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TITLE:

COVID-19 Management in Spain. Errors to Avoid and the Need of a Post-Confinement Longitudinal Epidemiological Study

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Abstract

Some of the European countries affected by COVID-19 have not learned from previous experience in China. Italy did not learn from China and Spain did neither learn from China nor from Italy. Confinement in Spain was postponed due to pressure from economic interests and traveling of infected people, especially from Madrid to the beaches in South-East Spain, was allowed. Strict confinement and border closure came late, when the curve of infected people and the death toll already had the worse trend worldwide. Tests to SARS-CoV-2 RNA detection by PCR, were first unavailable and, later, faulty and/or detecting antibodies and not the virus itself. Instead of mobilizing research laboratories for making tests, and instead of making masks and ventilators, mediatic scientists asked for money for controversial clinical trials and for obtaining a vaccine. In this scenario, common sense indicates that *ad hoc* measures should be taken at the end of confinement in order to minimize pain. The chain of errors should be avoided in the management of next pandemics by designing Good Practice Rules (GPRs). In addition, post-confinement measures should be implemented as soon as possible to be ready for SARS-CoV-2 return next season. In this sense a longitudinal study in the most affected cities (Madrid, Barcelona, Vitoria and Pamplona) should be performed with the primary objective of detecting carriers with no symptoms, to stratify patients according to symptoms, and to early detection of virus reappearance. Also relevant is to sequence as many viruses as possible to detect possible variants; there are still patients that are PCR positive.

Keywords: COVID-19; SARS-CoV-2; pandemic; ethics; public health; longitudinal clinical trial; silent virus carrier

Some of the errors in COVID-19 pandemic management in Spain

Spain has failed to appropriately address the SARS-CoV-2 pandemic. Measures came late, mainly due to pressures from “economic powers”. In return the trends in the curves of affected individuals and number of deceases were the worst to date. As of April 8 there were doubts on whether the plateau had been reached or not. As of May 3, the death toll is among the highest worldwide and deconfinement rules are confusing and not well

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designed from a Public Health point of view; confusing rules leading to confusing interpretations by the population represent a risk of pandemic reactivation.

Spanish citizens have suffered from shortage of protection devices (masks, gloves, disinfectants, etc.), virus detection tests and even ventilators needed to save lives in critical care units. There is even the suspicion that, during the worst phase of the pandemics, doctors had to decide who got access to the ventilators; it is hypothesized that,in Spain and in France, age was one criterion used in such decisions.

Surely the "sanitarios" (sanitary workers) are globally considered today's heroes in Spain, presenting a high rate of infection (more than 36,000, 16% of the total 218,000 cases as of May 3, 2020). Many of infections were the result of the above-mentioned lack of protection devices. Also the general population has helped to invent how to protect themselves by making masks or wearing scarves and putting protective plastic bags on their bodies. In contrast, the Government and its experts have led to dozens of anecdotes; one very commented was the lack of knowledge by the main responsible of COVID-19 response team about chloroquine, an anti-malarial drug used in China for the therapy of COVID-19 and whose use was soon (beginning of March 2020) recommended by the French Health Ministry [1]. Another significant example of the lack of skills for managing this sad situation was the acquisition by the central Spanish administration of hundred of thousand suboptimal serological tests (real sensitivity lower than 40%) from a Chinese provider, investing a significant amount of money; before acquisition the test was not checked by any real microbiology expert.

The lack of masks is still evident and, besides a lack of pedagogy to the general population in the need to wear masks, it was May 1rst, when the Government ruled that masks are mandatory… but only in public transportation.

Nobody was ready for such a pandemic despite Bill Gates already warned a few years ago (2015, TED talks; available at www.youtube.com/watch?v=6Af6b_wyiwI). As a scientist, I have missed a task force to, at the very least, i) mobilize all research laboratories to make reagents and to make tests, ii) mobilize Spanish pharmaceutical companies to synthesize chloroquine and other medications that are out of patent (known in Spain as "genéricos") and iii) order Spanish companies to make masks, gloves and ventilators. Fortunately, individual initiatives fueled by contacts via Twitter, Facebook, etc. and aided by, among other, a car maker (Seat), led to produce ventilators (they were not perfect but saved lives of COVID-19 infected individuals suffering from pneumonia).

