Type of Article: Mini Review

Title: EXPLORING URGENT NON-PHARMACOLOGICAL AND SOCIOECONOMIC INTERVENTIONS FOR THE COVID 19 EPIDEMIC IN SPAIN.

Running title: Non-pharmacological interventions for COVID 19

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Abstract: English

Non-pharmacological interventions in the fight against COVID 19 include: a) suppression, which facilitates its extinction; and b) mitigation, which reduces its speed of spread. Left unmitigated, the intensive care unit bed capacity (ICU) is exceeded over its maximum supply, resulting in increased deaths. Suppression has shown in simulation models the potential for decreasing ICU occupation below its surge limit, effectively decreasing mortality. However, for avoiding a rebound in transmission, suppression must be maintained intermittently until a vaccine is available (which may take up to 2 years). The objective of this paper was to describe the mortality patterns observed in Spain, Italy and South Korea for discussing a hypothetical combined public health policy and socioeconomic model that could potentially reduce mortality while reducing the economic impact of this pandemic in Spain. The plan is based on a progressive-voluntary reinstatement to work of the population exposed to the lowest risks (healthy non-immune family units <50 y/o and immune population) and it depends on having sufficiently available ICU beds for providing adequate support. This model, if proven correct for Spain, could eventually be followed by other countries facing a similar impact of the present pandemic.

Keywords

Non-pharmacological interventions; COVID 19; health policy; mortality; economic; intensive care unit.

Abbreviations

NPI: non-pharmacological interventions; GB: Great Britain; US: United States of America; ICU: intensive care unit; Case fatality ratio (CFR).

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Introduction

There are two fundamental non-pharmacological interventions (NPI) in the fight against the COVID 19 pandemic[1]: a) suppression, which attempts to reverse epidemic growth below a level that facilitates its extinction; and b) mitigation, which attempts to reduce the speed of spread of the outbreak without extinguishing it. In a simulation model done at the Imperial College, Ferguson et al[1] compared the results from an unmitigated strategy (avoiding any NPI) versus the implementation of mitigation (case isolation, household quarantine and social distancing of the elderly) versus a suppressive strategy (social distancing of the entire population, case isolation, household quarantine and school and university closure) in Great Britain (GB) and in the United States of America (US).

In an unmitigated epidemic scenario, Ferguson et al[1] estimated that 81% of the population would be infected over the course of the epidemic and that the intensive care unit bed capacity (ICU) would be exceeded in GB by a demand over 30 times greater than its maximum bed supply, resulting in approximately 510,000 deaths in the GB and 2.2 million in the US. In a mitigated scenario, they expected that the surge limits for ICU beds would be exceeded by at least 8-fold, resulting in 250,000 deaths for GB and 1.1 to 1.2 million in the US. Suppression showed the potential for decreasing ICU occupation below its surge limit, resulting in their best strategy for decreasing mortality. However, for avoiding a rebound in transmission, suppression would be maintained for at least 66% of the time until a vaccine was available for immunizing the population – which could take 1.5 to 2 years[1]. Thus, suppression would require an "on / off" implementation, so that the entire population would be allowed to return to work (maintaining mitigation measures) each time the number of ICU weekly admission rates decreased below a value ("off" mechanism); whereas the entire population would be re-suppressed each time the ICU admission rate exceeded a value ("on"). The application of this method would generate "contained epidemic waves" until the entire population acquired immunity (possibly after around 80% of the population had been infected or vaccinated)[1].

The population of Spain, Italy and South Korea is fairly close in size (46.7, 51.2 and 60.5 million, respectively)[2]; however, these countries had shown different mortality rates during this pandemic at the time at which this manuscript was written (April 16th, 2020). Case fatality ratios (CFR) and total deaths had been much higher in Spain and Italy[3-5]. The objective of this paper was to describe the mortality patterns observed in Spain, Italy and South Korea for discussing a hypothetical combined public health policy and socioeconomic model that could potentially reduce mortality while reducing the economic impact of this pandemic in Spain.

