

## Review

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# Booster or additional vaccination doses in patients vaccinated against COVID-19

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## ABSTRACT

Several health organizations, mainly in Western countries, have recently authorized the use of a booster dose of the COVID-19 vaccine for patients previously vaccinated with mRNA vaccines, with criteria that do not always coincide.

The COVID Scientific Committee of the Illustrious College of Physicians of Madrid (ICOMEM) has received and asked several questions about this situation, to which the group has tried to give answers, after deliberation and consensus.

The efficacy of the vaccines administered so far is beyond doubt and they have managed to reduce, fundamentally, the severe forms of the disease. The duration of this protection is not well known, is different in different individuals and for different variants of the virus and is not easily predictable with laboratory tests.

Data on the real impact of a supplementary or "booster" dose in the scientific literature are scarce for the moment and its application in large populations such as those in the state of Israel may be associated with a decrease in the risk of new and severe episodes in the short observation period available.

We also lack sufficient data on the safety and potential adverse effects of these supplementary doses and we do not know the ideal time to administer them in different situations.

In this state of affairs, it seems prudent to administer supplemental doses to those exposed to a higher risk, such as immunocompromised individuals and the elderly. On the other hand, we consider that this is not the time to accelerate, on the spur of the moment, a massive administration of a third dose to other population groups that are less exposed and at lower risk, without waiting for adequate scientific information, which will undoubtedly arrive gradually.

We do not believe that this position is incompatible with the practical and ethical warnings made by the World Health Organization in this respect.

**Keywords:** COVID-19, SARS-CoV2, vaccines, additional doses, third dose, booster

## Dosis vacunales de recuerdo o adicionales en pacientes vacunados frente a COVID-19

## RESUMEN

Varias organizaciones sanitarias, fundamentalmente de países occidentales, han autorizado recientemente el uso de una dosis de refuerzo de la vacuna frente al COVID-19 para pacientes previamente vacunados con vacunas mRNA, con criterios no siempre coincidentes.

El Comité Científico de COVID, del Ilustre Colegio de Médicos de Madrid (ICOMEM) ha recibido y se ha formulado diversas preguntas sobre esta situación, a la que el grupo ha tratado de dar respuestas, tras deliberación y consenso.

La eficacia de las vacunas administradas hasta el momento está fuera de toda duda y han logrado disminuir, funda-

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mentalmente, las formas graves de enfermedad. La duración de esa protección no se conoce bien, es diferente en distintos individuos y para distintas variantes del virus y no es fácilmente predecible con pruebas de laboratorio.

Los datos sobre el impacto real de una dosis complementaria o "booster" en la literatura científica son escasos por el momento y su aplicación en grandes poblaciones como las del estado de Israel pueden asociarse a una disminución del riesgo de nuevos episodios y episodios graves en el corto periodo de observación disponible.

Carecemos también de datos suficientes sobre la seguridad y potenciales efectos adversos de estas dosis complementarias e ignoramos el momento idóneo de administrarlas en distintas situaciones.

En este estado de cosas, parece prudente administrar dosis complementarias a aquellos expuestos a un mayor riesgo, como pueden ser los individuos inmunodeprimidos y las personas mayores. Por el contrario, consideramos que no es este el momento de acelerar improvisadamente una administración masiva de una tercera dosis a otros grupos de población menos expuesta y de menor riesgo, sin esperar la adecuada información científica, que sin duda irá llegando paulatinamente.

No creemos que esta posición, sea incompatible con las advertencias prácticas y éticas que realiza la Organización Mundial de la Salud a este respecto.

**Palabras clave:** COVID-19, SARS-CoV2, vacunas, dosis adicionales, tercera dosis, booster

## INTRODUCTION

Several health organizations, mainly in Western countries, have recently authorized the use of a booster dose of COVID-19 vaccine for previously vaccinated patients, with criteria that do not always coincide. In this regard, the European Centre for Disease Prevention and Control (ECDC) on September 1st, 2021 [1], stresses the importance of distinguishing between booster doses and additional doses. The former (booster doses) are those administered to persons with normal immune systems, who have responded adequately to vaccination, to reestablish protection after it has decreased, and the latter (additional doses) refer to those administered to persons with weakened immune systems, who did not respond adequately to vaccination. For the sake of simplicity we will refer to both as complementary doses.

