COVID-19 Advisory Committee to the Local Medical Associations positioning report, 20/07/2020

REPORT #7 CA-COVID-19-OMC on *effective and accessible vaccines at reasonable prices*

WE MUST SECURE EFFECTIVE AND ACCESIBLE VACCINES FOR OUR POPULATION, AND AT REASONABLE PRICES

Executive Summary and key proposals:

The initial response to the COVID-19 pandemic has included Public Health actions with intensive medical care but with little evidence for the emerging condition of SARS-CoV-2. As the epidemic develops and experience, knowledge, and research increase, there is a need to clarify the confusion and noise and promote the actions of healthcare and scientific authorities to assess the numerous ongoing studies transparently.

Time is short in the search for effective treatments and vaccines; we must face the many challenges that we formulate here as **proposals**:

a) Push forward a debate on the **priorities in the application of vaccines** in the likely case that it is an initially scarce resource: the vulnerability and greater health benefit in the medium term are two criteria that can guide the identification of those who must be vaccinated first.

b) **Manage in advance the conditions of ownership and patents** that will determine the price to pay: although it is not foreseeable that funding will be spared to buy vaccines, it is especially important to ensure that they are cost-effective.

c) Approach the challenge of **fostering an autonomous, safe, and sovereign manufacture of vaccines and medications**, stimulating complete chains coupled with research, development, innovation, manufacture, and consumption, which entails an authentic investment in scientific and economic fabric of high added value.

The Local Medical Associations Advisory Committee for COVID-19, is an expert panel from various professions, fields, and specializations, which was launched on 21 April 2020 to advise the Spanish General Medical Council regarding several scientific, technical, and organizational issues that arise due to the pandemic, in order to propose actions, and to generate technical reports that justify the public positioning of the Spanish General Medical Council.

PRELIMINARY CONSIDERATIONS

A concerning starting point situation

The pandemic caused by SARS-CoV-2 has had all types of consequences: personal (disease, sequelae, and deaths), social (confinement, job losses), and economic (record of temporary employment regulation, decrease in the social security affiliations, additional assets of the Bank of Spain for €120 billion[1], €150 000 billion of European funds[2], etc.).

This is why more countries and governments are interested in accessing funds to help face both the healthcare crisis and the economic one. In this sense, therapies must be considered a fundamental instrument for preventing second and third waves of this pandemic, which will clearly occur[3].

On May 19, there were more than 20 active clinical trials about vaccines, and over 200 about various therapeutic agents[4] (in different clinical development phases) involved in the treatment and prevention of SARS-CoV-2 to avoid COVID-19. Some available treatments are molecules of recent development. However, most are new uses of already authorized medications for other indications.

Countering the noise and confusion

All this constantly generates a **great amount of information that must be analyzed, compared, and verified**, which is why an Agency that compiles this information and ensures that it is available and easy to access for healthcare professionals is needed.

The **use and abuse of press releases and the publishing of article pre-prints** that have not been peer-reviewed are combined with high media attention and sensationalist news. Also, as this news affects the stock value of pharmaceutical and technological companies and provides visibility and fame (as short-lived as it may be) to the researchers, this trend is reinforced and becomes self-sustaining.

The result is a lot of noise, confusion, frustrated expectations, and more distancing and misunderstanding of science by the population. All this makes more necessary than ever the intervention of public authorities to **assess the quality of studies and communicate the proven evidence** of treatments, technologies, or interventions.

BUILDING EFFECTIVE AND EFFICIENT RESPONSES

The basis of an effective response has to start from our Agency of Medicines. Time is short, and many challenges need to be solved: social, healthcare, economic, and productivity.

a) The Spanish Agency for Medications and Medical Devices (AEMPS) should have a fundamental role.

The **Spanish Agency for Medications and Medical Devices** is playing, and must play, a fundamental role as a resource for assessment and management of knowledge; in this way, continuously monitoring everything related to the new COVID-19 treatments, together with the network of agencies at the European level and outside of Europe.

However, it would be convenient (almost indispensable) to reinforce the **agility** of elaborating and publishing reports based on studies that transmit **true, verified, and tested information** to all professionals. In this sense, the Spanish Agency for Medications and Medical Devices has provided professionals with various study **reports and records** about the different aspects for diagnosis and treatment:

- **Clinical trials** have a space of their own in which their characteristics are published, the Spanish Clinical Trials Registry (**REec**)[1].
- Listing of **post-authorization studies**, promoted by the healthcare administrations[2].
- **Clinical trials with authorized medicines** in the European Union (EU) in the EU Clinical Trials Register[3].
- Information regarding **other studies** on COVID-19 in the platform of the International Clinical Trials Registry of the WHO[4], or the platform of the US National Library of Medicine[5].

