cities for work, study or holidays.

– Non-pharmacological interventions: considers individual or health authority actions to mitigate infection: chewing masks, social distancing and mobility restrictions.

– Vaccination model: Includes different efficacy, guidelines and recommendations for each of the vaccines used in Spain until March 2021.

The model considers an urban area of 500,000 inhabitants, with a population of and demographics in Spain.

Model 3: UNED and INVERENCE. Time series model. The effective reproductive number is considered to be a dynamic factor that depends on the level of censoring of the observation and is modified by observable and unobservable variables. The same is true for conversion rates between observed infections, hospitalisations and confirmed mortality.

The characteristics of the model mean that reproductive numbers are conditioned by vaccination and the timing of its administration, as well as by contact restriction measures adopted by health authorities, in addition to the measurable behaviour of the population, and other unobserved factors.

All time series representing the cascade of relationships from contagion to incremental mortality are characterised by dynamic gains, i.e. unstable relationships in the parameters.

Variables included in the models:

a) Priority groups for vaccination.

The initial prioritised groups included in each model can be seen in Table 1.

b) Vaccine efficacy: In all studies, the most conservative data are used.

Model 1: Based on the evidence available at the time, 95% efficacy was considered for mRNA vaccines, maintained 1 year after the second dose administered at 21 or 28 days. Both mRNA vaccines would prevent 20% transmission.

Model 2: Efficacy for mRNA vaccines, 2 weeks after 1 dose, would be 86% and 95% 2 weeks after 2 doses. For neighbourhood vaccines, an efficacy of 60% would be achieved with the 1st dose in people under 56 years of age and 30% in people older than 56 years of age. In both cases it would decrease to 25% after one year. With 2 doses, 70% efficacy would be achieved in people aged <56 years and 50% in people aged 56 years and over (after 4 weeks). In both cases it decreases to 25% in the following 12 months. There would be no community effect.

Model 3: The following effi- ciencies were considered according to vaccine type (table 2).

Table 1
Priority vaccination groups included in each model.(*)

MODEL 1. Staggered vaccination	MODEL 2. Strategy by vaccine type		MODEL 3. Includes 1 or 2 doses of the mRNA vaccines
Sanitary + Residential	mRNA	Adenovirus vectors	Toilets and >80 years old
≥80 years	1st line health care and residences	Health care / social and health care 18-56 years old	56-79 years
70-79 years	Other health care and seniors	Security Forces 18-56 years	18-55 years old
60-69 years	Security forces and education	Education 18-56 years	-
55-60 years	Remaining population in descending bands of age	Populatio n 18-56	-
		Rest of the population: decreasing age bands	-

(*) The rows correspond to the different population groups prioritised in the Vaccination Strategy and the specific form of incorporation in each model.

Table 2
Efficacy by type of vaccine included in Model 3.

Vaccine type	Groups	Effectiveness 1st dose	Effectiveness 1st dose after 52 weeks(*)	Effectiveness 2nd dose	Efficacy 2nd dose after 52 weeks
mRNA	All	0,86	0,20	0,95	0,95
Vectors	Toilets and <55 years	0,60	0,20	0,70	0,70
Vectors	56-79 years	0,30	0,20	0,50	0,50

(*) Decreasing exponentially.

c) Vaccination coverage.

Model 1: Administration of 50,000 doses per day.

Model 2: An administration is considered dose rates as shown in table 3.

Model 3: Behaviours of fully vaccinated populations with 18 different vaccination strategies are analysed.

d) Other variables of interest: As these are dynamic models, they allow for the incorporation of new information relevant to the epidemiology of the infection and the development of vaccination. Thus, the following have been incorporated information on estimated doses available, effect of vaccination on disease transmission, vaccination coverage achieved or characteristics of new variants, the impact of which is observed in successive updates of the results. In all cases, they refer to a time horizon of 9 months.

RESULTS

All three models show a reduction in infection, hospitalisation and mortality with small differences. The figures shown correspond to Model 1 developed by the University of Barcelona, which best exemplifies the results obtained.

Table 3
Administration of vaccine doses considered in Model 2.

Laboratory	First trimester	Second quarter	Third trimester
Modern	10.000	11.000	11.000
Pfizer	50.000	88.000	111.000

AstraZeneca	86,000 (Feb and Mar)	208.000	300.000

Reduction of infection: 9 months after the start of the programme, an overall reduction in infections of 18% is estimated if only healthcare workers, people over 80 years of age and institutionalised persons (BUs) are vaccinated and distancing and viral circulation measures are maintained (Figure 1).