Spain, like other countries in its environment and situation, has authorized the use of complementary doses for certain segments of the population.

In contrast to this situation is the proposal of the World Health Organization (WHO), which advocates vaccinating millions of people around the world who have not yet had the option of receiving any dose, before proceeding to the massive use of complementary doses in economically more affluent countries.

The COVID Scientific Committee of the Illustrious College

of Physicians of Madrid (ICOMEM) has received and asked several questions about this situation, to which the group has tried to give answers, after deliberation and consensus.

The following pages contain not only the scientific evidence that we have managed to collect on the questions received immediately, but also the opinion of the group where evidence is scarce or non-existent at this time. It should be noted that the vast majority of the information available at this time is that of the Pfizer mRNA vaccine.

### 1.- IS THERE, AT THIS TIME, A LOSS IN THE DURATION OF PROTECTION MORE THAN SIX MONTHS AFTER VACCINATION?

The efficacy of the different vaccines has been demonstrated both in clinical trials and in post-vaccination observational studies. However, from the beginning there has been uncertainty about the duration of protection, particularly in those subjects in whom an adequate antibody response to the vaccines was not detected. In relation to this, the need for a supplementary dose has been raised, making a speculative balance between risks and benefits, in some population groups. Months after the start of vaccination in some countries, data are becoming available that attempt to answer these open questions.

In the 5-month blinded follow-up phase of trials conducted with both the mRNA-1273 (Moderna) and BNT162bm (Pfizer) vaccines, data have been reported showing an overall clinical effectiveness of over 95% for severe disease and around 65% for asymptomatic disease. Efficacy is lower for the 65-75 age group [2]. These data extend those reported in the clinical trial with the mRNA Pfizer's vaccine in which follow-up was limited to two months [3].

Already in real life, studies in large populations confirm the efficacy data found in clinical trials [4,5]. However, as observation time progresses, there are some differences related to age groups and in some cases to disease progression.

In the Glatman-Freedman study [4], carried out in Israel, efficacy data were obtained at 14, 21 and 28 days post-vaccination follow-up. The infection rates found were very low, with an estimated efficacy of over 95% for overall infection, symptomatic infection, hospitalization and death. Butt et al., in the United States, report an incidence of COVID at 3 months, in vaccinated population, of 0.1% compared to 6% in the unvaccinated population [5]. In Qatar, a study was conducted to determine the severity of disease in vaccinated versus unvaccinated patients, including 456 cases in each group, finding a marked reduction in severe disease in vaccinated patients, 10.1% vs. 46% [5]. Age is the main risk factor for severity which spikes in both groups above the age of 60 years.

The concern arises when the incidence is broken down by months post-vaccination. In a study published in July 2021 [6] 3 cohorts were analyzed corresponding to those vaccinated with mRNA-1273, with BNT162b2,3 and those not vaccinated, with a follow-up of 6 months. With both cohorts there

was a drop in disease prevention, which was 86% with mRNA-1273 and 76% with BNT162b2. In the analysis performed by months, the figures for disease prevention drop to 76% and 52% respectively, but the effectiveness in reducing hospitalization and severity is maintained. Although speculative, the authors point out that both the loss of effectiveness and the difference between vaccines could be related to the different variants, predominantly alpha at the beginning and delta in July. These results are similar to those published in October 2021 in *Lancet* in which the effectiveness of the BNT162b2 vaccine above the 5th month is 53% for delta variant infection and 67% for other variants, but remaining at around 90% for hospitalizations [7].

The loss of effectiveness, especially in the elderly, could be due to the different immune response. In a cohort study comparing the elderly and health care workers, both with a complete vaccination schedule, antibodies measured six months after immunization were significantly lower in the elderly than in the health care workers [8]. The possible impact of previous infection on the occurrence of disease in vaccinated patients has also been analyzed. A large retrospective study carried out in Israel comparing 3 cohorts (vaccinated with complete regimen, unvaccinated infected and infected and vaccinated) concludes that natural immunity confers greater duration and protection against reinfection by the delta variant so that those vaccinated and not previously infected have a 5.96-fold increased risk (95% CI, 4.85 to 7.33) of reinfection, compared with the two cohorts previously infected and even greater in the group over 60 years of age [9].

Finally, the results obtained with the application of a complementary dose of vaccine have recently been published, which would increase the effectiveness to 90%, although the results are only at 3 weeks [10].

