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Insights for COVID-19 in 2023

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ABSTRACT

Predictions for a near end of the pandemic by the World Health Organization should be interpreted with caution. Current evidence indicates that the efficacy of a fourth dose of classical mRNA vaccines (BT162b2 or mRNA-1273) is low and short-lived in preventing SARS-CoV-2 infection in its predominant variant (Omicron). However, its efficacy is high against severe symptomatic infection, hospitalization and death. The new vaccines being introduced are bivalent and active against the Omicron variants. Potential new vaccines to be introduced in the coming year include a vaccine based on a recombinant protein that emulates the receptor binding domain of the Spike protein under development by the Spanish company Hipra, as well as vaccines for nasal or oral administration. Available information suggests that vaccines against COVID-19 can be administered in association with influenza vaccination without particular complications. New drugs against COVID-19, both antiviral and anti-inflammatory, are under investigation, but this does not seem to be the case with monoclonal antibodies. The indication to use masks in some circumstances will be maintained next year in view of the accumulation of scientific data on their efficacy. Finally, the long COVID or Post-COVID syndrome may continue to affect a very high proportion of patients who have had the disease, requiring combined diagnostic and therapeutic resources.

Keywords: COVID-19, SARS-CoV2, Vaccination, bivalent vaccines, nasal and oral vaccines, investigational drugs against SARS-CoV2, use of masks, Long-term COVID

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Perspectivas de COVID-19 para 2023

RESUMEN

Las predicciones para un próximo fin de la pandemia de la Organización Mundial de la Salud deben interpretarse con precaución. La evidencia actual indica que la eficacia de una cuarta dosis de las vacunas clásicas ARNm (BNT162b2 o mRNA-1273) es baja y de corta duración para prevenir la infección de SARS-CoV-2 en su variante predominante (Omicron). No obstante, su eficacia es alta frente a la infección sintomática grave, hospitalización y muerte. Las nuevas vacunas que están siendo introducidas son bivalentes y activas frente a las variantes Omicron. Entre las potenciales nuevas vacunas que se introducirán en el próximo año, se encuentra una vacuna basada en una proteína recombinante que emula el dominio de unión al receptor de la proteína Spike en desarrollo por la compañía española Hipra, así como vacunas de administración nasal u oral. La información disponible apunta a que las vacunas frente al COVID-19 podrán administrarse asociadas a la vacunación antigripal sin particulares complicaciones. Se encuentran en investigación nuevos fármacos frente a COVID-19 tanto antivirales como anti-inflamatorios pero no parece ocurrir lo mismo con los anticuerpos monoclonales. La indicación de utilizar mascarillas en algunas circunstancias se mantendrá el próximo año en vista a la acumulación de datos científicos sobre su eficacia. Finalmente, el síndrome del COVID largo o Post-COVID puede que siga afectando a una proporción muy elevada de los pacientes que sufrieron la enfermedad, requiriendo recursos diagnósticos y terapéuticos combinados.

Palabras clave: COVID-19, SARS-CoV2, Vacunación, vacunas bivalentes, vacunas nasales y orales, fármacos en investigación frente a SARS-CoV2, uso de mascarillas, COVID-largo

INTRODUCTION

At present, many uncertainties persist about the situation and, particularly, about the future of the COVID-19 pandemic. Looking ahead to the year 2023, the most important uncertainties are related to the future of this infection and this disease. We do not know very well what can be expected from the booster vaccination of the population already vaccinated with a fourth dose of the classical vaccines, nor do we know much about the advantages and potential risks of re-vaccination with bivalent vaccines that include the most recent variants in their spectrum.

There are other uncertainties related to the treatment of the disease, the use of masks and post-COVID syndrome. Firstly, most experts do not know what to expect in terms of new drugs against COVID-19 in the coming year. Secondly, part of the population is already wandering around without masks while another persists in their use and the recommendations of the health authorities are, to say the least, ambiguous in the balance between scientific evidence and political expediency. Finally, time has not yet fully clarified what can be expected from the so-called post-COVID syndrome or long COVID, its clinical reality, its therapeutic needs and the healthcare resources it will require during the coming year.

With these doubts "in mind", the Scientific Committee of COVID-19 and Emerging Pathogens of the Illustrious College of Physicians of Madrid (ICOMEM) has formulated a series of specific questions on the aforementioned topics. The present work gathers the result of these deliberations, in which the best information found in the literature at the time of consultation has been included, to which our opinion has been added when the level of evidence was not ideal.

IS THE WHO'S PREDICTION OF A NEAR END OF THE PANDEMIC REALISTIC?

In a statement in mid-September 2022, the Director General of the World Health Organization (WHO) compared the race to control the COVID-19 pandemic to a marathon and said, "Last week's death toll from the pandemic was the lowest since March 2020. We are in a position to win, but now is the worst time to stop running, it's time to accelerate. We already see the finish line." Like all policy makers, Tedros Ghebreyesus combined evidence, such as the number of deaths, with calls for action in the various countries; and to reinforce the message in the war against the coronavirus, he came to say, like a good strategist, that victory is possible and close at hand [1]. Probably everything he said is true, although WHO senior epidemiologist Maria van Kerkhove also emphasized that "we expect future waves of infections, potentially at different times around the world caused by Omicron subvariants or even different variants of concern."

It is true that never before in the pandemic have we been so prepared to control it, since the population has a high degree of protection against serious infection, derived both from vaccination and from the high frequency of acquired infections (often repeated). In addition, vaccination boosters (against the original Wuhan variant and Omicron) are already being massively administered to the most vulnerable (over 60 years of age or with severe chronic pathologies), which will strengthen protection. On the other hand, the virus will probably continue to circulate, because immunity or vaccines do not substantially reduce the risk of infection; although this will lead to a certain increase in the number of severe cases during periods of high transmission, with the consequent overload of the health system, it should not produce a proportional increase in hospitalizations or a dramatic increase in deaths and will contribute to maintaining a high level of community protection. A different issue is the lack of knowledge about the dynamics of interaction between coronavirus and other respiratory viruses (e.g. influenza), making it difficult to anticipate the total number of respiratory infections, as well as their health impact. These perspectives, quite positive, could change due to an important mutation(s) in the virus that would increase its virulence and/or immune escape. There is nothing concrete to suggest that this will happen, but it is not possible to rule it out with this virus either. However, the virus is not intelligent and does not do what it wants; only what we let it do. Therefore, the sensible thing to do is to continue working to control its damage, by monitoring the emergence of new variants of potential relevance, vaccine boosters and, if necessary, the temporary reactivation of some control measures (e.g. use of masks, ...). We share the optimistic message of the WHO, we trust in a favorable evolution of the pandemic, but we will continue to be alert and to work "to reach the goal", as it may be close.

WHAT IS THE EVIDENCE OF PROTECTION OF NEW DOSES OF ANTI-COVID-19 VACCINES WITH CLASSIC VACCINES?

Current evidence indicates that the efficacy of a fourth dose of classical mRNA vaccines (BT162b2 or mRNA-1273) is low and short-lived in preventing SARS-CoV-2 infection in its predominant variant (Omicron). Despite this, it is highly effective (about 80%) and long-lasting against severe symptomatic infection, hospitalization and death.

