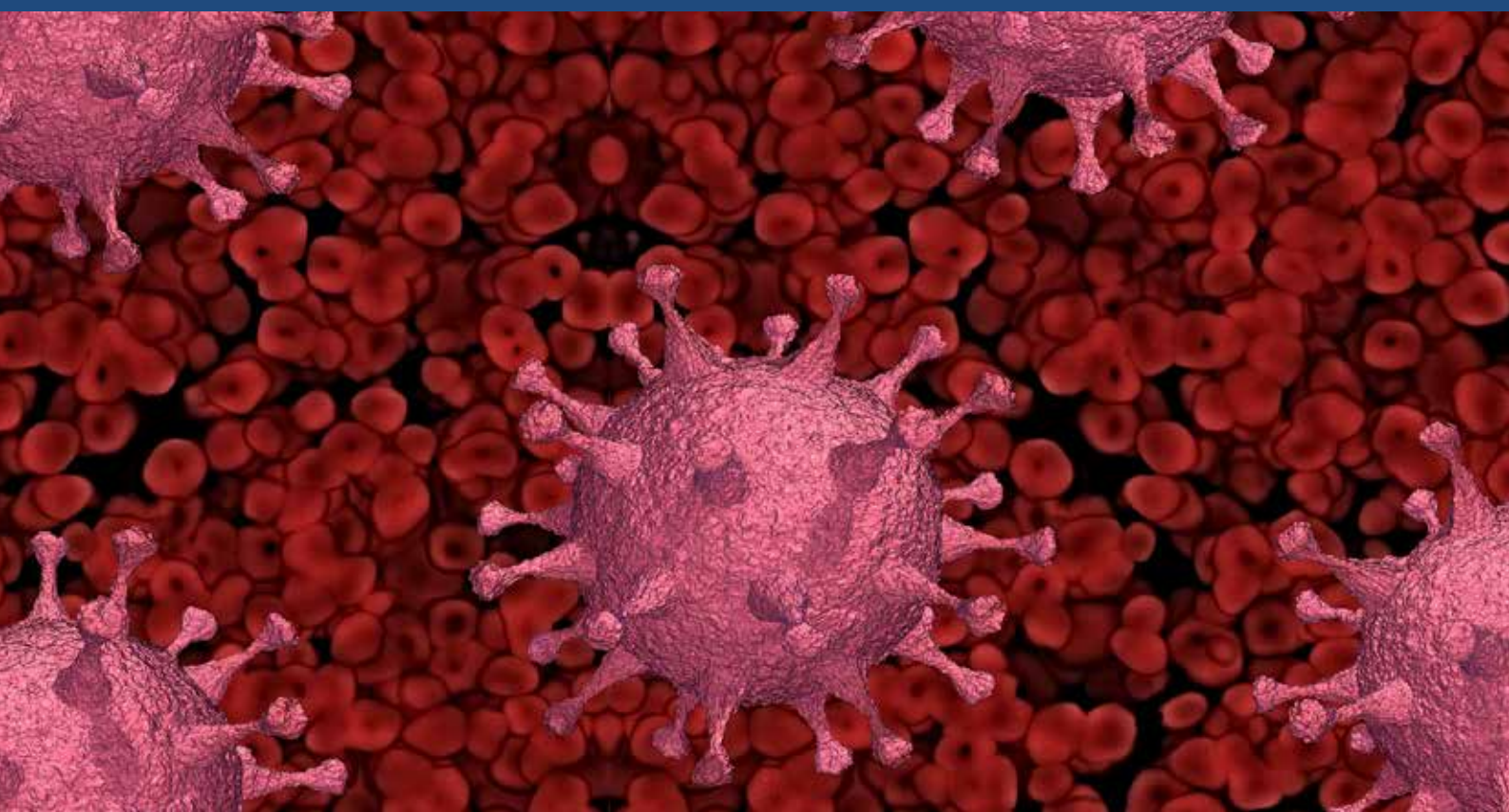


BA.5 Omicron subvariant in Catalonia: Current impact and recommendations for booster vaccination strategies

**A report of the Multidisciplinary Collaborative
Group for the Scientific Monitoring of COVID-19
(GCMSC) with the backing of the “Comitè
Científic Assessor de la COVID-19 (CCAC)”**