In summary, with up to 6 months of follow-up after vaccination, although good protection against infection and complicated disease continues to be observed, data have emerged that point to loss of vaccine efficacy over time, with some discordance in relation to severity. Although with reservations, due to the scarce evidence available, and the need to replicate results, the need for a vaccine booster is being debated, at least in the most vulnerable population.

## **2.- ARE THERE RELIABLE LABORATORY MARKERS TO DETERMINE THE RISK OF INFECTION OR REINFECTION?**

At present, there is no agreement on which laboratory markers can ensure or predict the risk that a person who has been vaccinated against SARS-CoV-2 without having previously had COVID-19 will develop a SARS-CoV-2 infection. Nor is it possible to evaluate the risk of reinfection by SARS-CoV-2 in vaccinated individuals who have had COVID-19 prior to vaccination. In the latter, the immune response is higher since vaccination would reactivate the memory B cells, stimulating the humoral response and could generate greater protection [11].

IgG antibodies to N antigen (nucleocapsid) or S antigen (spicule) can now be routinely measured. Both can be positive in persons who have been naturally infected, whereas in those who have been vaccinated and have not been infected, only IgG antibodies to the S antigen will be positive [12]. The measurement of neutralizing antibodies or the cellular response to SARS-CoV-2 is not currently standard practice and is performed in research work or specific series of individuals. However, tests are being introduced that detect IgG against the RBD (Receptor Binding Domain) of the spike and whose result, due to its good correlation, could be used as a surrogate value for neutralizing antibodies determined with cell culture reference techniques [13].

In the analysis of gap infections in individuals vaccinated with both doses of Pfizer's vaccine and who had IgG-anti S antibody data, gap infections occurred more severely in those with lower antibody rates with no significant difference [14]. In addition, antibody levels were measured with two different techniques depending on the patient, and no common pattern could be observed when comparing the values of both techniques. In many of the patients, the values exceeded the cut-off values for positivity established by the manufacturer, resembling those that may be present in vaccinated individuals without subsequent infection. Cases of infection have also been reported in vaccinated individuals with adequate neutralizing antibody titers [15]. In cases of reinfection, what has been demonstrated is a rapid reduction in neutralizing antibody titers prior to reinfection. [16].

Although at present, at least in Spain, a specific type of variant (Delta variant) dominates, in the future it will be important to clarify not only which are the antibody titers that determine the specific level of protection of the individual but also whether these breakthrough infections are more related to the type of variant than to the quality of the previous immune response. What is easier to affirm, and on which there is unanimous agreement, is that the populations of immunosuppressed individuals, patients with immunosuppressive treatments, older and with worse immune response are those with the highest risk of reinfection or gap infection and in whom it will be necessary to establish priority plans for the administration of additional doses of vaccine or with vaccines directed at new variants.

## **3.- WHAT IS THE POSITION OF THE U.S. FDA AND CDC ON THE ADMINISTRATION OF ADDITIONAL AND BOOSTER DOSES OF VACCINE?**

Following an initial FDA proposal, on September 24, 2021, the Director of the CDC approved and adopted the recommendations of the ACIP (Advisory Committee on Immunization Practices) for the administration of booster doses of the Pfizer-BioNTech Covid-19 vaccine in persons selected by age, underlying disease or population considered at high risk of exposure and infection by COVID-19 due to their professional or institutional activity [17].

It will be administered to persons who meet the defined recommendations and who have previously received the complete vaccination with Pfizer-BioNTech Covid-19 vaccine. The additional booster dose will be with the same vaccine and at least 6 months after completion of the primary vaccination.

Recommendations to administer supplemental doses in the U.S. are as follows:

- Persons 65 years of age or older, and/or residents of long-stay facilities.
- Persons aged 50-64 years with underlying medical conditions.
- Persons aged 18-49 years with underlying medical pathology, in whom the risk-benefit of receiving the booster dose will be assessed on an individual basis.
- Persons aged 18-64 years with high risk of exposure and transmission of COVID-19, due to work or institutional circumstances may receive the "booster", individually assessing their risk-benefit of being vaccinated.