The vaccines achieved to curb the SARS-CoV-2 pandemic have been the most decisive achievement in modifying very favorably the severity of the pandemic, mainly for the large risk group of elderly patients [2,3]. Thus, the advent of the vaccines provided, against pre-Omicron variants, about 87% protection against hospitalization and death from severe COVID-19 disease after a two-dose schedule of BNT162b2 (Pfizer), mRNA-1273 (Moderna, or ChAdOx1-S (Oxford/Astrazeneca) [3]. Subsequently, the drop in immunity showed the need for a booster dose (third dose), after six months of complete vaccination, with any of the commonly used mRNA-based vaccines, thus significantly reducing the chances of infection or reinfection with SARS-CoV2. However, the emergence of SARS-CoV-2 variant B.1.1.529 (Omicron) changed the pandemic landscape once again. The protective capacity of vac-

cination against infection has been decreasing even lineage by lineage [4]. Omicron has infected people who have complied with primary vaccination doses, who have boosted their immunity with booster doses of appropriate immunogens, and even who have had the disease before or after these compliances [4-6]. However, their efficacy in reducing mortality and severe disease rates has been maintained with little loss, both for the original strains for which they were designed and for successive strains (with notable antigenic variation in neutralization targets). The sixth and seventh waves have shown similar incidences of infection in those over 60 years of age as in the first waves, especially in the elderly and frail population, both in the community and in social and healthcare centers [7], so the clamor for booster vaccines has once again reached its peak [8]. Observational studies from Israel, during a predominant Omicron period, revealed that a fourth dose of BNT162b2 in persons over 60 years of age produced low protection in preventing infection of short and uncertain duration (between 3 to 8 weeks) but with lower rates of severe disease, (75% effective against COVID-19 mortality compared to the third dose) [9-11]. In all these studies, subjects under 80 years of age were included for the most part and residents of long-stay centers, who represented a very small percentage of the sample, were excluded. Subsequently, therefore, two large retrospective population-based cohort studies conducted in social and health centers for the elderly showed similar results with both mRNA-1273 and BNT162b2 (up to 80% reduction in hospitalization and mortality due to COVID-19 from a fourth dose) [11,12]. These results have led some countries, including Spain, to include this fourth dose in this population group.

Fortunately, successive doses have not led to an increase in adverse reactions. There was no increase in the local reaction to the inoculation or in the systemic symptoms associated with the immediate days following the dose [13]. Myocarditis as a side effect of RNA-mRNA vaccines, more associated with adolescents and young people, is not a drawback. In fact, there seems to be a lower incidence than in the primary vaccination series [14]. It is confirmed that the initial fear of generating antibodies that would block an effective neutralizing response (potentiation of the disease with the vaccine), does not occur with booster doses, as it has not occurred in the initial vaccination.

Therefore, the possible indication for classical vaccines should be reduced to groups at higher risk of mortality when bivalent vaccines are not available. In our opinion, a fourth dose with classical vaccines in the general population would provide a minor benefit until vaccines including the new Omicron variants become available.

WHAT VARIANTS WILL THE NEW VACCINES INCLUDE, AND WHEN WILL THEY BE AVAILABLE?

The vaccination strategy against SARS-CoV-2 infection until the summer of 2022 in Spain has been based on the use of prepared vaccines based on the original Wuhan strain. Essentially, the Pfizer and Moderna vaccines have been used, both based on messenger RNA technology for the expression of the SARS-CoV-2 spicule (S) protein, and, to a lesser extent, the AstraZeneca vaccine (AZD1222), based on a nonreplicating recombinant viral vector (adenovirus) expressing the S protein. In all cases, the immunogenic antigen of these vaccines was identical to that of the original Wuhan strain of SARS-CoV-2 [15]. As mentioned above, the strategy followed to date has been shown to be effective against severe disease, hospitalization and mortality, but not against reinfection.

The rapid emergence of successive variants of concern, with a large number of mutations (Omicron variants have more than 50 mutations in their spicule), has led to the development of a different strategy with vaccines based on these new variants [16-18]. This is mainly due to the loss of efficacy of classical vaccines against infection by successive new variants and the need for continuous booster doses to maintain acceptable levels of neutralizing antibodies to protect against infection and successive reinfections [19]. It is evident that re-vaccination with vaccines prepared against the original strain does not seem to be a wise strategy, especially in a country with high vaccination and reinfection rates. In addition, data have been published indicating that the possible use of vaccines with different antigens does not diminish efficacy and favors the immune response, a situation endorsed by both the EMA and the FDA in the approval of new vaccines [20-22].

The accumulated experience with the use of mRNA vaccines and the relative ease of their manufacture, including that of the new variants, the few doubts about their safety and the robust pharmacovigilance system, as reported by the vaccine expert committees, suggest a dual strategy: vaccination and revaccination with a new vaccine whose composition would be immunogenic against the original SARS-CoV-2 strain and also against the most recent variants. This would provide adequate coverage against the emergence of possible new variants close to the original Wuhan variant, as occurred with Omicron, which is closer to it than to its predecessor in time, the Delta variant, and the eventual emergence of variants or subvariants of Omicron that dominate the current (October 2022) panorama of infections and reinfections [17,18,23].

Therefore, the EMA and the FDA have approved the so-called bivalent vaccines adapted to the new variants [20-22]. They are mRNA vaccines against the original Wuhan strain and the Omicron BA.1 variant (Pfizer and Moderna) and also against the original strain and the Omicron BA.4/BA.5 variant. All of them are included in the recommendations for vaccination against COVID-19 in Spain in the early fall of 2022 [24].

For the moment, regulatory agencies require safety studies of vaccines against new variants of SARS-CoV-2 and, although they have an accelerated evaluation process, it is possible that, in the future and given the need to create new vaccines against emerging variants, this procedure will be relaxed and follow a model similar to that of influenza vaccines. The latter are clearly safe, with fewer safety studies required for their commercialization. However, this situation does not exempt the performance of follow-up studies in accordance with pharmacovigilance standards.

WHAT WILL BE THE FUTURE ROLE OF HIPRA'S SPANISH VACCINE?

The European Medicines Agency (EMA) is evaluating the Spanish Hipra vaccine against COVID-19, as a booster dose for those who have received the primary vaccination regimen with a different vaccine.

The Hipra vaccine is based on a recombinant protein that emulates the receptor binding domain (RBD) of the Spike (S) protein of the Alpha and Beta variants of the SARS-CoV-2 virus. This antigen is accompanied by an adjuvant that enhances the immune response.

Clinical trials in adults compare the immune response to Hipra's vaccine, through the level of antibodies against SARS-CoV-2, with that observed with Pfizer's messenger RNA vaccine. A total of ten Spanish hospitals are currently participating in a clinical trial to evaluate the efficacy of Hipra's COVID-19 vaccine, as a fourth dose, in subjects previously vaccinated with three doses of the Comirnaty vaccine (Pfizer), provided that the last dose was administered within the previous 6-12 months and that they had not had COVID-19. A 30-month follow-up has been established for immune response and safety. The most common adverse effects have been pain in the area of inoculation, headache or fatigue, which have disappeared in the following days and have not prevented them at any time from leading a normal life [25].