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Index

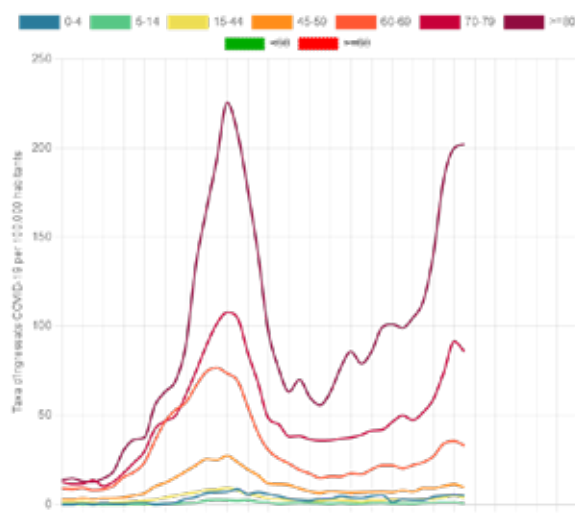
01	Epidemiological situation of SARS-CoV-2 infections, hospitalizations and severe cases in Catalonia.	3
02	Immunity against Omicron subvariants	4
03	Impact of boosting and breakthrough infections	5
04	Strategies to increase neutralization titers against Omicron subvariants, specifically BA.5, might require newly designed vaccines	7
05	Current recommendations on second booster dose (fourth dose). Prioritizations of population groups	8
06	Conclusions and Recommendations.....	9
07	References	10

01 Epidemiological situation of SARS-CoV-2 infections, hospitalizations and severe cases in Catalonia

Since January 2022 most SARS-CoV-2 infections are caused by the **Omicron variant of concern (VOC) and its subvariants**. The original Omicron subvariant BA.1 has been overtaken by its more transmissible successors. Currently, **BA.5 is the dominant subvariant worldwide** and represents more than **80% of new infections in Catalonia**. Its emergence is associated with increased viral circulation, and pressure on the health-care system (primary care and hospitals) but has a limited impact on COVID deaths, similar to what is reported in other countries.

According to data of the Sistema d'Informació per a la Vigilància d'Infeccions a Catalunya (SIVIC) (sivic.salut.gencat.cat), dated June 26, 2022, the global incidence rate of COVID-19 is 404 cases/100,000 hab., with higher incidence (622 cases/100,000 hab.) in people ≥ 60 years. Over the last 3 weeks, we have observed a **sustained increase in the number of SARS-CoV-2 infections** (21% increase, last week), with a significant **impact on hospitalizations** (24% increase, Figure 1). The highest burden of cases requiring hospitalization occurred in the **old age groups** (≥ 60 years; 77% of cases), most notably in those aged 80 years or more. In the last week, an 18% increase in cases has been observed in nursing homes. New hospitalizations are mainly affecting patients with comorbidities whose baseline clinical situation are decompensated as a result of SARS-CoV-2 infection. Although an increase in ICU admissions has also been observed, this is much less marked than what is occurring in conventional hospitalization wards.

Figure 1. Weekly rate of hospital admissions for COVID-19 by age group in Catalonia.



Source: https://sivic.salut.gencat.cat/covid_ingressats, as accessed July 12th, 2022

02 Immunity against Omicron subvariants

There is now strong evidence indicating a **decay in the level of neutralizing antibodies 4-6 months after the second vaccine dose** in the general population. This decay in neutralizing antibodies, along with the **greater capacity of new viral variants to evade humoral immune responses** generated by vaccination or previous infection, are the main reasons behind the **increase in reinfections or breakthrough infections** observed during the Omicron BA.1/BA.2 waves and the current BA.5 wave. The number of reinfections has soared: before mid-November, reinfections accounted for about 1% of reported COVID-19 cases, but the rate increased to around 10% after Omicron emergence (1). Thus, **omicron and its subvariants have gained transmission fitness** due to a larger capacity to evade humoral immune responses (2). Currently, the **humoral immunity** generated by a booster dose or by Omicron infections (mostly occurring in the period December 2021-February 2022) **is decaying**. This decay is concomitant to the recent spread of the more immune-evasive subvariant BA.5, resulting in a clear increase of infections in naïve but also in vaccinated and or previously infected individuals.