The CDC justifies the booster dose in the chosen groups because they were the first to be vaccinated at the beginning of the vaccination campaigns and can now benefit from additional protection. Given that the Delta strain is still circulating in the United States, the booster would help the most vulnerable population by protecting them against severe COVID-19 and its complications, which are more frequent in these groups. The CDC is committed to continuing to monitor the safety and effectiveness of the COVID-19 vaccines so that new booster recommendations can be added in the coming weeks for other population groups and for those who have previously received the other vaccines.

CDC Director Dr. Walensky acknowledges the great challenge of making high-impact decisions when analyzing very complex situations with insufficient and sometimes poor-quality data to make very specific recommendations. In a pandemic, the greatest benefit is obtained if action is taken in anticipation of its evolution despite the uncertainty with which we have to work.

These are the first steps in the indications of the "booster", which will be completed in the near future. It is important not to forget and to insist on the need to achieve greater vaccination coverage with complete primary vaccination in the population not yet vaccinated, both in the United States and in the rest of the world.

#### 4.- WHAT IS THE EUROPEAN POSITION, PARTICULARLY THAT OF THE ECDC?

The ECDC, bearing in mind that the primary objective of the vaccination strategy is to prevent severe cases of COVID19, was in favor of considering the administration of a supplemental vaccine dose, as an extension of the vaccination series, to persons who may experience a limited response to the primary COVID-19 vaccination series, such as some categories of immunocompromised individuals (e.g., solid organ transplant

recipients) [18]. In addition, they advised considering, as a precautionary measure, the possibility of providing a booster dose for the elderly and frail, particularly those living in closed environments (socio-health centers) [18]. Regarding the need for the administration of booster doses of vaccines to fully vaccinated individuals in the general population, they considered that this was not an urgent decision, as the evidence available at this time regarding "real world" vaccine effectiveness and duration of protection shows that all licensed vaccines in the EU are highly protective against COVID-19-related hospitalization, severe illness and death. In this situation, they noted that the priority should be to vaccinate all those who have not yet completed their recommended vaccination course [18].

In a statement dated September 2, 2021 [1], the EMA aligned itself with the positioning of the ECDC technical report. On October 4, 2021, the EMA's Committee for Medicinal Products for Human Use (CHMP), following an accelerated evaluation of the results of studies on the efficacy of administering additional doses of mRNA vaccines [19,20], both in immunocompromised adults and in vaccinated individuals with healthy immune systems, reached the following conclusions:

Administer an additional dose of the COVID-19 vaccines Comirnaty (BioNTech / Pfizer) and Spikevax (Moderna) to people with severely weakened immune systems at least 28 days after the second dose. The recommendation comes after studies showed that an additional dose of these vaccines increased the ability to produce antibodies against the virus that causes COVID-19 in organ transplant patients with weakened immune systems.

a) Consider a booster dose of COVID-19 Comirnaty vaccine (BioNTech / Pfizer) at least 6 months after the second dose for persons 18 years of age or older with normal immune systems. The data evaluated show an increase in antibody levels when a booster dose is administered approximately 6 months after the second dose in persons aged 18 to 55 years.

b) At the national level, public health agencies in EU states may issue official recommendations on the use of booster doses, taking into account emerging efficacy data and limited safety data.

Currently, the Committee for Medicinal Products for Human Use is evaluating data to support a booster dose of Spikevax (Moderna) [20].

#### 5.- WHAT DOES THE WHO RECOMMEND AT THIS TIME REGARDING THE ADMINISTRATION OF BOOSTER DOSES TO PEOPLE WHO HAVE ALREADY BEEN VACCINATED?

In a press release dated August 10, 2021 [21], WHO stated that "In the context of current global vaccine supply constraints, the administration of booster doses will exacerbate inequities by increasing demand and consuming a scarce supply, while priority populations in some countries, or subnational settings, have not yet received a primary vaccination series. For the time being, the goal remains to increase global vacci-



nation coverage with the primary series (one or two doses for current vaccines)."

Furthermore, WHO adds that "the introduction of supplementary doses should be strongly evidence-based and targeted to the population groups most in need. The rationale for booster doses should be guided by evidence of decreased vaccine efficacy, in particular decreased protection against severe disease in the general population or in high-risk populations, or due to a coronavirus variant of concern. To date, evidence remains limited and inconclusive on the widespread need for booster doses following a primary vaccination series. WHO is carefully monitoring the situation and will continue to work closely with countries to obtain the necessary data for policy recommendations.