Regarding the researched active agents, it is worth noticing that currently there are **71 registered clinical trials in Spain**, and that it is necessary to have clear criteria to decide when the benefit/risk relationship is acceptable so that said clinical trial is allowed to continue or no, despite the uncertainty, the pressure lobbies, and information noise.

[1] WEB of the Spanish Registry of Clinical Trials: https://reec.aemps.es/reec/public/web.html
[2] Information regarding COVID-19 clinical investigation: https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%e2%80%9119/informacion-sobre-investigacion-clinica-sobre-la-covid-19/
[3] EU Clinical Trials Register: https://www.clinicaltrialsregister.eu
[4] Web of the International Clinical Trials Registry Platform: https://www.who.int/ictrp/search/es/
[5] Web of the US National Library of Medicine "Clinical Trials": https://www.clinicaltrials.gov/

Despite the many studies started, there is currently no evidence provided by controlled clinical trials that allow the recommendation of a specific treatment for SARS-CoV-2, neither is there a glimpse of an effective treatment for infection prevention nor for disease treatment (suffice to remember the great clinical complexity of the infectious process that attacks many physiological systems).

b) Time is short in the search for effective treatments and vaccines: we must face diverse challenges with many uncertainties that must be clarified.

Before this context, it is urgent at the social and healthcare level to identify or develop both new treatments for the disease once it is established, as well as treatments to prevent the infection (mainly vaccines).

Regarding the currently researched treatments, they do not stop being empiric treatments that are used due to indirect evidence about their usefulness (as there is no specific treatment yet, and we are dealing with an emerging disease with many aspects of its physiopathology still unknown).

These treatments (and many others being tested) will still have to demonstrate their effectiveness in treating the disease and the benefit for the patient, as during the disease course, many other treatments might induce or cause interactions with the antivirals. Therefore, again, analyzing and considering the **benefit/risk balance** is fundamental.

However, the fundamental treatments that will be effective for prevention will be **vaccines**, and it is written in plural because **more than 20 compounds** of different origins (live and/or inactivated and/or genetically modified virus) are undergoing clinical trials, with researchers having the advantage of not starting from scratch for the SARS-CoV-2 vaccine as the research performed in the past for vaccines for SARS and for MERS has identified possible approaches.

Due to the (healthcare and economic) severity of the COVID-19 pandemic, it is very likely that the regulators (Food and Drug Administration, European Medicines Agency) speed up some of the fundamental and necessary steps in the development of new medications (animal studies, phases I, II, and III). However, we can be sure that **they will not be available earlier than 6 months** after starting the clinical trials.

If the vaccine is approved, its **manufacture, distribution, and global administration** will take time, and as people do not have immunity against COVID-19 (5% in Spain[6]), they will probably need two doses of the vaccine, with a gap of three to four weeks and people will start attaining immunity against COVID-19 in one or two weeks after the second dose.

Therefore, there is still much work to do. Nevertheless, the number of pharmaceutical companies, governments, and other agencies working on a COVID-19 vaccine is a reason to have hope (in public-private alliances).

In addition, the complexity of the situation makes it even more challenging to make decisions and make strategic plans at different levels. The uncertainty invades the fundamental aspects of SARS-CoV-2 and COVID-19. To date, we cannot know what type of vaccine, technologically speaking, will be first, nor how effective it will be. We also do not know the necessary dose, nor the number of doses needed, both in the young and the elderly populations (with worse immune response, population at risk). All these questions enormously restrict the global manufacturing capacity and the prioritization need.

The ideal objective is to prevent infection and block transmission, but the first results of the more advanced vaccines do not seem to have achieved the second objective. This means that eventually, many more people would need to be vaccinated (over 6 billion people). However, we can continue to work on foreseeing the challenges that disease prevention using vaccination will involve.

From our perspective, 4 challenges arise: social, healthcare, economic, and manufacturing. These will have to be solved to gain space and time in our country and on a global scale. These challenges are: social (how much), healthcare (to whom), and economic (how do we pay).

c) Social and healthcare challenge: the possible substitution – flu vs COVID.

Of the entire current industry that is dedicated to the manufacture, distribution, and marketing of vaccines, many do so with the flu vaccine. Therefore, in order to meet the demand due to COVID-19, a substitution effect could be produced, one for the other, and this without a doubt will have social repercussions (remember the importance of seasonal flu, where, more than the severity of the disease itself, its effect is based on the number of affected individuals). Furthermore, the possible concurrence during fall/winter of both diseases (COVID/flu) makes it logical not to reduce flu vaccination but to generalize it in at least certain demographic groups such as healthcare professionals and high-risk patients with poor prognoses if they contract COVID.

A decrease could also occur in the manufacturing of other very necessary vaccines in countries of low incomes (yellow fever, zika, malaria pilot, etc.).

d) Healthcare challenge: to whom.