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Catalonia reacted quicker and *catalans* were confined earlier than in other Spanish regions. However the Catalonian Government failed to mobilize resources and industries to make reagents, tests, protection devices, etc. Also failed to hire a Catalan company that has been distributing quick tests to several countries. The company is not devoted to the Health Industry and was just taking advantage of its contacts to buy and distribute without making money (i.e. altruistically). Importantly, from the very beginning this company was distributing the right quick tests, i.e. those detecting the RNA of the virus. In addition, the administration "scientific bedside" advisors have been more mediatic than real experts able to detect the needs and assess on where to buy, how to act, etc. They even got the Spanish drug agency to approve in record time a controversial clinical. Some issues in such clinical trial were: i) no clear primary outcome (how to determine the curing or the delay in transmission rate?), ii) lack of appropriate management and iii) independent use of two different drugs, chloroquine that was already used elsewhere, and an inhibitor of the protease of HIV-1, the virus producing acquired immunodeficiency syndrome (AIDS). While no single results was provided to sustain the use of such inhibitor, a German laboratory, based in its knowledge on SARS-Co viruses, has already reported the 3D structure of the main protease also suggesting the structure of a specific inhibitor [2]. The same experts started the experiments to obtain the vaccine and promoted a campaign to raise funds. Surely promoters of the vaccine and of fund-raising acted *bonafide* but Spain has never provided a commercially-available vaccine. This contrast with the useless investment of money in the purchase of suboptimal serological tests. Should instead the money be used to palliate the above-mentioned shortcomings?

In summary, the lack of worldwide experience on fighting a dangerous virus plus the mistakes in management has led to the (almost) certainty that the real amount of infected individuals in Spain is much higher than that suggested by the official numbers (140,500 on April 7; circa 218,000 on May 3, 2020) (Source Ministerio de Sanidad, date April 7: (

https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/situacionActual.htm

Web page last checked on May 4, 2020). In fact, the already famous study of the "Imperial College COVID-19 Response Team" released on March 30, 2020, predicts for Spain 15% infected population (95% confidence interval: 3.7%-41%) [3]. Even if we take the most conservative figure, 3.7%, the past + present virus carriers would be more than 1.4 million. In relation to this a recent study on seroprevalence in sanitary workers indicate that 11%

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of this collective has been contact with COVID19, and a preliminary study among Barcelona population reveals a 5% of seroprevalence, which seems to agree with the predictions of bad consequences of shortage of protections devices for hospital workers.

Yet more mistakes

Suspicions on the presence of SARS-CoV-2 in Spain was not taken into account until recently (end of April). Data on where and when the virus appeared is fundamental to understand the specifics of the pandemic in the Country and to undertake appropriate measures. There are confirmed cases of COVID-19 infection in January 2020 and suspicions of COVID from strange "flu" also occurring in January/February.

The lack of testing, even in the most favorable conditions, has led to the highest death toll in nurse homes for the elderly. If no protective resources/means are properly allocated and no samples are taken, you end up with workers infected and deceased residents. In some cases all residents died. Sample collection in nurse homes is easy and can be quickly performed to both workers and residents. A pity that nobody thought of that "easy" intervention. Both in Barcelona and Madrid authorities have had to implement urgent measures in Nurse homes that come, once more, late. Being evident (and well known) that the elderly are high-risk population due to COVID19 severity and risk of fatal consequences, it is difficult to understand why nursing homes were not considered from the beginning and why the necessary resources were not provided. Perhaps this would have prevented the death in these nursing homes of circa 17,000 human beings, 68% of total death toll in Spain as of May 3, 2020.

Confusing deconfinement rules

Recently, memes/jokes on Spanish deconfinement rules became viral in Social networks. Not only rules are obscure but the criteria may change from one day to the next one. Again, population was not taught that caution and preventive measures are still needed; consequently, it is usual to see many individuals or entire families without wearing masks or without maintaining the security distance while they are walking on streets.

The words of the prime Minister, Pedro Sánchez, leave no room for doubts. He recently said that there will be four deconfinement phases. In the same speech he said that in "*each*

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of the three de-escalation phases described" (sic). He chronologically added that each phase will have a duration of 2 weeks (minimum) and, among other, that i)"*the first phase or phase zero… or …. preparation phase or …. initial phase*", ii) "*phase 2 or intermediate phase*", iii) "*third phase is the advanced (!) phase … is the last one*" iv) "*the first phase or zero phase*" … and so on. By the way in one of the "four" phases, one may already be able to drink a beer with friends despite to eat a paella will be forbidden; friends and paella must go home to eat. These sentences results from a fear to do it wrong, something that one may understand. However, erratic and sloppy rules on the where/when, how and whys, are absolutely unacceptable to deal with next pandemics or SARS-CoV-2 reappearance next season.