Notably, a recent seroprevalence study (n=885) conducted in the Comunitat Valenciana between April 4-7, 2022 revealed that the proportion of people who have been exposed to the vaccine or the virus (anti-RBD positivity) is 97%, while 43% of the population had been infected by SARS-CoV-2 (anti-N positivity). This latter proportion is higher in young populations and drops to less than 20% in those aged > 77 years . This suggests that a large number of people in the > 77 age group have not yet been infected with any SARS-CoV-2 VOC and their protection relies on vaccine-induced T cells and antibody titers, to which Omicron subvariants are particularly resistant. This is highly relevant since aged uninfected individuals in long-term care facilities show lower neutralizing responses than those previously infected three months after 2-doses of mRNA-based COVID-19 vaccines (3) and booster doses (Trigueros et al, unpublished data).

Despite the high increase in the number of new infections, the reported deaths have not increased significantly over the last months. This is because **memory B and T cells** (which protect against severe disease) **have been repeatedly shown to remain stable over time** (at least 9-12 months) even in the absence of reinfection (4). One recent study found that 40-50% of vaccine-induced memory B cells could simultaneously bind all VOCs, including Omicron, and that Omicron-reactive B cells were reactivated by a booster with wild-type Spike (5). Furthermore, numerous studies show that T cells are hardly affected by mutations in the Spike of VOCs. For example, a recent study on healthcare workers found that vaccine-induced memory T cells exhibit substantial polyfunctional responses to the Omicron spike protein, with no difference between those who received two versus three vaccine doses (6). This helps explain why **protection against severe disease and death during the Omicron wave remained high in the general population** even without a booster dose, around 70% at seven months or more after the second dose, according to a recent study in Qatar (7).

03 Impact of boosting and breakthrough infections

Even so, the **need for a third dose of vaccine to restore protection against symptomatic disease caused by Omicron has been clearly supported** by neutralization assays in the laboratory using sera from primary vaccinated versus boosted individuals (8), and by the observed increase in potency and breadth of RBD-specific memory B cells after a booster dose, with more than 50% of the analyzed antibodies in the memory compartment capable of neutralizing Omicron (9).

The **impact of a third dose** in increasing protection against symptomatic disease and hospitalization by Omicron is also evident from epidemiological data (10). UK data from the ends of March show that vaccine effectiveness against Omicron was underestimated due to unplanned hospitalizations, especially for adults 18-65. When redefining hospitalization cause (hospitalized with SARS-CoV-2 infection and not because of COVID-19), vaccine effectiveness 175 or more days after dose 2 was 82.3% instead of 34.6% originally calculated, and around 90% up to 4 months after the booster dose (11).

Regarding the different Omicron subvariants, **vaccine effectiveness seems similar for both BA.1 and BA.2** according to data from the UK (12) and Qatar (7). Protection against infection and symptomatic disease falls below 50% within 4-6 months after the third dose, but protection against hospitalization remains high at 15 weeks or more after the booster (80% for BA.1 and 57% for BA.2 although this lower figure was likely due to higher infection rates when BA.2 was predominant).

As for the **BA.4/5 and BA.2.12.1 subvariants**, preliminary data suggest they may be **more resistant to neutralization** by sera from mRNA-vaccinated individuals and BA.1-infected patients compared to BA.1 and BA.2 variants (11). Still, there are no definitive studies on vaccine effectiveness (expected to be lower than for BA.1).

Available evidence indicates that **the second booster dose can restore the humoral immune response to levels similar to those after the first booster dose** and restore vaccine effectiveness against infection (13). However, it seems to wane rapidly. Regarding severe disease, available evidence indicates that the second booster dose can restore protection to that seen after the first booster, but it is not known for how long (14,15).

Efficacy data on the impact of giving a second booster (or fourth dose) is still preliminary. In an Israeli study, a second mRNA booster (total of 4 doses) in adults aged over 60 offered short-lived protection against Omicron infections but longer protection against severe disease, a three-fold rate reduction as compared to three doses, for at least six weeks (14). However, the added effectiveness provided by the fourth dose seems to wane faster than that of the third; by 10 weeks it had fallen to 22%, according these data (14). Data from Sweden suggest a slightly longer-lived effect. A second mRNA booster in individuals over 80 reduced the risk of death by 42% compared to one booster, four months or more since it was given (16). Conversely, in younger populations, such as healthcare workers the benefit of a fourth dose looks relatively modest (13).