Discussion

1. Methods applied in this review.

We descriptively studied the number of deceased patients, the number of confirmed infected cases and CFR (deaths due to coronavirus/ number of confirmed cases), based on the latest available data by age range published by the Ministries of Health of Spain[4], Italy[5] and South Korea[3] on April 15th, 2020 (Table 1). These countries were chosen for being well developed countries, with a population relatively similar in size to Spain but with different CFRs.

The true proportion of the total population infected in the country (attack rate) was estimated for Spain on March 28th by the Imperial College[6] suggesting that, cumulatively, 7,040,195 people had been infected, giving an average attack rate of 15.0% of the population. Based on this attack rate and on the CFR reported on March 28th in Spain[7] (Table 2), we estimated the death rate that would have occurred in a hypothetical scenario where the entire Spanish population <50 y/o would have become infected after being allowed to restart work unsuppressed on March 28th, while the rest of the population (>50 y/o) was kept under suppression.

2. Description of the mortality patterns observed in Spain, Italy and South Korea.

The data published on April 15th at the Spanish Ministry of Health[4], showed an overall 10.46% CFR. Data for age groups (Table 1) showed a 0.43% CFR (163 deaths in 37,498 cases) for patients younger than 50 y/o. On April 15th, 2020, the Korean Center for Disease Control and Prevention[3], reported lower mortality rates than Spain, with a 2.12% CFR and a 0.065% CFR in patients <50 y/o (4 deaths in 6,135 cases). Italy had presented their statistics[5] for the general population on April 9th, with mortality rates relatively similar to Spain: a 12.2% CFR and a 0.54% CFR in patients <50 y/o (197 deaths in 36,431 cases). Italy had also described that their health workers had much lower mortality rates, with a 0.34% CFR for all ages and a 0.066% CFR for patients < 50 y/o (5 deaths in 7,568 cases) (Table 1).

3. Mortality rate estimation if we had allowed the Spanish population <50 y/o becoming infected after March 28th: hypothetical scenario.

On March 28th, the Spanish Ministry of Health[7] had reported an overall 7.9% CFR and a 0.26% CFR in patients <50 y/o (Table 2). Assuming a 15% attack rate, the true mean infection lethality rate for the population of the entire country was possibly around 8 deaths per 10,000 infected cases (5,690 total reported deaths in 7,040,195 mean estimated infections). Furthermore, on March 28th, only 2.15% of the deceased patients were <50 y/o (31 deaths <50 y/o out of 1,442 total deaths); thus, by extrapolating this data, the approximate true infection lethality rate in patients <50 y/o in the entire country would have been around 0.29 deaths per 10,000 cases (2.15% of the 5,690 total deaths over the 7,040,195 estimated infections reported in the country), which is a mortality rate 46 times lower than for the general population (Table 2). Therefore, for our hypothetical scenario, where the entire Spanish population <50 y/o would have become infected after being left unsuppressed, 815 patients would have been expected to die.

4. Importance of CFR and true infection lethality rates in patients <50 y/o: implications for health policies.

Following Ferguson's model[1], decreasing ICU occupation below its surge limit, should result in the best strategy for decreasing mortality. In the following weeks after this manuscript was written, we expected to see Spain decreasing its ICU occupation below its surge limit[8]. Moreover, there was an intense ongoing debate for deciding how to implement further NPI. If we followed Ferguson's model[1], we risked inducing "contained epidemic" waves by applying an "on and off" suppression strategy to our entire society for up to 2 years. Each wave could increase mortality if ICU occupation raised above surge limit, and it could severely affect the economy.