Puzzling COVID-19 related research projects

Scientific research is absolutely needed to combat SARS-CoV-2. Accordingly Spanish public and private bodies have allocated funds for COVID-19-related research projects. The main National Body for Public Health and disease control, *Instituto de Salud Carlos III*, has received >1,300 applications!!! This is a complete nonsense as nonsense is the objective of some of the applications, even of some of the ones that have been successful. It is pretty obvious that Spain cannot compete with China, the U.S., France (Pasteur was French), Germany (Koch was German) or the U.K. (Fleming was Scottish) in developing and producing a vaccine or a specific anti-SARS-CoV-2 drug. Alternatives exist that prioritize present and future patients also allowing better and faster turn-around times to deal with the come-back of the virus next season.

A further naïve example of the imagination of Spanish scientists has been recently disclosed and presented in the mass media. Unfortunately, the study is biased and, in my opinion, useless. The hypothesis is the wish of all citizens, i.e. that the virus will disappear in summer. Obviously, the hypothesis cannot be proved as of today. A popular Newspaper highlights that according to climatologists: "*Warmer months could attenuate the epidemics*" (La Vanguardia, April 30, 2020). It is funny that "climatologists" are so courageous to make predictions on pandemics but, worse, does the study does meet rigorous scientific criteria? The Catalonian weather information service (MeteoCat) in collaboration with a University Hospital in Barcelona has "demonstrated" that "*Average temperatures above 20ºC reduce to a half the expansion of the epidemics*" (La Vanguardia, April 30, 2020). Patients and families deserve that Spanish scientists, which are excellent,

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keep a low profile unless they have something relevant to say. Also important is that politicians look to scientists other than "bedside experts" whose controversial advices along pandemic time are counted by dozens. On the one hand, it is impossible to correlate the expansion of a pandemics with temperature in just one/two months. How "expansion" should be measured? A rhetoric question. On the other hand, the heat map of cases as of May 1rst (Figure 1) does not correlate with average temperatures on geographical locations. Notice that climate in Catalonia is colder going West and North. Then, such locations should have higher incidence of cases and higher death rates, but this is not the case. For instance compare Barcelona death toll (>1,900/million) with that of colder Girona (944) or much colder Lleida (570) (a detailed study on correlating death and average temperature is underway; Franco and Galo-Fernández in preparation).