As mentioned above, at least half of the population in Catalonia (and many other countries) is estimated to have been infected with Omicron over the last months. In vaccinated and boosted people, this may represent the equivalent of an additional dose, and, importantly, this would result in the so-called **hybrid immunity**. Numerous studies show that the hybrid immunity resulting from infection before or after vaccination is characterized by broader and stronger humoral and cellular responses to SARS-CoV-2 variants (17,18).

Recent studies with vaccinated persons infected with Omicron BA.1 show that they develop robust neutralizing antibody titers against BA.2, suggesting a substantial degree of cross-reactive natural immunity (8). Furthermore, antibodies isolated from vaccinated people with Omicron BA.1 breakthrough infections can broadly neutralize Omicron and previous VOCs (19). Interestingly, BA.1 breakthrough infections, but not vaccination-only, induced Omicron neutralizing activity in the nasal mucosa (20). However, BA.2.12.1 and BA.4/BA.5 display stronger neutralization evasion than BA.2 to plasma from 3-dose vaccination and, most strikingly, from post-vaccination BA.1 infection (21), and BA.5 shows a partial resistance to antibodies elicited by BA.1 infection, with at least a 4-fold reduction in neutralization titers (22).

04 Strategies to increase neutralization titers against Omicron subvariants, specifically BA.5, might require newly designed vaccines

Although the current vaccines targeting the original Spike continue to provide reasonable protection against severe disease caused by the different VOCs, future boosting with vaccines adapted to the circulating variants will likely be more effective. As mentioned above, currently all COVID-19 cases are caused by Omicron and its subvariants, so it would be logical to deploy **Omicron-adapted boosters**. In fact, Pfizer has developed an Omicron-specific Spike mRNA vaccine, although this new vaccine version showed slight advantage over the original vaccine in preclinical settings (23).

In this sense, developing **bivalent COVID-19 vaccines** (combining spikes sequences from different variants, ancestral, Beta or Omicron), such as those developed by [Moderna](#), [Pfizer](#), Sanofi (24) or Hipra (25) may be a better option. Clinical data from all these vaccines confirm a significant [increase in neutralization](#) titers after boosting; however, they showed a modest (2x) improvement when compared to original vaccine formulations. Moreover, as Omicron has taught us, the evolution of SARS-CoV-2 is still unpredictable (no VOC has emerged from the previously dominant one) and future variants could differ considerably from the Omicron subvariants currently circulating Omicron subvariants. Altogether, these data suggest that BA.1-derived vaccine boosters may not achieve broad-spectrum protection against new Omicron variants (21).

Alternative approaches to optimize boosting strategy with current vaccines are based on **combining different vaccine platforms**. There is accumulating evidence, including that of the COV-Boost Trial with seven COVID-19 vaccines, that heterologous boosting works better than homologous boosting (26). Even for those who received a single dose of Ad26.COV2.S as primary vaccination, a single booster dose of an mRNA vaccine provided protection close to that of three-mRNA doses against symptomatic Omicron infections (27).

05 Current recommendations on second booster dose (fourth dose). Prioritizations of population groups

In addition to **immunocompromised individuals**, several countries are currently recommending a second booster dose for different vulnerable population groups, such as **residents in long-term care facilities** and the **elderly**, with varying cut-offs of age.

There is strong evidence for a **positive impact of a second booster dose (fourth dose) against hospitalization and death among residents of long-term care facilities**. A large study on 43,775 residents that received a fourth BNT162b2 COVID-19 vaccine dose during the Omicron wave (BA.1/BA.2) in Israel showed protections compared (to 3 doses) of 34%(95%CI, 30%-37%), 64%(95%CI, 56%-71%), and 67% (95%CI, 57%-75%) against overall infection, hospitalizations for mild-to-moderate illness, and severe illness, respectively, and 72%(95%CI, 57%-83%) against related deaths (28).

Based on the epidemiological situation, evidence on vaccine effectiveness, and mathematical modeling, the European Centre for Disease Prevention and Control (Technical Report 28 April 2022) considered that the public health benefit of administering [a second booster dose is relevant in individuals aged 80 years or more](#) in countries with continued high or increasing viral circulation, and more recently has [recommended to roll out boosters for all people aged over 60](#), with a focus on people who received the previous booster more than 6 months ago (Press release July 11).