There are some causes of death at an epidemic scale in our world that do not trigger suppression strategies. Road traffic accidents have been considered by the World Health Organization as a hidden global epidemic[9], and the 2018 motor-vehicle death rate in the US was 1.42 per 10,000 vehicles[10] on the road per year (0.014%). The CFR for Hepatitis A in adults[11] is around 1,8%, and the CFR for Influenza A[12] is somewhere around 0.1%. Despite this data, vaccination for Hepatitis A and Influenza A is not compulsory in most countries in the European Union[13]. Moreover, despite the previous death rates in the previous epidemic conditions, the population circulates by road vehicle freely, and no suppressive measures are routinely implemented for those infectious diseases. In Spain and Italy, the CFR for patients <50 y/o has been < 0.55%, which is lower than the one for Hepatitis A in adults. Furthermore, the Italian working-population in the health sector (potentially exposed to the highest viral loads) have shown a CFR <0.1% for patients < 50 y/o, which is similar to the one for Influenza A (Table 1).

Flaxman et al[6], in a study analyzing the impact of NPI in 11 European countries, estimated that there are orders of magnitude fewer infections detected than true infections, mostly likely due to mild and asymptomatic infections as well as limited testing capacity. For Spain, Flaxman[6] estimated an average attack rate of 15.0%. Based on his data, we believe that the true overall lethality rate for the entire Spanish population could possibly be much lower (8 per 10,000) than its CFR (10.46%). Moreover, for the population <50 y/o, we could be facing a lower true lethality rate (0.29 per 10,000) than the annual mortality rate derived from driving a car in the US. This mortality rate would be 45.5 times lower than the expected true overall lethality rate in our population >50 y/o, if left exposed to the infection (Table 2). Furthermore, based on the Italian

experience in their health workers, we should also hypothesize that the true lethality rate should be much lower in the healthy actively working population.

The Spanish population under 50 y/o currently represents 59.34% [14] of the entire country's population, and it comprises 74% of the population under 65 y/o (which includes the working age population). Based on our discussion, we hypothesize (Figure 1) that a selective suppression of the population should further reduce the number of deaths and lessen the impact on the economy if, when having enough ICU beds available for our population:

1. We allowed the healthy non-immune family units with all members <50 y/o to return voluntarily to their work (or studies) under mitigating conditions for achieving herd immunity (without no longer suppressing them again). We would define "healthy patients" as the ones without risk factors[15] for developing a lethal from of infection (e.g.: diabetes, hypertension, cardiovascular disease, chronic respiratory disease, cancer, immunodepression and pregnancy). Further studies should detail these risk factors.
2. We allowed all the immune family units to return voluntarily to their normal daily activities under mitigating conditions (without no longer suppressing them again). The methods for determining immunity would depend on technology that should be deployed in the coming weeks (e.g. IgG detection).
3. Our state provided support to family units that had some non-immune members ≥ 50 y/o and/or unhealthy, but whose other members (<50 y/o, healthy, immune) were fit for voluntarily returning to work. Hotels, residences or duly qualified media could temporarily house these members at risk.
4. We allowed age ranges ≥ 50 y/o to return voluntarily to work, once we had achieved sufficiently safe herd immunity (e.g. 80%) for the population under 50 y/o[1].
5. We maintained suppressive measures in the population that did not match the above indications.

Under Ferguson's model[1], we would basically be exposing the entire population to the virus every time that the suppression is "off", which could translate into having epidemic waves with a 2.12% CFR (Korea) to 12.2% CFR (Italy). Moreover, under Ferguson's model[1], we would only allow full working conditions for 33% of time in the 24 months following the first epidemic peak (due to multiple re-suppressions). On the other hand, by selectively unsuppressing the population <50 y/o, our model could witness an expected number of deaths up to 46 times lower than the one derived from exposing the entire population to the virus, and it could allow up to around 80% of our work force to resume work full-time (with no re-suppressions) once our ICU occupation dropped below its surge capacity and we had sufficient ICU beds for supporting our population at risk (possibly, in days or weeks after this manuscript was written).

Conclusions

Based on our analysis of the existing literature, we propose a combined public health and socioeconomic model that could theoretically seek to provide our decision makers in Spain with alternative tools to the ones that are being implemented at present for: quickly achieving immunity with the lowest possible mortality, while propping up the fall of our economy. The plan is based on a progressive-voluntary reinstatement to work of the population exposed to the lowest risks (healthy non-immune family units <50 y/o and immune population) and it depends on having sufficiently available ICU beds for providing adequate support. This model, if proven correct for Spain, could eventually be followed by other countries facing a similar impact of the present pandemic.