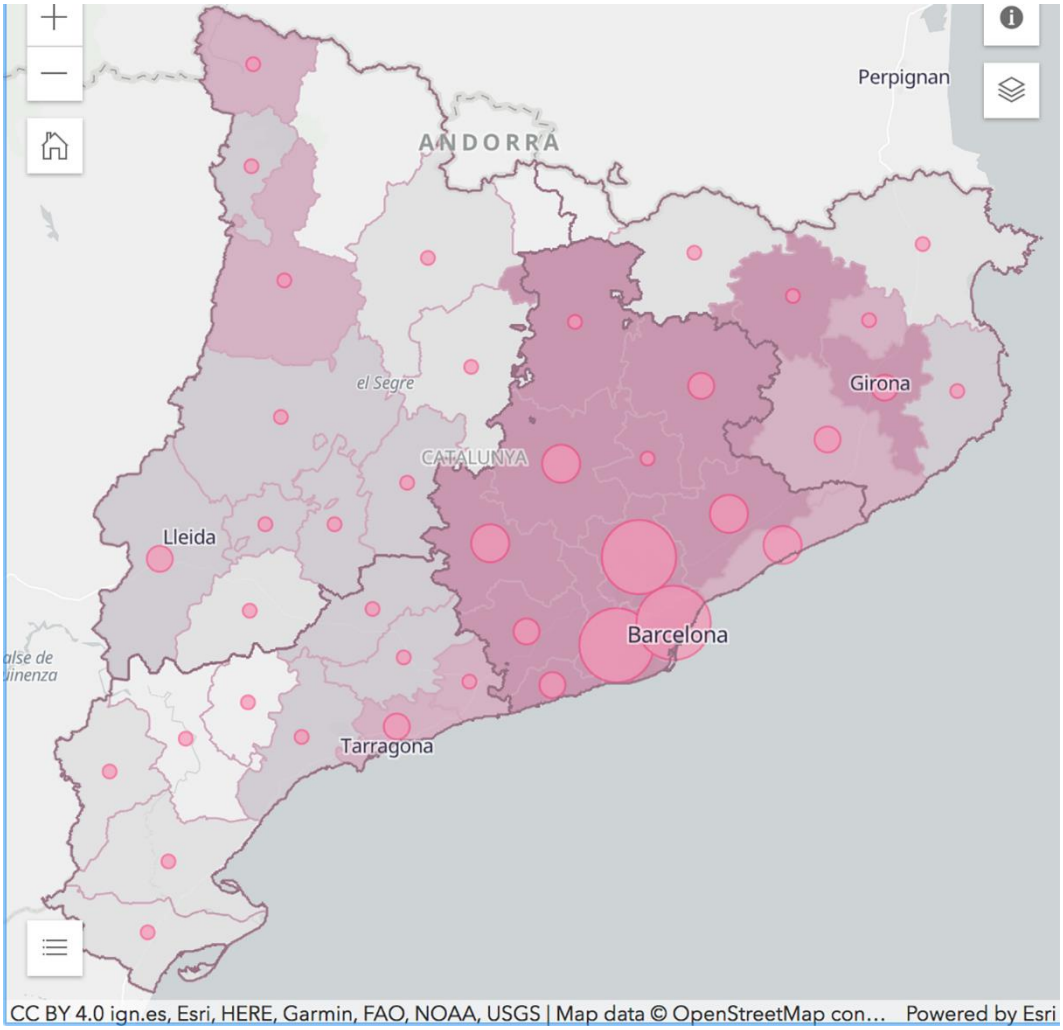

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Figure 1. Heat map of death rates in Catalonia. Relatively low death rates (normalized by million population) are in grey color scale and relatively high death rates are in pink/magenta color scale; the darker the color the higher the death rate. The diameter of the pink circle is roughly proportional to the normalized death rate. Taken on May 1rst, 2020 from National.cat on-line newspaper (https://www.elnacional.cat/es/salud/coronavirus-mapa-contagios-catalunya-municipios_485916_102.html

Web page last checked on May 4, 2020).

The design of post-confinement "good practice" rules (GPRs)

The above-described scenario correlates with one of the highest death tools on Earth and also with the failure of the Spanish society to deal with epidemics. Back in time Spanish was, again, leading the number of SIDA cases within developed Countries. Spain have the tools and expertise to change this trend and must do it. I pose that a correct management of next state of alarm would require preparation and considering the critical voices. Obviously, bad management is not only occurring in Spain, I am thinking in Trump's press conferences and in Trump's recommendations to take pills or to disinfectant ingestion. Also noxious are opinions of bedside experts in the USA disguised as scientific-based truths. To be a prestigious scientist in a prestigious US University and able to publish in top-notch journals does not guarantee reliable information when beliefs are put ahead of Science. On the other hand, I fully agree with Vinay Prasad and Jeffrey S. Flier opinion, which was published on April 27, 2020: "*Scientists who express different views on Covid-19 should be heard, not demonized*" [4].

Wishing not to be demonized, my opinion is that Spain must design "good practice" rules (GPRs) and enforce them. The main objectives are i) a safe return to "normal" life, ii) anticipate the reappearance of SARS-CoV-2 in the coming winter and iii) have clear the actions and ready the resources to minimize the impact of next epidemic.

First of all I would recommend to take into careful consideration the general pitfalls arising when a new threat appears. This issue has been appropriately and timely addressed n relationship with COVID-19 infection [5].

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Secondly, Spain must have a plan to, within a week, obtain/produce as many masks as required. Spain has got the personal and material resources, but coordination is required. To produce masks no bedside experts are needed. In addition, it is needed to be able to perform PCR assays by thousands per day. Spain has got the personal and material resources but, again, coordination is required and no bedside experts are needed. Experts must indicate how many types of masks are needed and which reagents are needed and which equipment is ready to be used in a state of alarm. One of the biggest failures revealed during this pandemic has been the lack of use of scientific equipment (thermocyclers) in top-notch research Institutes. COVID-19 has underscored the lack of returns from investment of public money in such institutes. Instead of being useful for society/tax-payers, often, they behave as branches of well-positioned laboratories in the States or in other Countries.

Experts must also supervise any purchase to certify quality. For instance the serological tests arriving to Spain have up to 98% sensitivity but neither a sensitivity assay has been performed in Spain nor the tests reach 40% sensitivity in samples from people living in the Country. Accordingly, experts should now be working on addressing the whys: are purchased tests not working properly? Are serum IgGs declining fast? Is there any antigenic shit/drift in the Spanish population? Responses to these questions are crucial to deal with deconfinement (see below).