Preliminary data show a good immune response against beta and Omicron variants of SARS-CoV-2. A recent study shows a strong immune response against all variants studied (Wuhan, Beta, Delta and Omicron (BA.1) at 14 and 98 days, being these increases statistically superior to those obtained with the booster dose with the Pfizer-BioNTech vaccine at 98 days against Beta, Delta and Omicron (BA.1) variants, and at 14 days against Beta and Omicron (BA.1) variants) [26,27]. The biotech pharmaceutical company Hipra has shown in recent analyses that its vaccine also confers protection against the Omicron BA.2 and BA.4/BA.5 subvariants, as evidenced by an increase in neutralizing antibodies against the BA.2 and BA.4/BA.5 subvariants of Omicron. These data would indicate a more sustained response over time, suggesting a more durable and effective protection against the new circulating variants.

The Spanish Hipra vaccine has demonstrated a good safety profile. Among the advantages of this vaccine is that it can be stored at 2 to 8 ºC, which would facilitate its logistics and distribution. It is currently ready for intramuscular (IM) use and clinical trials are underway.

WHAT ROLE CAN NASAL VACCINES AGAINST COVID-19 PLAY?

COVID-19 vaccines administered IM have been shown to effectively reduce disease severity and, to a lesser extent, infection or transmission [28,29], as they allow the replication of SARS-CoV-2 in the upper respiratory tract of vaccinated persons and the elimination and transmission of the virus [30,31]. Moreover, they do not induce a neutralizing IgA antibody titer effectively in the mucosa of the upper respiratory tract, which is necessary to achieve sterilizing immunity against SARS-CoV-2.

In contrast, mucosal vaccines, administered orally (OV) or intranasally (IN), can provide a more rapid and intense local antiviral immune response in the mucosa of the upper and lower respiratory tract, mediated primarily by neutralizing IgA secretion [30,32]. Activation of mucosal protective immunity offers the possibility of inhibiting viral multiplication and decreasing virus excretion through the respiratory tract mucosa. In this way it acts as a first-line barrier to virus entry, as well as against spread to the lungs. It can also prevent the transmission and spread of SARS-CoV-2, contributing to achieve herd immunity in the population [30]. In addition, these mucosal vaccines induce a potent systemic immune response against COVID-19 [33].

Inhaled (IN) mucosal vaccines appear to have great potential for preventing highly contagious respiratory viral infections such as measles, influenza and COVID-19 [34]. There are precedents with vaccines administered by OV or IN that have demonstrated their effectiveness in the clinical management of gastrointestinal and respiratory tract infections (poliovirus, rotavirus, adenovirus, influenza) [30,34]. Currently, there is evidence, in experimental animal models, in favor of the ability, mainly of IN mucosal vaccines, to induce sterilizing immunity against COVID-19 [31,32,35]. However, so far the evidence in humans is limited [31].

More than 100 OV or IN vaccines against COVID-19 are currently under development worldwide, and at least 20 prototypes are already being tested in humans [35,36]. In September 2022, two adenovirus-vectored mucosal vaccines against COVID-19 have been approved for human use. In both cases they have passed Phase III clinical trials, although the results have not yet been published [36]. In China, an IN vaccine has been approved as a booster after IM primary immunization, both with the same composition. This booster has been shown to be safer and persistently more immunogenic than the IM booster, although the immune response decreases over time [37]. In India, a vaccine administered by nasal drops has been approved for primary immunization in humans [28,32]. Among these new IN vaccines is a Spanish vaccine developed by the company Hipra, which contains recombinant proteins of the alpha and beta variants of SARS-CoV-2, currently under investigation in a phase III clinical trial.

Respiratory mucosal vaccines against COVID-19 offer several logistical advantages over current IM, which would facilitate mass vaccination campaigns: greater stability and shelf life of the vaccines, allow self-administration, better compliance and lower technological requirements for storage, distribution, and transport [34,36].

CAN THE NEW VACCINES BE ADMINISTERED TOGETHER WITH THE INFLUENZA VACCINATION?

The interaction between influenza and COVID-19 has been of interest since the beginning of the pandemic. Co-infection

by both viruses, although rare, has been [38], associated with more severe respiratory symptoms and longer ventilatory support times [27]. In addition, the possibility was initially raised that the influenza vaccine might have a protective effect against SARS-CoV2 infection, reducing both the risk of infection and limiting the severity of the disease [39,40]. In animal models, it has been observed that joint vaccination against influenza virus and SARS-CoV2 generates effective protection and even potentiation of both vaccines [41]. In addition to this rational basis for joint vaccination, there is the logistical problem of having to carry out two vaccination campaigns almost simultaneously. The possibility of administering both vaccines in a single event would reduce organizational costs and facilitate adherence of the population [42]. In order to analyze the safety of this strategy, several co-administration studies have been launched [42-44]. Overall, these investigations have demonstrated efficacy and safety, although the evidence may be considered limited. The three trials included small groups (679 cases in the largest of them) and the vaccination strategies differed both in the selection of the type of influenza vaccine and of the vaccine against SARS-CoV2 (different in each of them and therefore difficult to generalize). However, the fact that no serious safety incidents have been found, despite using the most immunogenic vaccines of all those tested, mRNA-123 for SARS-CoV2 and a high-dose quadrivalent vaccine for influenza, supports this strategy [44].

Therefore, it seems reasonable to proceed with simultaneous vaccination against influenza and COVID-19 in the general population at risk. Nevertheless, it may be prudent to separate the vaccines in those persons who have had relevant adverse effects from either of them. Nor would it be recommended to combine them in young people, especially males under 40 years of age, in whom adverse effects may be more frequent [45] and the risk of both diseases is low. In future campaigns it is likely that vaccines will be available to protect against both viruses in a single dose [46-48] and even against SARS-CoV2 and pneumococcus [49], but its efficacy and safety have yet to be demonstrated in humans.

WHAT INDICATIONS MAY THE USE OF MASKS HAVE THROUGHOUT 2023?

The use of facemasks is intended on the one hand to reduce the emission of particles by infected persons, both symptomatic and asymptomatic ("source control"); and on the other hand to protect the uninfected population by reducing inhalation of particles ("user protection"). Therefore, the use of facemasks in pandemic control seems to be fully justified and, in fact, their widespread use has been a basic element in the management of the COVID 19 pandemic. After some initial erratic or contradictory indications, most governments, although not all, introduced mandatory standards for their use in both open and closed spaces. The reason for these differences between countries, apart from the socio-political characteristics of each of them, has been justified by alleging a lack of scientific evidence for their use. And the fact is that, although their mechanical capacity to filter medium and small particles has been demonstrated, they do not have the capacity to filter small-sized particles [50-53], its clinical efficacy, according to the principles of scientific evidence, was not sufficiently demonstrated up to the time of the pandemic. Thus, a Cochrane review of 2020, based on observational studies and few clinical trials, which did not include results of impact in COVID-19, concluded that the evidence on the protective capacity of masks in the clinic was weak. These results were also the conclusion of a first review, published early in 2020, already conducted with studies in SARS-CoV-2 infection [54, 55].