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Tables.

		Spain, April 15th			South Korea, April 15th			Italy, general population, April 9th			Italy, health workers, April 9th		
		Deceased patients	Confirmed Infected cases	CFR	Deceased patients	Confirmed Infected cases	CFR	Deceased patients	Confirmed Infected cases	CFR	Deceased patients	Confirmed Infected cases	CFR
Total		18,579	177,633	10.46%	225	10,591	2.12%	16,654	136,110	12,2	48	14,032	0.34%
Age	0 to 9	1	382	**0.26%**	0	132	**0.00%**	1	938	**0.11%**			
	10 to 19	1	682	**0.15%**	0	569	**0.00%**	0	1,432	**0.00%**			
	20 to 29*	17	6294	**0.27%**	0	2,895	**0.00%**	7	6,360	**0.11%**	0	1,284	**0.00%**
	30 to 39	35	11752	**0.30%**	1	1,131	**0.09%**	36	9,956	**0.36%**	2	2,346	**0.09%**
	40 to 49	109	18388	**0.59%**	3	1,408	**0.21%**	153	17,745	**0.86%**	3	3,938	**0.08%**
	50 to 59	284	22844	**1.24%**	14	1,937	**0.72%**	638	26,391	**2.42%**	14	4,809	**0.29%**
	60 to 69	887	20137	**4.40%**	33	1,339	**2.46%**	1,957	21,734	**9.00%**	20	1,568	**1.28%**
	70 to 79	2633	19042	**13.83%**	68	702	**9.69%**	5,366	22,934	**23.40%**	9	87	**10.34%**
	80 to 89	4016	16962	**23.68%**	106	478	**22.18%**	6,711	21,636	**31.02%**			
	90+	1622	6335	**25.60%**				1,784	6,842	**26.07%**			
	Sub-totals	*9,605*	*122,818*	**7.8%**	*225*	*10,591*	**2.12%**	*16,653*	*135,968*	**12.2%**	*48*	*14,032*	**0.34%**

Table 1. Case fatality ratio (CFR) distribution by age groups in the general population for Spain, South Korea and Italy. CFR = deceased patients / confirmed infected cases. *For the population of health workers in Italy, the lower age range studied was 18 to 29 y/o.

		Spain, Ministry of Health, March 28th			True estimates for a 15% attack rate, March 28th		Expected deaths if entire country became infected
		Deceased patients n (%)	Confirmed Infected cases	CFR	Infections (n)	Lethality /10,000	Deaths (n)
Total		5,690 (100%)	72,248	7.9%	7,040,195	8.08	37,933
Age	0 to 49	31 (2.15%)	11,916	0.26%	4,181,876	0.29	815
	50 to 90+	1,411 (97.8%)	24,289	5.80%	2,858,319	19.48	37118
	Sub-totals	1,442 (100%)	36,205	4%			

Table 2. Estimation of the true number of infections and true lethality rate / 10,000 population, for Spain on March 28th; and expected number of deaths if the entire country had become infected with our ICU occupation above its surge capacity. Data is calculated for a 15% attack rate, based on the data provided by the Spanish Ministry of Health on March 28th. Population for Spain in 2019 was 46,934,632 (59.4% were <50 y/o). Case fatality ratio (CFR) = deceased patients / confirmed infected cases.