Experts are needed to convince politicians that everybody should wear masks, that PCR must be done by thousands per day and defined populations that must be tested first. All together would avoid the creepy number of infected hospital workers, of normalized total deaths and of deaths in nurse homes (the highest in the world). Experts must appear on TV wearing masks. Roughly, 50% of population going out in deconfinement cero/one phase are not wearing masks. Along the pandemics I have never seen in Wuhan (China) or in South Korea people on the streets without masks. Hospital workers are amazed at such behavior which undoubtedly is a consequence of errors by Governments (National and Regional) and their expert advisors.

Finally, there is an issue in which everybody agrees, namely the detection of silent carriers. On the one hand, silent carriers have probably contributed the most to SARS-CoV-2 spreading. On the other hand, there is a need to identify those silent carriers. Remarkably, recently performed (beginning of May, 2020) tests to 2,500 soccer players in Spanish teams have led to detect 5 active infections without any significant symptom. Despite all

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the evidence, there is not, as of today, any sound epidemiological proposal to deal with this issue and I fear that more mistakes will compromise the success of future actions if asymptomatic carriers are not quickly identified and quickly isolated.

Post-confinement longitudinal epidemiological study

One appropriate post-confinement action consists of performing as many tests as possible to identify individuals that have got COVID-19. Also important is collecting data all around Spain on the variety of symptoms, from the asymptomatic to the critically ill. The latter require to be sure about exposure to SARS-CoV-2, something that at this point is conceptually easy and just requires to measure specific antibodies (IgM and/or IgG) in serum/plasma. Also important is to measure the temporal course of anti-SARS-CoV-2 immunity in the Spanish population, i.e. the rate of antibody drop over time. As testing the whole population is not possible (in Spain), I pose that a longitudinal study is required with these three objectives: i) identify carriers with none or mild symptoms, ii) measure the level of serum/plasma anti-SARS-CoV-2 antibodies and iii) evaluate how immunity against viral proteins falls with time looking for reinfections within the next 12 months (taking samples at 0, 3, 6, 9 and 12 months).

Despite clinical histories are often undervalued by clinical researchers, the study would require performing a good anamnesis, which among COVID-19 sufferers should include: fever, symptoms, number of days with fever/symptoms, lack-of-breath sensation, vomiting, etc.

The study should focus on obtaining data to be useful in Spain, i.e. data from Spanish individuals to be useful in next “infection season”. Similar studies in other Countries would be helpful in identifying similarities and differences in the response to the virus. I would recommend to recruit equivalents populations, e.g. workers and students in a given University Faculty, in 4 different cities with high COVID-19 incidence (e.g. Madrid, Barcelona, Vitoria and Pamplona) and in one with less incidence (e.g. Murcia). Optimal design of the study should allow:

1. Identifying individuals early having COVID-19
2. Identifying individuals exposed to the virus but resistant to infection
3. Defining the different symptomatic responses and correlate them with the level of anti-SARS-CoV-2 antibodies

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4. Assessing the anti-SARS-CoV-2 antibody level decay with time
5. Identifying comorbidities
6. Detecting the onset of new outbreak

Vaccines? Drugs? When and how

Finally, I would like to add that instead of working in developing several vaccines and new drugs the Spanish National and Regional Administrations and their advisors should be already working in i) securing that the first vaccines/drugs are tested in Spain because it is the Country with highest death toll and ii) securing availability of enough vaccines/drugs when they become commercially available.

In summary, Spain needs to learn from past errors, hear the advice from bedside and non-bedside experts and focus on what Spanish citizens need to fight back next SARS-CoV-2 attack.

Conflict of interests

Author declare no conflict of interests

References

1. Conseil H. Avis: relatif à la prise en charge des cas confirmés d'infection au virus SARS-CoV21. *Haut Cons la santé publique*. 2020:1-4.
2. Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science (80-).* March 2020:eabb3405. doi:10.1126/science.abb3405
3. Flaxman S, Mishra S, Gandy A, Al E. *Imperial College London. Faculty of Medicine. COVID-19 Reports. Report 13: Estimating the Number of Infections and the Impact of Non-Pharmaceutical Interventions on COVID-19 in 11 European Countries*.; 2020. https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/. Accessed April 7, 2020.

 doi:10.20944/preprints202005.0137.v1

4. Prasad V, Flier J. Scientists who express different views on Covid-19 should be heard, not demonized. https://www.statnews.com. https://www.statnews.com/2020/04/27/hear-scientists-different-views-covid-19-dont-attack-them/. Published 2020. Accessed May 3, 2020.

5. Redelmeier DA, Shafir E. Pitfalls of judgment during the COVID-19 pandemic. *Lancet Public Heal*. 2020;0(0). doi:10.1016/S2468-2667(20)30096-7