However, since these first months, more and more data have emerged that demonstrate the efficacy of the masks [56]. Studies comparing results in the general population with those of healthcare personnel show that these results are better in the latter [55,57,58], probably due to the higher exposure burden. It was also observed that the more widespread the population use of the mask, the greater the impact on transmission [58]. It should be noted that a recent study in our country shows that up to 89% of the surveyed population correctly followed the rules of use [59]. This is in line with other publications that show that the existence of clear and strict regulations, such as those in our environment after the hesitant beginnings, favor adherence and the perception of risk (high in the Spanish population) [60].

Although there is no doubt about the contribution that the use of masks has had in the control of the pandemic, the mandatory use of masks has been progressively limited. The regulation was extended to all public spaces, then to enclosed spaces, and finally to health institutions and public transport, given that a large part of the population is vaccinated, the incidence of COVID-19 is relatively low, and health care systems are not under stress [61].

The reality is that the use of masks is currently only contemplated in healthcare institutions in most countries. In Spain, the use of masks is still mandatory in health care centers and public transport, although in the latter area it is becoming increasingly controversial (some communities are already advocating its elimination).

Until now, CDC recommendations did not advocate the elimination of facemasks in enclosed spaces, adjusting them to criteria of disease incidence and population vulnerability. However, as of September 28, they assumed their suppression even in hospital centers, if there is low transmission and the population is not vulnerable. As for public transport, it is not even mentioned despite the fact that very recently an article in JAMA echoes the results obtained in a study sponsored by the California Department of Public Health, which shows the higher risk of COVID infection in public transport workers compared to other workers [62]. In our environment, several factors must be taken into account. In them, the pandemic can by no means be considered over, and although hospital and intensive care admissions are low and do not generate any concern, the incidence is medium, not low.

We are facing the winter season, in which in addition to SARS-CoV-2 infection, influenza and other respiratory diseases, such as Respiratory Syncytial Virus (RSV), must be taken into account. In this sense, it seems reasonable to establish the following recommendations for the use of masks: 1) health and social-health centers, both health personnel and visitors; 2) public transport; 3) vulnerable persons and their caregivers in any enclosed space, especially if a social distance cannot be maintained, while the pandemic state persists; 4) subjects with symptoms of acute respiratory infection.

This Committee would like to emphasize that, given the possible feeling of inconsistency due to the appearance of variable recommendations, the public should be given a clear message that variability of recommendations may be inevitable and is determined by the changing circumstances of the pandemic.

SHOULD CHILDREN BE INCLUDED IN UPCOMING ANTI-COVID VACCINATION PROGRAMS?

Childhood vaccination started 6 months after adult vaccination, with different age groups being progressively incorporated depending on the availability and authorization of vaccines. In May 2021, adolescents aged 12 to 19 years were vaccinated first, with mRNA vaccines equal to those for adults. Then, in November 2021, children aged 5 to 11 years were vaccinated with two new vaccines of lower antigenic load. Finally, in June 2022, the FDA approved the following vaccines [63] and the CDC recommended [64] vaccinate children from 6 months of age with mRNA vaccines of lower antigenic load (30mcg for both manufacturers).

Vaccination of adolescents in the United States with 2 doses of Comirnaty [65], demonstrated high effectiveness against COVID-19 in real life (94% protection against hospitalization and 98% against ICU admission, where 7 deaths occurred in unvaccinated patients); despite the fact that at that time (July-October 2021) the Delta variant was the predominant circulating strain. In children aged 5-11 years, vaccine effectiveness against infection was lower than expected, as shown by studies in Italy [66] and New York [67]. In Italy [66], vaccine effectiveness in preventing severe forms of COVID-19 could be demonstrated, despite the rapid decline of vaccine antibodies in the following 40-80 days post-vaccination. Several studies have shown that healthy children are at low risk of severe COVID-19 complications, regardless of their vaccination status [66-68]. These vaccination results in children aged 5-11 years are probably influenced by their late incorporation to vaccination, when many had already been infected, exposure to new variants of the virus not contained in the original vaccines and the use of vaccines with low antigenic load, so that protection is lower than that achieved in other age groups [69].

mRNA vaccines in children have been shown to be safe post-implantation [11]. In the United States, after 38 million doses administered in children aged 5-17 years, post-vaccination myocarditis (the most serious complication) was a rare event, of variable incidence according to age (4.3 cases per million doses in children aged 5-11 years), and of spontaneous evolution to cure [70]. The remaining adverse effects, although more frequent (fever, headache, asthenia, myalgia, etc) were mild and rapidly resolved without sequelae.

We can summarize that, in our environment, children and adolescents currently have good protection against COVID-19 due to vaccination and to the fact that they have been continuously exposed, infected and reinfected by the virus and its variants during the last two years of the pandemic.

For the reasons indicated above, at the present time and probably in the medium term, it does not seem a priority or urgent to include the pediatric population in the new anti-COVID-19 vaccination programs. Bivalent vaccines are only authorized for adults and those over 12 years of age, and we have no information on trials underway for pediatrics. The future of childhood vaccination will depend on the evolution of the pandemic, which could modify the current situation, and on the availability and authorization of the new vaccines (bivalent) in children. The Spanish Ministry of Health [71] recommends : 1) maintain childhood vaccination with the original mRNA vaccines against SARS-CoV-2 currently available and licensed; 2) complete vaccination (2 doses in healthy children and 3 doses in immunocompromised), respecting the intervals between doses according to age and vaccine (older than 12 years with intervals between doses of the primary series will be 3 weeks for Comirnaty and 4 for Spikevax; in children aged 5-11 years the interval is 8 weeks; in immunosuppressed or immunosuppressive children the primary series is 3 doses of vaccine, the last dose separated from the previous one by at least 28 days); 3) do not revaccinate children until the entire adult population has been vaccinated. It is highly recommended to vaccinate children against influenza to prevent the co-infection of COVID with influenza, which can worsen the pandemic and its complications, especially in adults. This has been considered by the Community of Andalusia, which in a pioneering way has authorized in October 2022, the universal vaccination against influenza in all children between 6 and 59 months of age.

IS THE INTRODUCTION OF NEW DRUGS EFFECTIVE AGAINST SARS-COV-2 EXPECTED IN 2023?

The treatment of SARS-CoV-2 has been enriched by the incorporation of drugs with different mechanisms of action (antivirals, monoclonal antibodies, anti-inflammatory drugs, etc.), which have been shown to be effective in different clinical situations (mild disease, moderate/severe disease). In some cases, they have been the result of original research and, in others, a consequence of the repositioning of drugs designed for other indications. In some way, the needs of most patients with COVID-19 have been covered.