These data depend on virus circulation and physical distancing (UCIII), so that if the percentage of the infected population decreases in the unvaccinated, infections in the vaccinated would also decrease by 5-10% compared to the unvaccinated at week 30, which would mean that up to 45% of infections would be avoided, especially in the group of people over 80 years of age. In addition, the impact of physical distancing is important, so that the reduction in social contacts lowers the incidence of infection. This isolated measure lowers the percentage of the infected population from 31% to 11% and consequently reduces mortality by 66%, even without the vaccine (1,350 deaths compared to 450).

A staggered vaccination, starting with toilets and 80+ years, followed by the 56-79 years strategy, and then to 15+ years, according to estimated vaccination coverage predictions, 9 months after the start of mRNA vaccines, and with adenovirus vector vaccines in the 56-79 years population, would prevent 60% of infections (UNED+INVERENCE).

Reduction of hospitalisation: The greatest impact on hospitalisation (obtained with Model 1), is achieved with the strategy of vaccinating people over 80 years of age, the institutionalised and healthcare workers. This vaccination would prevent 42% of hospitalisations in the entire population 9 months after the start of vaccination (figure 2).

This figure is increasing with vaccination in descending steps by age group.

Mortality reduction: The first vaccination strategy of vaccinating people over 80 years of age, institutionalised persons and health care workers prevents 59% of deaths in all age groups (figure 3). This percentage would decrease only slightly (UCIII) if social distancing is modified.

Staggered vaccination reduces mortality by more than 60%.

Analysis of different vaccination strategies: Various vaccination strategies have been analysed, using 1 or 2 doses and with variable spacing between doses. In general, the number of cases averted for the different strategies varies little.

Vaccination at the beginning of the campaign with a single dose of mRNA vaccines would have prevented a slightly higher number of cases by vaccinating more high-risk individuals in a shorter period of time.

Figure 1
Predicted reduction of infections with vaccination strategy for most vulnerable groups vs. non-vaccination.

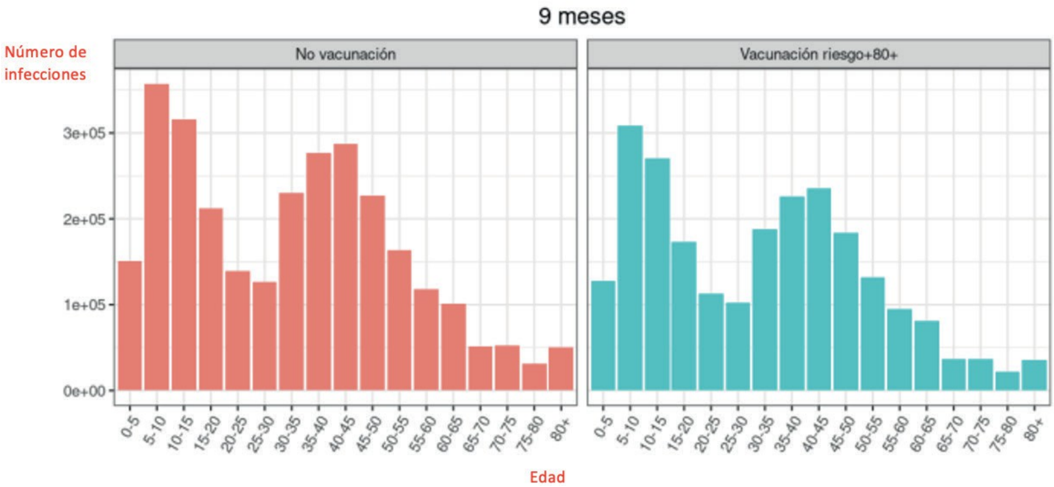


Figure 2
Predicted reduction in hospitalisations with vaccination strategy for most vulnerable groups vs. non-vaccination.