On September 11, 2021, Katherine O'Brien, director of WHO's Department of Immunization, Vaccines and Biological Medicines, ratifies this same position in a statement on the Organization's own website [22].

Finally, Mike Ryan, Executive Director of WHO's Health Emergencies Programme, during a live question and answer session broadcast on September 22, 2021 on the Organization's social media channels [23] said what WHO is advocating is that booster doses in the general population, who have had broad access to vaccines and have already been vaccinated, are not the best option at this time. However, Ryan indicated that WHO is not against giving a third dose to people who may have significant benefit, such as the elderly, the medically vulnerable, and anyone who needs an immune system booster after a full regimen of COVID-19 vaccines. Dr. Ryan understands that this is compatible with giving the primary vaccine series to everyone in the world who needs it because there is enough vaccine.

## 6.- WHAT IS THE RECOMMENDATION AND EXPECTED EFFICACY OF COMPLEMENTARY VACCINE DOSES IN IMMUNOSUPPRESSED PATIENTS?

It seems to be demonstrated that, in general, COVID-19 is more severe, more prolonged, with a greater possibility of maintaining a high viral load for a longer period of time and, therefore, with a greater capacity for transmission in the immunocompromised population. [24-28].

Likewise, the humoral response to vaccines and in particular to those available against COVID-19, is lower in immunocompromised patients, both in primary deficiencies and in those associated with infectious and autoimmune diseases. [14, 29-31], as well as in oncology patients and notably more evident in certain tumor and treatment subgroups. [14, 29, 32, 33].

The "booster" effect of the antibody level response with the second dose of the vaccine and with vaccination after the infection has passed is also certain.

Due to this foreseeable immunogenic potentiation of additional doses to the standard vaccination, the CDC and then other global health agencies were ahead of the evidence and

recommended in the summer of 2021 the third dose for the population that had had a worse response to the vaccine (immunosuppressed) and have recently ratified and have proposed the extension to other risk groups and even to the general population from the 6th month after vaccination.

There were not enough studies of extra doses when the first recommendations were made and we still have little evidence of increased efficacy in the real world, given the very short time elapsed since the beginning of the administration of "third doses" and the obtaining of evolutionary data that can be analyzed beyond the titration of antibodies.

It occurs in both the general population [10], as in the aforementioned immunosuppressed groups.

**Solid organ transplant recipients.** The first information demonstrating the potentiating effect of the third dose comes from series of patients with solid organ transplants [34-36] and whose review concludes that:

- The 3rd dose of mRNA vaccine against COVID-19 in solid organ transplant recipients (with a high percentage of renal transplants), improves immunogenicity, reaching neutralizing antibody titers in half of the patients who did not have them after the second dose.

- In some studies the levels achieved would correspond to neutralizing capacity against the virus in in vitro studies.

- The results obtained on the activation of cellular immunity do not allow a correlation with the clinical efficacy of this response.

- The existing series do not report cases of COVID-19 after the 3rd dose, but the follow-up is too short to be able to verify clinical efficacy.

- In solid organ transplant recipients who receive a 3rd dose of vaccine, there are no serious adverse side effects.

- Objective signs of organ rejection after the 3rd dose have only been reported in one heart transplant recipient, with no organ failure in the follow-up up to the date of publication.

- The presence of neutralizing antibodies, even at low doses, after the 2nd dose, predicts an enhanced response after the 3rd dose.

- The more immunosuppressive drugs, the less response from the 3rd dose.

- Corticosteroids, tacrolimus, mycophenolate and belatacept, decrease the response to the 3rd dose and more in combination.

- Slightly more than half of solid organ transplanted patients do not seroconvert after the 3rd dose of vaccine.

**Renal transplant and dialysis patients.** France authorized in April 2021, the additional doses for renal patients (transplanted or on dialysis), their series were brought forward to add knowledge of the response in this group [37-39] and their conclusions are:

- The third dose in renal transplant patients and in dia-

lyzed patients, increases the immunogenic response, although more than 50% of complete vaccine non-responders remain non-seroconverted.

- The higher the immunosuppressive treatment load, the lower the humoral response. In dialyzed patients it is significant in those receiving immunosuppressants for myeloma or amyloidosis.

- There are no serious adverse side effects.