Despite the availability of existing drugs, research continues to increase the treatment options for the disease. In this regard, the efficacy of some existing drugs is being explored in indica-

tions other than those approved or in specific situations. Various clinical trials are under way: nirmatrelvir/ritonavir, effective in outpatients with mild disease, is being tested in hospitalized patients with severe disease; remdesivir is being studied in oral formulation; various antivirals are being investigated in the special group of immunocompromised patients, who are particularly in need of therapeutic options for severe disease.

As for new drugs, mainly antivirals and, to a lesser extent, anti-inflammatory drugs are being developed. No new monoclonal antibodies are at an advanced stage of research. Without claiming to be exhaustive, we discuss below some of the drugs in advanced development that could be marketed during 2023.

With regard to new antivirals, we will discuss ensitrelvir, ensovibep and aplidin. Ensitrelvir (S-217622, Xocova®) is an oral 3CL protease inhibitor developed by the company Shionogi [72]. Has activity against all known variants of SARS-CoV-2, including the recently released Omicron BA.2.75 subvariant [73]. In phase 2 clinical trials conducted in Japan and Korea, the drug showed a significant and rapid decrease in viral load compared to placebo, with no significant toxicity, but no effect on symptom progression [74]. Phase 3 trials are currently being completed [75].

Ensovibep belongs to a novel class of designer proteins (ankyrin) that can block all three units of the SARS-CoV-2 protein S trimer and inhibit ACE2 binding with high potency [76]. It is administered as a single dose intravenously. Following promising results in a Phase 2 trial, demonstrating a 78% reduction in the risk of hospitalization, a Phase 3 clinical trial has been conducted in patients with severe disease. In this trial, compared to placebo, ensovibep did not improve the clinical outcome of patients hospitalized with COVID-19 who were receiving standard of care, including remdesivir, although it was shown to be safe. The trial was stopped due to futility and the intended sample size was not reached [77].

Aplidin (plitidepsin) is a marine cyclic peptide that inhibits SARS-CoV-2 replication, at nanomolar concentrations, by inhibiting host protein translation elongation factor 1A [78]. A Phase 1 clinical trial has been conducted in 46 hospitalized patients with COVID-19, which demonstrated a favorable safety profile and decreased viral load by up to 3.8 log10 per day 31 [79]. Phase 2-3 trials are currently underway and are planned in special subgroups of immunocompromised patients.

Regarding anti-inflammatory drugs, sabizabulin is a new investigational oral microtubule disruptor with antiviral and anti-inflammatory activities. It was originally developed to treat metastatic castration-resistant prostate cancer [80]. Because of its mechanism of action, it has been investigated to treat pulmonary inflammation in patients with COVID-19. In a double-blind phase 3 clinical trial, sabizabulin reduced the risk of death by 55%, independent of standard of care treatment received, baseline WHO scores, age, comorbidities, vaccination status, SARS-CoV-2 variant and geography [81]. Although the company has applied for emergency clearance by the FDA, the small sample size (204 patients) may determine that its efficacy is lower than published.

WHAT WILL BE THE STATUS OF THE SO-CALLED EXTENDED OR LONG-TERM COVID IN 2023?

Since the beginning of the SARS-CoV-2 pandemic, it has been documented that a significant percentage of patients had persistent alterations of the disease after the acute episode, known as post-COVID syndrome, persistent COVID or Long-Term COVID. Its incidence, which varies according to the criteria used, ranges between 20-90%.

In 2021, WHO published a consensus definition "post-COVID-19 condition occurs in persons with a history of probable or confirmed SARS- CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, but also others that generally have an impact on daily functioning. Symptoms may recur, after initial recovery from an acute episode of COVID-19, or persist from the initial illness. Symptoms may also fluctuate or relapse over time." [82].

This Committee has already taken a position in a document on how the health care of these patients should be organized, with a multidisciplinary vision, through protocols and clinical pathways, and on the uncertainty derived from the real impact of this syndrome in the coming years [83].

There are still many unknowns in the current understanding of the pathogenesis of prolonged COVID. There are current factors that could influence the impact of this syndrome, such as vaccination, the emergence of new variants of the virus, as well as other social factors that could influence the incidence and severity of these sequelae [84].

Studies with low level of evidence (grade III, case-control, cohort studies) indicate that vaccination prior to SARS CoV2 infection may reduce the risk of prolonged COVID, as well as a reduction of persistent symptoms after vaccination with the first dose and a sustained improvement of symptoms after the second dose, even in patients with significant functional impairment [85,86].

Most studies of prolonged COVID include early variants of the virus. Recent results indicate that early variants of Omicron are associated with an approximately 50% reduction in the risk of developing prolonged COVID compared with delta variant [87,88].

Despite the paucity of data, the number of patients with persistent COVID is expected to be very high given the magnitude of the pandemic. Considering a low estimate, more than 9.6 million people in the U.S. may have developed prolonged COVID. This poses a challenge to healthcare systems. In addition, very high related costs are estimated ($2.6 billion US) given the impact on work activity [89]. Other studies, such as the one carried out in the Netherlands, show that one in eight patients are affected by persistent symptoms [90].

Although several clinical trials are currently underway, there is no specific treatment for persistent COVID. While

awaiting results that can guide us towards more effective and specific therapies, symptomatic treatment is mostly used, both pharmacological (analgesics, anti-inflammatory drugs, bronchodilators, antitussives, antiemetics, antidepressants, anxiolytics, etc.) and food supplements and vitamin complexes (vitamin B12, vitamin D, omega 3). Psychological and emotional support is also essential for these patients and the need for multidisciplinary intervention of rehabilitation and stimulation programs (occupational therapy, physiotherapy) should be considered [91].

In the initial phase of the pandemic, monographic units and multidisciplinary teams were created for the follow-up and care of these patients. In the current phase, many of these devices have considered restructuring these monographic units, given the reduced number of COVID patients, assigning symptom control to the usual consultations of different specialties without having defined the optimal model to offer effective, efficient, equitable and accessible care to all patients [92].

In order to advance research and create new scientific evidence, it is necessary to have a set of results that can evaluate the impact of interventions in persistent COVID, taking into account the opinion of patients and family members. It is crucial to promote research strategies to improve knowledge of the pathophysiological aspects of the syndrome, harmonize diagnostic criteria and develop effective therapies In addition, it is necessary to have registries, ideally international, that allow progress in the knowledge of the disease and adjust the health support structures to the real needs of these patients, considering especially vulnerable or specific populations such as pediatrics [93].