From February 2022, the second booster (fourth dose) is recommended in Spain only in immunocompromised and people with very high risk (group 7) ([Actualización 11 de la Estratega de Vacunación frente a la COVID-19 en España](#)). Elderly people and residents in long-term care facilities received the first booster (third dose) starting in November 2021 ([Actualización 9 de la Estratega de Vacunación frente a la COVID-19 en España](#)), but a second booster has not been yet recommended. However, at the moment of closing this document, Spanish authorities have announced it will roll out boosters for people over 60 years of age, although the timing has not been detailed.

06 Conclusions and Recommendations

1. Although the effectiveness of current vaccines against infection has dramatically decreased since the arrival of Omicron and its subvariants, **protection against severe disease and death remains high in the general population**, particularly after a first booster (third dose).
2. **Natural infection by previous SARS-CoV-2 VOC** including Omicron BA.1 and BA.2 (affecting more than 50% of the population) does not fully protect against reinfection by the BA.5 subvariant, but **contributes to protection against severe disease** (hybrid immunity).
3. Given the increasing circulation of BA.4/BA.5 subvariants in Europe, **ECDC has recommended immediate administration of a second mRNA COVID-19 booster dose (fourth dose) in those aged 80 or more**, and more recently in those aged 60 or more, with a focus on those who received the previous booster more than 6 months ago.
4. BA.5 has become the dominant SARS-CoV-2 variant in Catalonia with an increase in COVID-19 cases and hospitalizations, mainly in elderly people. Thus, **administering a second booster (fourth dose) to elderly populations (>80 y.) and residents in long-term care facilities will increase protection against severe disease/death**.
5. It is necessary to increase the vaccine uptake of the first booster dose in the general population ≥ 18 y. However, in the current epidemiological setting, **we do not recommend a second booster (fourth dose) in the general population**, given the low cost/benefit ratio and the large proportion of this population who has been recently infected.
6. **Continued protection against severe disease will need to be monitored in the groups receiving a second booster** (fourth dose). Viral evolution and epidemiological data will define the need for additional doses in future waves.
7. The benefit of new VOC-based vaccines seems to be limited compared to current boosters. Therefore, when indicated, **boosting strategies using currently available vaccines should not be delayed**.
8. **Boosting with upcoming bivalent vaccines** (original plus Omicron or Beta Spikes) **should be considered** when these vaccines are authorized.
9. **Boosting the general population with a second booster (fourth dose) could be necessary for the future**; however, the optimal time and vaccine composition is still undefined.
10. **A general communication plan targeting vulnerable groups will be necessary** to achieve high uptake of the second booster dose.

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Grup Col·laboratiu Multidisciplinari per al Seguiment Científic de la COVID-19



COMPARTEIX



Un repte clau en una crisi sanitària i social sense precedents com la provocada per la irrupció de la COVID-19 és la generació i la síntesi de l'evidència científica per informar les decisions tècniques i polítiques. Malauradament, el paper dels experts com a element clau en la resposta a la pandèmia s'ha vist desbordat i les estructures que de manera natural haurien de liderar i orquestrar la resposta, tal com les agències de salut pública, s'han vist sobrepassades per la velocitat i la magnitud dels esdeveniments.

En aquestes circumstàncies, amb la perspectiva de la complexitat del COVID-19 i amb la certesa que cal reforçar tant com sigui possible el rol del coneixement científic i la seva

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COVID-19 (GCMSC-COVID-19).

Aquesta plataforma té com a objectiu principal efectuar un seguiment continuat de l'evidència científica directament relacionada amb el control de la COVID-19, de manera que els seus informes puguin resultar d'utilitat per les administracions, entitats privades i el conjunt de la societat. La necessitat d'aquesta iniciativa es basa en el repte que suposa establir una síntesi rigorosa de l'evidència científica, amb la velocitat i les garanties que la situació exigeix.

El grup està impulsat per l'Institut de Salut Global de Barcelona (ISGlobal) i el Col·legi de Metges de Barcelona (COMB), amb la col·laboració de l'Associació d'Entitats de Recerca de Catalunya (ACER), tres institucions complementàries en la recerca sobre la salut i la seva translació social.