**Other cohorts of patients with immunosuppression and booster doses.** There are no analyzable series, for the moment, of 3rd dose or additional dose to the standard vaccine in patients under immunosuppressive treatment of patients with autoimmune diseases or other types of oncologic patients (solid organ or hematologic) different to those already mentioned. Neither in patients under immunotherapy, a group in which the safety of the vaccine was especially valued due to initial suspicions of the possibility of potentiation of adverse effects.

Only the sum of particular actions in this group are available without alarm bells ringing in the updated literature [40, 41].

## 7.- WHAT IS KNOWN ABOUT THE INDICATION AND EFFICACY OF BOOSTER DOSES OF NON-mRNA VACCINES?

Existing information on the efficacy of additional doses of vaccines other than mRNA vaccines is still very scarce. The available data refer mainly to the Johnson & Johnson vaccine. Two studies, not yet published, have been carried out with this vaccine. The first phase 3 study (ENSEMBLE-2) is a double-blind, placebo-controlled study evaluating the safety and efficacy of a two-dose regimen of the vaccine administered at an interval of 56 days to adults over 18 years of age at high risk of severe COVID-19 [42, 43]. After a median follow-up of 36 days, a second dose was shown to achieve 100% (CI, 33%-100%) protection against severe/critical COVID-19 at least 14 days after the final vaccination, 76% (55%-88%) against symptomatic COVID-19 globally, and 94% (58%-100%) against symptomatic COVID-19 in the United States. The second dose of vaccine was generally well tolerated [44]. In the second study, the second dose was administered 6 months after the first dose. In this case, a 9-fold increase in antibody levels was observed at 1 week after administration and increased up to 12-fold at 4 weeks. By comparison, when the second dose was administered two months after the first dose, antibody levels had risen 4 to 6-fold [45]. The data are not yet published and approval for the administration of the booster dose of this vaccine has not yet been received.

## 8.- IS THERE REALLY A CONFLICT IN THE USE OF BOOSTER DOSES OF VACCINES IN HIGHLY DEVELOPED NATIONS VERSUS LESS FAVORED ONES?

In view of the dilemma that could arise regarding the administration of a supplementary dose to fully vaccinated

patients in certain countries versus achieving a complete vaccination schedule in the unvaccinated population worldwide, a certain debate has been established [46]. Most institutional positions recommend the administration of the booster dose in certain vulnerable populations (immunocompromised, elderly, nursing homes) but not to the entire population in a comprehensive manner, for which there would not be as much evidence or urgency to do so. Regardless of the relevance of a booster campaign, this situation may generate an ethical debate, balancing the national and international responsibilities of the states [47]. The WHO already states that this situation may increase the inequality of access to vaccines in the different countries of the world, where there are still countries such as the African continent where the complete vaccination rate is around 3%. Thus, although there are cosmopolitan positions that consider a global strategy to defeat the pandemic (reduction of transmission and possibility of new variants) to be pragmatic, the reality is that countries have adopted national policy strategies in the absence of a consensus. This nationalism as a strategy would be based on the investment of local resources and public funds in vaccine research and the concept of protecting their population as much as possible. The question is whether the booster dose in certain countries is really an opportunity cost for the poorest countries or whether there are other barriers beyond vaccine shortages that prevent vaccines from reaching the unvaccinated population [46]. Thus, increasing global access to vaccination should be a priority for all states, while seeking to improve the evidence of the effectiveness of a booster dose in certain populations.

Perhaps it is not a matter of choosing between one option or another, but rather of seeking alternatives that favor global vaccination aimed at solving certain issues such as the loss of the cold chain, the possibility of heterologous vaccination or local production together with compliance with the established distribution agreements through programs such as COVAX, which have not met their expectations at present [48]. The objective would be to reduce inequity in the poorest countries, while maintaining the national commitment of the richest countries in the development of vaccines and promoting their distribution in an international framework.

## 9.- WHAT IS THE FUTURE OF VACCINATION AS A COVID-19 PREVENTION TOOL? WILL PERIODIC VACCINATION WITH THE COVID VACCINE BE NECESSARY?