The Spanish Research Network on Persistent COVID (REiCOP), led by the Spanish Society of General and Family Physicians (SEMG), has recently been set up with the collaboration of 57 scientific societies, professional associations and other entities including patient groups and associations. Its main objective is to increase the evidence regarding persistent COVID and to facilitate the care of those affected from a holistic and multidisciplinary viewpoint through clinical guidelines, training activities, the creation of a registry and the development and validation of a care scale, among others. It also includes the development of a care model adapted to the needs of patients, defining patient flows and incorporating the patient's experience.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. O.M.S. Press Conference. Tedros Ghebreyesus. 22-09-22. 2022.
2. Chenchula S, Karunakaran P, Sharma S, Chavan M. Current evidence on efficacy of COVID-19 booster dose vaccination against the Omicron variant: A systematic review. J Med Virol. 2022 Jul;94(7):2969-2976. doi: 10.1002/jmv.27697
3. Külper-Schiek W, Piechotta V, Pilic A, Batke M, Dreveton LS, Geurts B, et al. Facing the Omicron variant-how well do vaccines protect against mild and severe COVID-19? Third interim analysis of a living systematic review. Front Immunol. 2022;13:940562. DOI: 10.3389/fimmu.2022.940562
4. Le TTB, Vasanthakumaran T, Thi Hien HN, Hung IC, Luu MN, Khan ZA, et al. SARS-CoV-2 Omicron and its current known unknowns: A narrative review. Rev Med Virol. 2022:e2398.
5. Ai J, Zhang H, Zhang Y, Lin K, Zhang Y, Wu J, et al. Omicron variant showed lower neutralizing sensitivity than other SARS-CoV-2 variants to immune sera elicited by vaccines after boost. Emerg Microbes Infect. 2022;11(1):337-43. :337-343. doi: 10.1080/22221751.2021.2022440.
6. Harder T, Koch J, Vygen-Bonnet S, Külper-Schiek W, Pilic A, Reda S, et al. Efficacy and effectiveness of COVID-19 vaccines against SARS-CoV-2 infection: interim results of a living systematic review., 1 January to 14 May 2021. Euro. Surveill. 2021 Jul;26(28):2100563. doi: 10.2807/1560-7917.ES.2021.26.28.2100563.
7. Ministerio de Sanidad. Actualización de la situación epidemiológica de las variantes de SARS-CoV-2 en España. 26 de septiembre de 2022. Available at: https://wwwsanidadgobes/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Actualizacion_variantes_20220926pdf.
8. Khan NA, Al-Thani H, El-Menyar A. The emergence of new SARS-CoV-2 variant (Omicron) and increasing calls for COVID-19 vaccine boosters-The debate continues. Travel Med Infect Dis. 2022;45:102246.
9. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Amir O, Freedman L, et al. Protection by a Fourth Dose of BNT162b2 against Omicron in Israel. N Engl J Med. 2022;386(18):1712-20.
10. Magen O, Waxman JG, Makov-Assif M, Vered R, Dicker D, Hernán MA, et al. Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2022;386(17):1603-14.
11. Arbel R, Sergienko R, Friger M, Peretz A, Beckenstein T, Yaron S, et al. Effectiveness of a second BNT162b2 booster vaccine against hospitalization and death from COVID-19 in adults aged over 60 years. Nat Med. 2022;28(7):1486-90.
12. Grewal R, Kitchen SA, Nguyen L, Buchan SA, Wilson SE, Costa AP, et al. Effectiveness of a fourth dose of covid-19 mRNA vaccine against the omicron variant among long term care residents in Ontario, Canada: test negative design study. Bmj. 2022;378:e071502.
13. Hause AM, Baggs J, Marquez P, Abara WE, Baumblatt J, Blanc PG, et al. Safety Monitoring of COVID-19 mRNA Vaccine Second Booster Doses Among Adults Aged ≥50 Years - United States, March 29, 2022-July 10, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(30):971-6.
14. Hause AM, Baggs J, Marquez P, Abara WE, Olubajo B, Myers TR, et al. Safety Monitoring of COVID-19 Vaccine Booster Doses Among Persons Aged 12-17 Years - United States, December 9, 2021-Feb-

ruary 20, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(9):347-51.

15. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 Vaccines. Jama. 2021;325(13):1318-20.
16. Shrestha LB, Foster C, Rawlinson W, Tedla N, Bull RA. Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: Implications for immune escape and transmission. Rev Med Virol. 2022;32(5):e2381.
17. Rana R, Kant R, Huirem RS, Bohra D, Ganguly NK. Omicron variant: Current insights and future directions. Microbiol Res. 2022;265:127204.
18. Barouch DH. Covid-19 Vaccines - Immunity, Variants, Boosters. N Engl J Med. 2022;387(11):1011-20.
19. Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet. 2022;399(10328):924-44.
20. EMA. First adapted COVID-19 booster vaccines recommended for approval in the EU. 01/09/2022. Available at: https://www.ema.europa.eu/en/news/first-adapted-covid-19-booster-vaccines-recommended-approval-eu.
21. EMA. Adapted vaccine targeting BA.4 and BA.5 Omicron variants and original SARS-CoV-2 recommended for approval. 12/09/2022. (Accessed, october, 2022). Available at: https://www.ema.europa.eu/en/news/adapted-vaccine-targeting-ba4-ba5-omicron-variants-original-sars-cov-2-recommended-approval
22. FDA. Coronavirus (COVID-19) Update: FDA Authorizes Moderna, Pfizer-BioNTech Bivalent COVID-19 Vaccines for Use as a Booster Dose. (Accessed on Jan 10th , 2022). 2022 . Available at: https://www.fda.gov/media/137566/download
23. Telenti A, Hodcroft EB, Robertson DL. The Evolution and Biology of SARS-CoV-2 Variants. Cold Spring Harb Perspect Med. 2022;12(5).
24. Consejo Interterritorial de Salud. Ponencia de Programa y Registro de Vacunaciones. Recomendaciones de vacunación frente a COVID-19 para el otoño en España. 22 septiembre 2022. (accessed october, 2022). Available at: https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/docs/Recomendaciones_vacunacion_Otono_Covid_VF.pdf
25. Corominas J, Garriga C, Prenafeta A, Moros A, Cañete M, Barreiro A, et al. Safety and immunogenicity of the protein-based PHH-1V compared to BNT162b2 as a heterologous SARS-CoV-2 booster vaccine in adults vaccinated against COVID-19: a multicentre, randomised, double-blind, non-inferiority phase IIb trial. medRxiv 2022070522277210; 2022.
26. Barreiro A, Prenafeta A, Bech-Sabat G, al. e. Preclinical efficacy, safety, and immunogenicity of PHH- 1V, a second-generation COVID-19 vaccine candidate based on a novel recombinant RBD fusion heterodimer of SARS-CoV-2. bioRxiv 2021: 20211122469117 2022.
27. Cheng SMS, Mok CKP, Leung YWY, Ng SS, Chan KCK, Ko FW, et al. Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. Nat Med. 2022;28(3):486-9.
28. Waltz E. How nasal-spray vaccines could change the pandemic. Nature. 2022;609(7926):240-2.
29. He X, Su J, Ma Y, Zhang W, Tang S. A comprehensive analysis of the efficacy and effectiveness of COVID-19 vaccines. Front Immunol. 2022;13:945930.
30. Focosi D, Maggi F, Casadevall A. Mucosal Vaccines, Sterilizing Immunity, and the Future of SARS-CoV-2 Virulence. Viruses. 2022;14(2).
31. Dhama K, Dhawan M, Tiwari R, Emran TB, Mitra S, Rabaan AA, et al. COVID-19 intranasal vaccines: current progress, advantages, prospects, and challenges. Hum Vaccin Immunother. 2022:1-11.
32. Russell MW, Mestecky J. Mucosal immunity: The missing link in comprehending SARS-CoV-2 infection and transmission. Front Immunol. 2022;13:957107.
33. Hartwell BL, Melo MB, Xiao P, Lemnios AA, Li N, Chang JYH, et al. Intranasal vaccination with lipid-conjugated immunogens promotes antigen transmucosal uptake to drive mucosal and systemic immunity. Sci Transl Med. 2022;14(654):eabn1413.
34. Heida R, Hinrichs WL, Frijlink HW. Inhaled vaccine delivery in the combat against respiratory viruses: a 2021 overview of recent developments and implications for COVID-19. Expert Rev Vaccines. 2022;21(7):957-74.
35. Waltz E. China and India approve nasal COVID vaccines - are they a game changer? Nature. 2022;609(7927):450.
36. Adashi EY, Gruppuso PA. Intranasal SARS-CoV-2 Vaccines: Indispensable and Inevitable. Am J Prev Med. 2022.
37. Jin L, Tang R, Wu S, Guo X, Hou L, Chen X, et al. Antibody Persistence and Safety through 6 Months after Heterologous Orally Aerosolised Ad5-nCoV in individuals primed with two-dose CoronaVac previously. medRxiv 2022072622278072; . 2022.
38. Krumbein H, Kümmel LS, Fragkou PC, Thölken C, Hünerbein BL, Reiter R, et al. Respiratory viral co-infections in patients with COVID-19 and associated outcomes: A systematic review and meta-analysis. Rev Med Virol. 2022:e2365.
39. Su W, Wang H, Sun C, Li N, Guo X, Song Q, et al. The Association Between Previous Influenza Vaccination and COVID-19 Infection Risk and Severity: A Systematic Review and Meta-analysis. Am J Prev Med. 2022;63(1):121-30.
40. Del Riccio M, Lorini C, Bonaccorsi G, Paget J, Caini S. The Association between Influenza Vaccination and the Risk of SARS-CoV-2 Infection, Severe Illness, and Death: A Systematic Review of the Literature. Int J Environ Res Public Health. 2020;17(21).
41. Bao L, Deng W, Qi F, Lv Q, Song Z, Liu J, et al. Sequential infection with H1N1 and SARS-CoV-2 aggravated COVID-19 pathogenesis in a mammalian model, and co-vaccination as an effective method of prevention of COVID-19 and influenza. Signal Transduct Target Ther. 2021;6(1):200.
42. Lazarus R, Baos S, Cappel-Porter H, Carson-Stevens A, Clout M, Culliford L, et al. Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): a multicentre, randomised, controlled, phase 4 trial. Lancet. 2021.
43. Shenyu W, Xiaoqian D, Bo C, Xuan D, Zeng W, Hangjie Z, et al. Immunogenicity and safety of a SARS-CoV-2 inactivated vaccine (CoronaVac) co-administered with an inactivated quadrivalent influenza vaccine: A randomized, open-label, controlled study in healthy