Característiques

- Liderat i coordinat per un conjunt de persones expertes, procedents de disciplines diverses, trajectòries de recerca i especialització reconegudes i rellevants en el context de la COVID-19.
- Participació cooptada d'una ampla xarxa d'experts en disciplines diverses (tals com epidemiologia, malalties infeccioses, virologia, immunologia, entre d'altres), amb l'oportunitat de fer contribucions, revisions i propostes, segons els temes abordats.
- Amb el suport d'un secretariat tècnic que garantirà un seguiment puntual de l'evidència científica en constant evolució i que prepara el material per a l'elaboració dels informes del GCMSC. A més a més, el grup analitza els millors informes internacionals disponibles i contextualitza el coneixement científic sobre la COVID-19 en base a les dades i circumstàncies de Catalunya.
- Els criteris bàsics de funcionament del Grup són els de qualitat, rigor científic, puntualitat, independència i transparència.

Línies de treball

El GCMSC-COVID-19 presta especial atenció als aspectes clau relacionats amb el control de la pandèmia a Catalunya, tals com:

- les estratègies d'identificació i aïllament de casos i contactes
- els criteris per establir mesures de confinament i desconfinament
- la utilització de tècniques diagnòstiques de la infecció i la seva immunitat
- l'efectivitat de les mesures d'intervenció
- les vacunes i la protecció de col·lectius especialment vulnerables.
- l'evolució del coneixement clínic de la malaltia i dels seus efectes crònics

El GCMSC-COVID-19 neix amb el compromís de servei al conjunt de la societat de Catalunya, així com a les diferents administracions públiques, i als principals col·lectius professionals i científics de l'àmbit de les ciències de la salut i de la medicina.

Composició

El GCMSC està format per Silvia de Sanjosé (epidemiòloga, PATH), Josep M. Miró (infectòleg, Hospital Clínic - Universitat de Barcelona), Quique Bassat (pediatre, investigador ICREA a ISGlobal), Magda Campins (epidemiòloga, Hospital Vall d'Hebron), Robert Guerri (internista, Hospital de la Mar), Carles Brotons (metge de família, EAP Sardenya), Juana Díez (viròloga, CEXS, Universitat Pompeu Fabra), Julià Blanco (bioquímic i immunòleg, IrsiCaixa-IGHTP), Mireia Sans (metgessa de família, CAP Borrell), i Adelaida Sarukhan (immunòloga i redactora científica en ISGlobal).

Documents elaborats pel GCMSC

 INFORME: COVID-19 Immunisation Strategy: Priority Populations (17/11/2020)



 Comunicat en referència a la variant VUI-202012/01 del SARS-CoV-2 (23/12/2020)



 Comunicat sobre l'estratègia de vacunació a Catalunya (05/01/2021)



 Recomanacions sobre la vacunació de persones amb evidència d'infecció prèvia per SARS-CoV-2 (15/02/2021)



 INFORME: What do we know about Immunity to SARS-CoV-2? Implication for Public Health Policies (24/02/2021)



 Comunicat sobre l'estratègia de vacunació a Catalunya (10/03/2021)



 Proposta d'allargar interval entre dosis en situació de lliurament insuficient de vacunes (04/05/2021)



 Alternatives de vacunació per menors de 60 anys amb una primera dosi d'Astra-Zeneca (10/05/2021)



INFORME: Síndrome de COVID postaguda (PACS): Definició, impacte i maneig (22/06/21)



Comunicat sobre l'estratègia de vacunació d'adolescents a Catalunya (12/08/2021)



Comunicat sobre la tercera dosi de les vacunes COVID-19 (16/09/2021)



COMENTARI: Post-Acute COVID-19 Syndrome: A New Tsunami Requiring a Universal Case Definition (Clinical Microbiology and Infection, novembre 2021)



DOCUMENT: Risc de miocarditis i pericarditis en la infància i l'adolescència en el context de la vacunació de la COVID-19 amb vacunes ARNm (20/01/2022)



Continguts relacionats



El GCMSC recomana l'administració de vacunes ARNm per a la COVID-19 en menors de 12 anys i en confirma la seguretat en aquest grup d'edat

20.01.2022

Dos experts d'ISC de Catalunya
30.09.2021

Una iniciativa de





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Institut de Salut Global de Barcelona (ISGlobal), 2018.