This challenge, which we should also solve (if we want to be up-to-date on the tasks), is what E. Castejón denominates as the prisoner dilemma[7]: what should a country such as ours do with a low immunity rate[6], *"prioritize its entire population for its own benefit in the immediate term or, follow the correct strategy, which is to prioritize globally according to the vulnerability of different collectives and obtain a greater benefit on the medium term".* This will be one more of the problems to solve.

There are recent attempts of prioritization in the world by referents such as GAVI, the Vaccine Alliance, that has launched, after the recent *Global*

Vaccine Summit 2020 in London, an initiative named GAVI *COVAX Advanced Market Commitment* aimed at raising 2 billion dollars to supply vaccines using the criteria of necessity. This is added to the commitment of 750 million dollars from the United Kingdom, Germany, Canada, and the Gates Foundation for Astra Zeneca (developing the most advanced vaccine, AZD1222) to guarantee 300 million doses to distribute in very low-income countries. It is not clear, however, if data and technology will be shared with any manufacturer who is legally authorized to produce this vaccine. As well as the Alliance established between France, Germany, Italy, and the Netherlands to ensure equal access to vaccines for the European population, or the Strategy of the European Commission itself for COVID-19 vaccines.

e) Economic challenge: how much will it cost.

If we take into account the economic disaster that this serious healthcare crisis has entailed (besides the healthcare expenditure[8], a loss between 9-13% of the Gross Domestic Product, etc.) a new challenge that needs solving and foreseeing has arisen: How much will we be willing to pay for a new vaccine? i.e., what is our willingness to pay, because as a scarce good (at least at the beginning), it will be subjected to strong market competitions, as occurred with face masks and tests.

A related economic challenge is that the longer it takes to vaccinate the entire population, the economic activity will be more affected. As expressed in the Economic and Social Rebuilding Commission of the Congress of Deputies, healthcare has turned into the first line of defense for the country's economy[6]. Therefore, **although it is not foreseeable that funding will be spared to buy vaccines, it is particularly important to ensure that they are cost-effective. T**his requires a preemptive management task.

In this sense, it is worth mentioning that, if the research of these vaccines is being developed using, in many cases, public-private collaboration formulas, the private part should not be the only one allowed to patent the products derived from the advancement of knowledge.

Likewise, it is necessary to establish strategies that mark the relationship between providers of raw materials, the vaccine manufacturers, and the countries that ensure the accessibility of vaccines for the populations. In fact, in its COVID-19 Vaccine Strategy, the European Commission establishes the foundation for some protection of the populations, even starting at the stage of research for the manufacturing of COVID-19 vaccines. In the US, BARDA (Biomedical Advanced Research and Development Authority) has financed the development of the Johnson & Johnson vaccine with 1 billion dollars, the US government has committed 1.2 billion with Astra Zeneca for 300 million vaccines if it is finally approved. The United Kingdom has provided resources in advance to Astra Zeneca, that on the other hand has used public institutional funds and private foundation funds (Participation and Integration Centers).

It seems evident that there exists a sensation of a **threat before the possible market turmoil** that will allow a repeat, in this case with the vaccine distribution, of the recent pictures of shortage and

[6] Video Grupo de Trabajo Sanidad y Salud Pública (Video: Group of Healthcare Work and Public Health) - 06/12/2020. Beatriz González López-Valcarcel, https://app.congreso.es/v/14651398

appropriation of healthcare material. In a recent article in *The Lancet* the need for an agreed global policy was proposed to avoid commercial wars and exaggerated protectionism, but this requires overall global governance.

In order to answer these new challenges (or not as much), it is convenient to also answer the open questions that Vicente Ortún[9] pose:

- *¿Is Spain trusting in multinationals?*
- *¿How to promote local R&D to be able to develop and produce vaccines?*
- *¿What public investment would be needed?*
- *¿Specific for each technology according to the type of vaccine or generic?*

f) Autonomous and collaborative but sovereign manufacture challenge.

The solutions to these posed questions are of such relevance that we can no longer ignore the need for robust and well-cared R&D (also clinical) in our country.

Healthcare workers (from every area: hospital, primary care, public health) have adapted, reinvented themselves, and have been agile in incorporating new knowledge, protocols, and administrative procedures. Society has given a wonderful example of solidarity, understanding of the situation, and enduring with the decisions.

It is time then, for our representatives to be more proactive, abandon their short-sighted vision centered on the political or electoral impact of the situations, and extend their **vision to the medium and long term**, offering serious and consistent answers to these challenges.

The manufacturing capacity of companies and within Spanish territory is important in many sectors, and could be strengthened for medicines and healthcare products. Few would doubt that Spanish transnational companies of clothing (INDITEX) could have enough capacity to manufacture any type of face mask (or Personal Protective Equipment) that is requested by the authorities (homologated by the Department of Health itself) and at a very reasonable price, without brokers and without having to be in the international markets submitting to the supply and demand ups and downs, shortage, etc.