adults aged 18 to 59 years in China. Vaccine. 2022;40(36):5356-65.

44. Izikson R, Brune D, Bolduc JS, Bourron P, Fournier M, Moore TM, et al. Safety and immunogenicity of a high-dose quadrivalent influenza vaccine administered concomitantly with a third dose of the mRNA-1273 SARS-CoV-2 vaccine in adults aged ≥65 years: a phase 2, randomised, open-label study. Lancet Respir Med. 2022;10(4):392-402.
45. Ling RR, Ramanathan K, Tan FL, Tai BC, Somani J, Fisher D, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. Lancet Respir Med. 2022;10(7):679-88.
46. Isakova-Sivak I, Stepanova E, Matyushenko V, Niskanen S, Mezhenskaya D, Bazhenova E, et al. Development of a T Cell-Based COVID-19 Vaccine Using a Live Attenuated Influenza Vaccine Viral Vector. Vaccines (Basel). 2022;10(7).
47. Cao K, Wang X, Peng H, Ding L, Wang X, Hu Y, et al. A Single Vaccine Protects against SARS-CoV-2 and Influenza Virus in Mice. J Virol. 2022;96(4):e0157821.
48. Ye Q, Wu M, Zhou C, Lu X, Huang B, Zhang N, et al. Rational development of a combined mRNA vaccine against COVID-19 and influenza. NPJ Vaccines. 2022;7(1):84.
49. Deng Y, Li J, Sun C, Chi H, Luo D, Wang R, et al. Rational Development of a Polysaccharide-Protein-Conjugated Nanoparticle Vaccine Against SARS-CoV-2 Variants and Streptococcus pneumoniae. Adv Mater. 2022;34(21):e2200443.
50. Lindsley WG, Blachere FM, Law BF, Beezhold DH, Noti JD. Efficacy of face masks, neck gaiters and face shields for reducing the expulsion of simulated cough-generated aerosols. Aerosol Sci Technol. 2021;55(4):449-57.
51. Fischer EP, Fischer MC, Grass D, Henrion I, Warren WS, Westman E. Low-cost measurement of face mask efficacy for filtering expelled droplets during speech. Sci Adv. 2020;6(36).
52. Verma S, Dhanak M, Frankenfield J. Visualizing the effectiveness of face masks in obstructing respiratory jets. Phys Fluids (1994). 2020;32(6):061708.
53. Bahl P, Bhattacharjee S, de Silva C, Chughtai AA, Doolan C, MacIntyre CR. Face coverings and mask to minimise droplet dispersion and aerosolisation: a video case study. Thorax. 2020;75(11):1024-5.
54. Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev. 2020;11(11):Cd006207.
55. Chou R, Dana T, Jungbauer R, Weeks C, McDonagh MS. Masks for Prevention of Respiratory Virus Infections, Including SARS-CoV-2, in Health Care and Community Settings : A Living Rapid Review. Ann Intern Med. 2020;173(7):542-55.
56. Li Y, Liang M, Gao L, Ayaz Ahmed M, Uy JP, Cheng C, et al. Face masks to prevent transmission of COVID-19: A systematic review and meta-analysis. Am J Infect Control. 2021;49(7):900-6.
57. Howard J, Huang A, Li Z, Tufekci Z, Zdimal V, van der Westhuizen HM, et al. An evidence review of face masks against COVID-19. Proc Natl Acad Sci U S A. 2021;118(4).
58. Tabatabaeizadeh SA. Airborne transmission of COVID-19 and the role of face mask to prevent it: a systematic review and meta-analysis. Eur J Med Res. 2021;26(1):1.
59. Mateos Mazón M, Martínez Caballero CM, Mateos Mazón JJ, de Carlos Negro L, Del Otero Sanz L. [Observational study of the adherence to the correct use of face masks by the general population in open public places during two periods of the COVID-19 pandemic in four Spanish cities.]. Rev Esp Salud Publica. 2022;96.
60. Wismans A, van der Zwan P, Wennberg K, Franken I, Mukerjee J, Baptista R, et al. Face mask use during the COVID-19 pandemic: how risk perception, experience with COVID-19, and attitude towards government interact with country-wide policy stringency. BMC Public Health. 2022;22(1):1622.
61. Bundgaard H, Bundgaard JS, Raaschou-Pedersen DET, von Buchwald C, Todsen T, Norsk JB, et al. Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers : A Randomized Controlled Trial. Ann Intern Med. 2021;174(3):335-43.
62. Kuehn BM. Bus and Urban Transit Workers Have Highest COVID-19 Risk. Jama. 2022;328(12):1173.
63. FDA news release. Coronavirus (COVID-19) Update: FDA Authorizes Moderna and Pfizer-BioNTech COVID-19 Vaccines for Children Down to 6 months of age. 2022.. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-and-pfizer-biontech-covid-19-vaccines-children.
64. Centers for Disease Control, Practices. ACoI. COVID-19 ACIP Vaccine Recommendations 2022. Available at https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html.
65. Wanga V, Gerdes ME, Shi DS, Choudhary R, Dulski TM, Hsu S, et al. Characteristics and Clinical Outcomes of Children and Adolescents Aged <18 Years Hospitalized with COVID-19 - Six Hospitals, United States, July-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(5152):1766-72.
66. Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. N Engl J Med. 2022;386(1):35-46.
67. Sacco C, Del Manso M, Mateo-Urdiales A, Rota MC, Petrone D, Riccardo F, et al. Effectiveness of BNT162b2 vaccine against SARS-CoV-2 infection and severe COVID-19 in children aged 5-11 years in Italy: a retrospective analysis of January-April, 2022. Lancet. 2022;400(10346):97-103.
68. Dorabawila V, Hoefer D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. Risk of Infection and Hospitalization Among Vaccinated and Unvaccinated Children and Adolescents in New York After the Emergence of the Omicron Variant. Jama. 2022;327(22):2242-4.
69. Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. N Engl J Med. 2021.
70. Su JR.Centers for Disease Control and Prevention. Advisory Committee on immunization practices COVID- 19 vaccine safety update 2022. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/06_COVID_Oliver_2022-01-05.pdf.