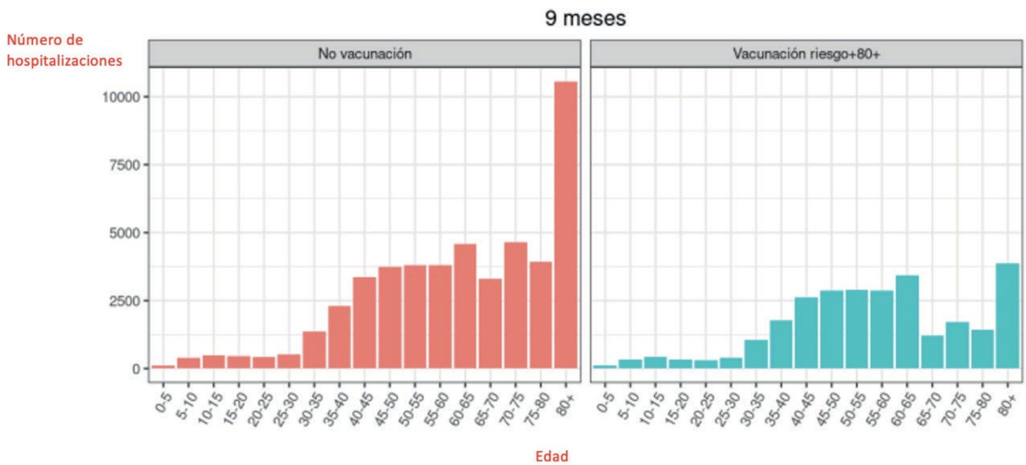
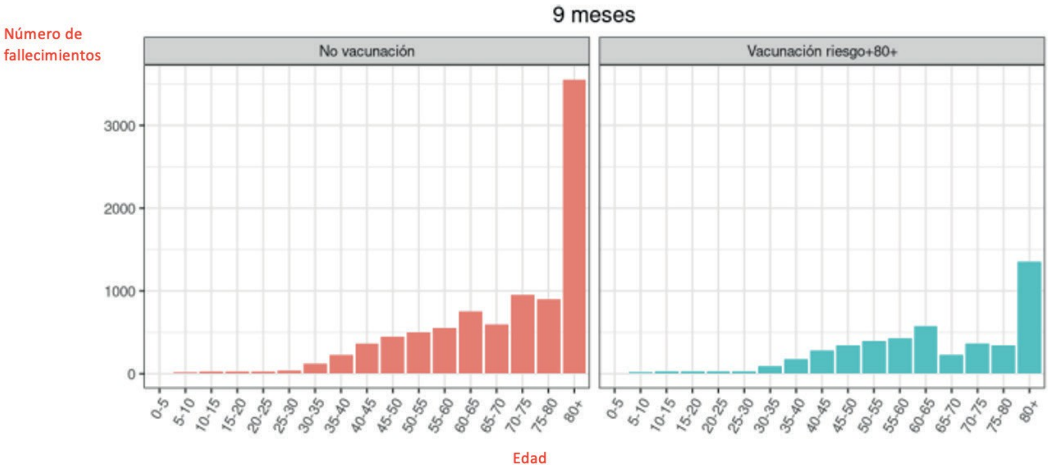


Figure 3
Predicted reduction in deaths with vaccination strategy for most vulnerable groups vs. no vaccination.



CONCLUSIONS

Mathematical models are powerful tools that can help make public health decisions and adjust vaccination strategies. The results of the models used to make predictions regarding vaccination against COVID-19 have been taken into account by the Vaccination Programme and Registry and the Technical Working Group on Vaccination against COVID-19 in Spain in the successive updates of the Strategy. These updates have been adjusted to changing epidemiological scenarios, and to variations in the number, characteristics and types of vaccines available throughout the vaccination campaign. However, not all the results have been incorporated into the updates, possibly due to the significant uncertainties of an ever-changing situation and the limited culture of mathematical modelling applied to vaccination programmes in our country.

Depending on the characteristics of each model, each was able to update the baseline data with some variation, which explains the difference in assumptions. Due to the different structure of the models, different questions regarding the impact of vaccines were answered. This shows the relevance of these powerful research and predictive tools in health crisis management.

The conclusions drawn from the results of the three models, taken together, are as follows:

– The three models take different methodological approaches to the epidemiology of infection and the impact of vaccines.

– All three use the best available data on the epidemiology of infection and the efficacy or effectiveness of vaccines.

– The three models predict similar outcomes in terms of reduced infection, hospitalisation and mortality for the various vaccination schedules analysed.

– The strategy of initially vaccinating the most at-risk subjects reduces hospitalisation and mortality the most in all models.

– There are no major variations in the impact of vaccination regardless of the vaccination schedules analysed. There is a slight trend towards fewer hospitalisations when the doses are separated, as this allows more people to be vaccinated with one dose in a shorter time. However, these results are conditioned by the limited knowledge of the effectiveness of a single dose of vaccine.

– Physical distancing shows a substantial impact on infection control, which increases when combined with vaccination.

Therefore, based on the same epidemiological information, vaccine efficacy/effectiveness data and other parameters of the vaccination programme available at the time of the simulations, results have been obtained that point in the same direction, which gives an idea of their robustness: vaccinating the most vulnerable people, together with the maintenance of non-pharmacological measures, is the strategy that most reduces mortality. It should be borne in mind that the evidence available at the time of the simulation was mixed in some respects, which may have added uncertainty to the results obtained.

Finally, these are live models that allow the incorporation of new relevant information in relation to the epidemiology of the infection and the development of vaccination, and that allow the parameters to be adapted to the new scientific evidence, making it possible to perform new impact evaluations in successive updates of the results. In addition, this type of study will broaden the field of research into the dynamics of infections in our country, which has been little developed to date, and which can be applied in vaccination programmes already in place or in future epidemic situations, helping to achieve the best health outcomes through the most efficient use of resources.

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