The need for repeat supplemental doses of the COVID vaccine depends on whether the pandemic evolves into an endemic form of infection, such as influenza. This is the future scenario that is considered most likely, both because of the evolution of previous pandemics and because of the existence of many conditions that make it easier for the virus not to be eradicated. Even with the best progress in vaccination, it seems likely that reservoirs of SARS-CoV-2 may remain in both unvaccinated populations and animals, as is the case with other coronaviruses. The ability of SARS-CoV-2 to mutate makes it possible for more

transmissible and vaccine-resistant variants to emerge, making it possible that a multivalent vaccine covering several SARS-CoV-2 strains may be required in the future. The possibility of an endemic infection will also depend on a possible waning of acquired immunity against the virus and its variants, something we will only know in the long term. If this is the case, the time when epidemic peaks are expected to occur will coincide with the influenza season, as the cold conditions less time outdoors and more personal contact. This makes it possible for both vaccination campaigns to coincide [49–51].

## 10.- WHAT IS THE POSITION OF THE COVID SCIENTIFIC COMMITTEE OF ICOMEM ON THE ISSUE OF THE ADMINISTRATION OF SUPPLEMENTARY DOSES OF VACCINES TO THE SPANISH POPULATION?

The efficacy of the vaccines administered to date is beyond doubt and they have managed to reduce, fundamentally, severe forms of disease, those requiring hospital admission, ICU admissions and deaths due to COVID-19. However, the vaccines administered to date do not totally prevent the acquisition of viral infection and transmission to third parties. The duration of this protection is not well known and it happens to be different in different individuals and for different variants of the virus. In any case, at present, protection cannot be firmly deduced from tests such as the determination of antibody titers or other immunological determinations.

There are breakthrough infections in vaccinees and reinfections in patients who have already had a primary episode of COVID, some of them severe and fatal.

Data on the real impact of a complementary or "booster" dose are scarce in the scientific literature. An additional dose may induce the appearance of antibodies for example in up to 50% of solid organ transplant patients who had not responded adequately to previous vaccination and booster doses in large populations such as those in the state of Israel may be associated with a decreased risk of new and severe episodes in the short observation period available.

On the other hand, data on the safety and potential adverse effects in vaccinated individuals when exposed to a new dose are limited and even less on the ideal timing of administration in different situations.

In this state of affairs, it seems prudent to administer supplementary doses to those exposed to a higher risk, such as immunocompromised individuals and the elderly, particularly among those most at risk because they live in health care facilities.

On the contrary, we consider that this is not the time to improvise a massive administration of a third dose to other population groups less exposed and at lower risk, without waiting for adequate scientific information, which will undoubtedly arrive gradually.

We do not believe that this position is incompatible with the practical and ethical warnings issued by the World Health Organization. The arrival of vaccines in the world with a low prevalence of vaccinated people should be compatible with the additional doses needed in countries of the economically richer world. It should not be forgotten that the arrival of vaccines to millions of disadvantaged human beings who have not received them so far depends not only on the will or generosity of the nations that possess them. We are aware that there are political, economic, logistical and technical factors that can make the best will to help and solidarity of some human beings with others fail.

## CONCLUSIONS

1.- More than six months after the application of the first vaccines against COVID, a high level of protection is maintained, particularly against severe forms of the disease.

2.- Vaccine failures are detected, however, particularly in patients with severe immunosuppression such as solid organ transplant recipients.

3.- Current routine laboratory markers do not allow definitive detection of the most exposed vaccinated population.

4.- Both North American and European health authorities admit, in the absence of very solid data on their efficacy, the administration of complementary doses for the most vulnerable population, the definition of these populations being somewhat diffuse and rapidly changing.

5.- Third doses are currently approved or in the process of being approved for at-risk populations, including those selected on the simple criterion of being over a certain age.

6.- The WHO, while not frankly opposing this trend, points to the need to vaccinate first those populations of the world that have not yet had access to the vaccine on a massive scale.

7.- There are very few studies that evaluate the potential adverse effects of receiving a complementary dose of vaccine in large segments of the population, but some health authorities point to the need to "go ahead" of the pandemic and increase, accepting the uncertainty, the degree of immunization of the population.

9.- This Scientific Committee of COVID, of ICOMEM, supports the attitude of administering a third dose (complementary dose) to particularly vulnerable population groups but wishes to express the necessary caution when extending this recommendation indiscriminately to large population groups until more studies on both the efficacy and safety of this medical practice are available.

10.- We consider that getting the necessary vaccines to the world that needs them is not only a decision of solidarity, but that it runs up against logistical and political problems that cannot always be solved from a purely technical point of view.

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None to declare

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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