71. Ministerio de Sanidad. Gobierno de España. Estrategia de Vacunación COVID-19. 2022. Available at: https://www.vacunacovid.gob.es/.
72. Unoh Y, Uehara S, Nakahara K, Nobori H, Yamatsu Y, Yamamoto S, et al. Discovery of S-217622, a Noncovalent Oral SARS-CoV-2 3CL Protease Inhibitor Clinical Candidate for Treating COVID-19. J Med Chem. 2022;65(9):6499-512.
73. Uraki R, Kiso M, Iida S, Imai M, Takashita E, Kuroda M, et al. Characterization and antiviral susceptibility of SARS-CoV-2 Omicron BA.2. Nature. 2022;607(7917):119-27.
74. Mukae H, Yotsuyanagi H, Ohmagari N, Doi Y, Imamura T, Sonoyama T, et al. A Randomized Phase 2/3 Study of Ensitrelvir, a Novel Oral SARS-CoV-2 3C-Like Protease Inhibitor, in Japanese Patients with Mild-to-Moderate COVID-19 or Asymptomatic SARS-CoV-2 Infection: Results of the Phase 2a Part. Antimicrob Agents Chemother. 2022:e0069722.
75. Tyndall JDA. S-217622, a 3CL Protease Inhibitor and Clinical Candidate for SARS-CoV-2. J Med Chem. 2022;65(9):6496-8.
76. Rothenberger S, Hurdiss DL, Walser M, Malvezzi F, Mayor J, Ryter S, et al. The trispecific DARPin ensovibep inhibits diverse SARS-CoV-2 variants. Nat Biotechnol. 2022.
77. Barkauskas C, Mylonakis E, Poulakou G, Young BE, Vock DM, Siegel L, et al. Efficacy and Safety of Ensovibep for Adults Hospitalized With COVID-19 : A Randomized Controlled Trial. Ann Intern Med. 2022;175(9):1266-74.
78. Ribeiro R, Pinto E, Fernandes C, Sousa E. Marine Cyclic Peptides: Antimicrobial Activity and Synthetic Strategies. Mar Drugs. 2022;20(6).
79. Varona JF, Landete P, Lopez-Martin JA, Estrada V, Paredes R, Guisado-Vasco P, et al. Preclinical and randomized phase I studies of plitidepsin in adults hospitalized with COVID-19. Life Sci Alliance. 2022;5(4).
80. Markowski MC, Tutrone R, Pieczonka C, Barnette KG, Getzenberg RH, Rodriguez D, et al. A Phase Ib/II Study of Sabizabulin, a Novel Oral Cytoskeleton Disruptor, in Men with Metastatic Castration-resistant Prostate Cancer with Progression on an Androgen Receptor-targeting Agent. Clin Cancer Res. 2022;28(13):2789-95.
81. Barnette KG, Gordon MS, Rodriguez D, al. e. Oral Sabizabulin for High-Risk, Hospitalized Adults with Covid-19: Interim Analysis. N Engl J Med 2022.
82. WHO. Post_COVID-19_condition/Clinical_case_definition/2021.1. 2021.Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
83. Bouza E, Cantón Moreno R, De Lucas Ramos P, García-Botella A, García-Lledó A, Gómez-Pavón J, et al. [Post-COVID syndrome: A reflection and opinion paper]. Rev Esp Quimioter. 2021;34(4):269-279. doi: 10.37201/req/023.2021.
84. Munblit D, Nicholson TR, Needham DM, Seylanova N, Parr C, Chen J, et al. Studying the post-COVID-19 condition: research challenges, strategies, and importance of Core Outcome Set development. BMC Med. 2022;20(1):50.
85. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. Bmj. 2022;377:e069676.
86. Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan FC, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. EClinicalMedicine. 2022;53:101624.
87. Mantovani A, Morrone MC, Patrono C, Santoro MG, Schiaffino S, Remuzzi G, et al. Long Covid: where we stand and challenges ahead. Cell Death Differ. 2022:1-10.
88. Morioka S, Tsuzuki S, Suzuki M, Terada M, Akashi M, Osanai Y, et al. Post COVID-19 condition of the Omicron variant of SARS-CoV-2. J Infect Chemother. 2022;28(11):1546-51.
89. DM. C. The Costs of Long COVID. . JAMA Health Forum 2022;3(5):e221809. .
90. Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. Lancet. 2022;400(10350):452-61.
91. López-Sampalo A, Bernal-López MR, Gómez-Huelgas R. Persistent COVID-19 syndrome. A narrative review. Rev Clin Esp (Barc). 2022.
92. Verduzco-Gutierrez M, Estores IM, Graf MJP, Barshikar S, Cabrera JA, Chang LE, et al. Models of Care for Postacute COVID-19 Clinics: Experiences and a Practical Framework for Outpatient Physiatry Settings. Am J Phys Med Rehabil. 2021;100(12):1133-9.
93. Wolf S, Zechmeister-Koss I, Erdös J. Possible long COVID healthcare pathways: a scoping review. BMC Health Serv Res. 2022;22(1):1076.