Figures.
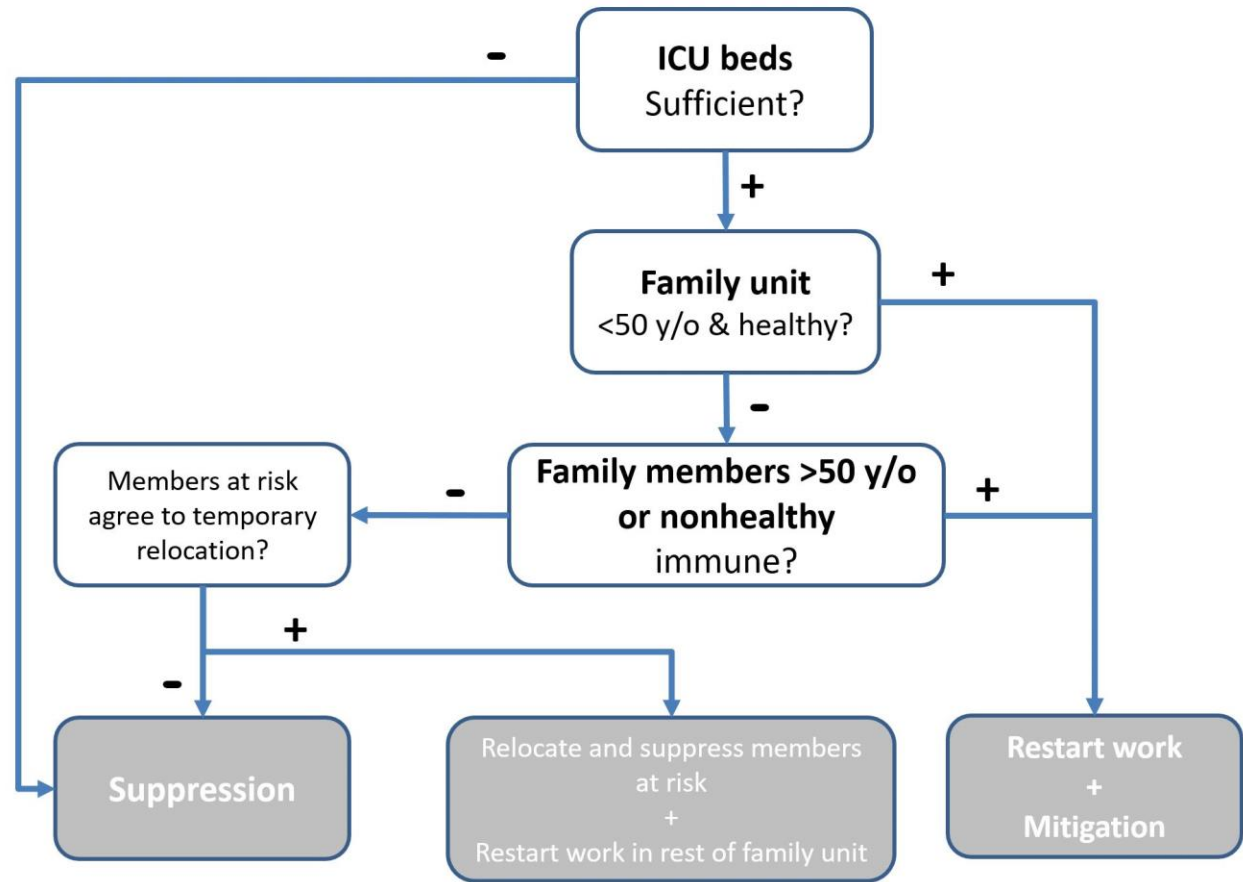
Figure 1. Flow diagram of a combined public health and socioeconomic model for policymakers for applying after the suppression of the first epidemic peak. The model would start its implementation when sufficient ICU beds were available (e.g.: 10 to 20% vacant). If all family members residing in the same location (family unit) were <50 y/o and healthy, they could restart work under mitigation. If some family members were >50 y/o or were tagged as "unhealthy" (diabetes, hypertension, cardiovascular disease, chronic respiratory disease, cancer, immunodepression and pregnancy), they could restart work under mitigation if they were already immune (due to previous confirmed infection and/or to thru IgG tests). If the family unit agreed to temporarily relocate their members at risk in safe environments supervised by the state (e.g.: hotels, etc..), the rest of the family unit could restart work under mitigation.