The same thing could happen with vaccines, maybe with a more intense work of **promoting industrial fabric**. Obtaining an effective vaccine and achieving its approval will only be the first step. Next is the enormous challenge of making billions of doses to distribute to the population, and here the public-private collaboration will be fundamental, where many **Spanish biotechnology companies** exist that are sufficiently prepared to manufacture and supply the very needed vaccine to the market. The Ministry or the Autonomous Communities themselves could be in charge of the distribution through their central services.

In any case, this stimulus for complete chains coupled to research, development, innovation, manufacture, and utilization means an authentic investment of scientific and economic fabric of high added value, and can act as a platform for new transnational initiatives in order to solve old and new clinical and public health challenges.

But this manufacturing challenge must be in line with the European and global manufacturing challenge and the challenge of fair accessibility of COVID-19 vaccines on a global scale, as in fact, the problem is a worldwide one and affects all countries.

Suppose global governance exists and each country reinforces its manufacturing capacity to the best of their abilities. In that case, there is hope of being able to cover the global need for vaccines. Thus, it is a good idea to repurpose the veterinary-vaccine manufacture plants in Spain, but it is insufficient. Therefore, we must define this as a strategic initiative, as it would not only guarantee the capacity to **meet our own needs, but we could also have an active role on a global scale.** Not to mention that we would also guarantee the manufacturing of vaccines as a product of our R&D, and together we would contribute to better our technological capacity and reinforce our productive fabric.

COLLABORATIVELY BUILDING IN EUROPE: THE EUROPEAN STRATEGY FOR THE COVID-19 VACCINE

It is worth describing briefly in the current report the **strategy that the European Commission** has established to ensure equal and adequate access to the COVID-19 vaccine in Europe. This strategy, that is aligned with the recommendations mentioned here, will have a fundamental influence in the implemented decisions and strategic actions in the Spain.

The Strategy has the following objectives:

- Guarantee the quality, safety, and effectiveness of the vaccines.
- Ensure quick access to the vaccines to the Member Countries and their populations, while leading the effort of global solidarity at the same time.
- Guarantee equal access to an affordable vaccine as soon as possible.

The European Union (EU) strategy is based on two pillars:

- **Ensure the manufacture** of vaccines in the EU and enough supply for its Member Countries according to the advanced purchasing agreements with the vaccine manufacturers through the Instrument of Support for Emergency. Aside from these agreements, additional funding and other forms of support can be provided.
- **Adapt the regulatory framework** of the EU to the current urgent situation and make use of the existing policy flexibility to accelerate the development, authorization, and availability of the vaccines, keeping at the same time the policies of quality, safety, and effectiveness of the vaccines.

Advanced purchasing agreements

To support companies in the rapid development and manufacture of a vaccine, the EU **will arrange agreements with different vaccine manufacturers of the Member Countries.** In exchange for the right to buy a certain number of vaccine doses within an established term, the Commission will finance part of the vaccine manufacturers' initial costs. This will take the form of advanced purchasing agreements. The provided funding will be considered an initial payment of the vaccines that the Member Countries will actually buy.

The funding will come from an important part of the Instrument of Support for Emergency of 2.7 billion euros. Additional support will also be available through loans from the European Investment Bank.

Funding criteria

By adopting the funding decision regarding which vaccines to support, the following non-comprehensive criteria will be taken into account: soundness of the scientific focus and technology used, delivery speed, cost, risk distribution, responsibility, coverage of the different technologies, early commitment with the EU regulators, global solidarity, and supply capacity through the development of the manufacturing capacity within the EU.

There is always the risk that the supported candidates fail during the clinical trials; therefore, what the EU does is **transfer some of the risks of the Financial Institutions to the public authorities** in exchange for ensuring the Member Countries equal and affordable access to a vaccine, in case it is available.

Regulation

The regulation processes will be flexible but will continue to be robust. Together with the Member Countries and the European Medicines Agency, the Commission will make maximum use of the existing flexibilities in the regulatory framework of the EU in order to accelerate the authorization and availability of effective COVID-19 vaccines. This includes an **accelerated procedure of authorization**, flexibility regarding labeling and packaging, and a proposal to establish temporal exceptions to specific law provisions about genetically modified organisms to accelerate the clinical trials for COVID-19 vaccines and medicines that contain genetically modified organisms.

Solidarity

The European Commission is committed to the principle of universal, equal, and affordable access to vaccines, especially for more vulnerable countries. It is willing to study, together with the international associates, the possibility that an important number of countries will agree on joining resources to reserve future vaccines from companies for both themselves and other countries of low and mid-income at the same time. The countries of high income could act as an inclusive group of international buyers, accelerating the development of safe and effective vaccines and maximizing access for everyone worldwide who needs them.

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