Superior
Health Council

SECOND BOOSTER VACCINATION AGAINST COVID-19

MAY 2022
SHC № 9706

.be

Federal Public Service Health, Food Chain Safety and Environment

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Superior Health Council

ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9706

Second booster vaccination against COVID-19

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides recommendations on the need of second booster vaccination against COVID-19 for the adult population.

Conclusions and recommendations approved by the members of the NITAG on 11 April 2022.
Approval of this full version of the advisory report by the NITAG on 22 April 2022.
Version validated by the Council on 4 May 2022.[1]

I INTRODUCTION

The Superior Health Council (SHC) received a request for advice from the Task Force Vaccination against COVID-19 on 30 March 2022 on the need of a second booster vaccination dose against Coronavirus disease 2019 (COVID-19) for the Belgian general population, more specifically for the elderly. The advice was requested by 13 April 2022.

On 6 April 2022, the joint statement from European Centre for Disease Prevention and Control (ECDC) and European Medicines Agency (EMA) on the administration of a second booster dose of mRNA vaccines was published. In this statement it was emphasised to take into account **local epidemiological data** when deciding on the vaccination strategy for the second booster.
https://www.ema.europa.eu/en/news/ecdc-ema-issue-advice-fourth-doses-mrna-covid-19-vaccines

Therefore, an overview of the Belgian epidemiological data and Belgian mathematical models were provided by Sciensano and the Simulation Models of Infectious Diseases (SIMID) consortium.

[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

II CONCLUSIONS AND RECOMMENDATIONS

Conclusions

- **Vaccine effectiveness (VE) against hospitalization remains** following primary dose(s) plus first booster dose scheme;

- **Protection against Covid-19 symptomatic infections (VE) declines faster than** protection against hospitalization, Intensive Care Unit (ICU) admission or death in all age groups;

- **In the context of Omicron, with the current mRNA vaccines**, VE against hospitalization is restored after the first booster. A waning against hospitalization for adults after the first booster is observed **after 3 to 6 months** (Tartof et al., 22/04/2022 ; CDC/VRBPAC, meeting 06/04/2022 ; Stowe et al., preprint 01/04/2022 ; Sciensano, 11/04/2022). But, ECDC and EMA noted that there is currently no clear evidence in the EU that vaccine protection against severe disease is waning substantially in adults with normal immune systems aged 60 to 79 years and thus no clear evidence to support the immediate use of a second booster dose (EMA/ECDC; 06/04/2022). Therefore, the extent of this decrease in VE in severe forms is still difficult to estimate.

- **In the context of Omicron, 2 months** after a second booster, **there is no more additional effect on confirmed infection (rapid waning).** A positive effect of the second booster on severe disease is observed up to at least 6 weeks (short evaluation period) with a wide confidence interval and therefore a large variability (Bar-On et al., 05/04/2022);

- At this stage of post-vaccination side effect surveillance, **there are no additional safety issues related to the administration of a second booster**.

- **Timing** of administering additional booster doses **is crucial** and needs to be based on the most recent epidemiological data from Sciensano and Belgium's predictive models. https://covid-19.sciensano.be/fr/covid-19-situation-epidemiologique

- SIMID models show for the months to come, a decrease in hospital admission and ICU load in the Belgian population. **At this moment the Belgian epidemiological situation is not worrisome and according to the models**, **an extra booster dose is not expected to have an impact on hospital admission or ICU load. The epidemiological situation needs to be followed up very carefully.**

- For the future of the Belgian vaccination campaign against COVID-19, **people over 80 years of age and residents of nursing homes and care communities (more comorbidities and more circulation of the virus) regardless of their age** should be considered to be at equal risk of severe forms of COVID-19. They both have a higher risk of complications if they contract COVID-19.

Recommendations

1) Primary plus first booster dose scheme remains priority in the fight against severe forms of COVID-19 and must be continued to be strongly promoted. The SHC reiterates the importance of the rapid administration of a first booster dose for all those for whom it is recommended and especially for persons aged **65 years or over and for all previously determined comorbidities** (SHC 9618, 05/02/2021).

2) At this time, the SHC **does not recommend a second booster dose for the general population.**

3) At this time, the SHC also **does not recommend a systematic second booster dose for people over 80 years of age and residents of nursing homes and care communities (regardless of their age).**

4) The SHC will collect more evidence from other countries who already introduced a second booster dose and will update this advisory report as soon as new important information becomes available on the local evolution of the epidemic, new variants of concern (VOC), hospitalization rates with new variants, new vaccines, evolution of VE, etc.

Remarks : On an individual basis and after consultation of your medical physician (individual assessment of the benefit/risk balance), a second booster (full dose for Comirnaty® - ½ dose for Spikevax®), at least 4 months after the first booster, could be administrated.

In this context, the SHC would like to make the following points:

- **ECDC and EMA** noted that there is currently no clear evidence in the EU that vaccine protection against severe disease is waning substantially in adults with normal immune systems aged 60 to 79 years and thus no clear evidence to support the immediate use of a second booster dose;
- For adults below 60 years of age with normal immune systems, there is currently no conclusive evidence that vaccine protection against severe disease is waning or that there is an added value of a second booster dose;
- So far, no safety concerns have emerged from the studies on additional boosters;

- Aged people and people with several comorbidities as described by the SHC are more at risk (SHC 9618, 05/02/2021).
  https://www.health.belgium.be/fr/avis-9618-la-priorization-des-groupes-risque-pour-la-vaccination-contre-le-sars-cov-2-phase-ib

- The administration of a second booster is currently an “off label use” of the vaccine but is supported by a joint statement of ECDC and EMA (06/04/2022);

- At this stage of our knowledge, a second booster at this time does not exclude the need for an additional booster before the next winter.

III METHODOLOGY

The request was treated by the standing group Vaccination (NITAG - National Immunization Technical Advisory Group) including experts in vaccinology, geriatrics, general medicine, pediatrics, microbiology, infectiology and epidemiology. The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific peer-reviewed journals, preprint articles and reports from national and international organizations competent in this field, as well as on the opinion of the experts.

Sciensano provided a report on the Belgian epidemiological data and the SIMID consortium on the Belgian mathematical modelling data. Both presented their reports at the NITAG meeting of April 11 2022.

Once the advisory report was endorsed by the NITAG, it was ultimately validated by the members of the Council of the SHC.

IV ELABORATION AND ARGUMENTATION

Keywords

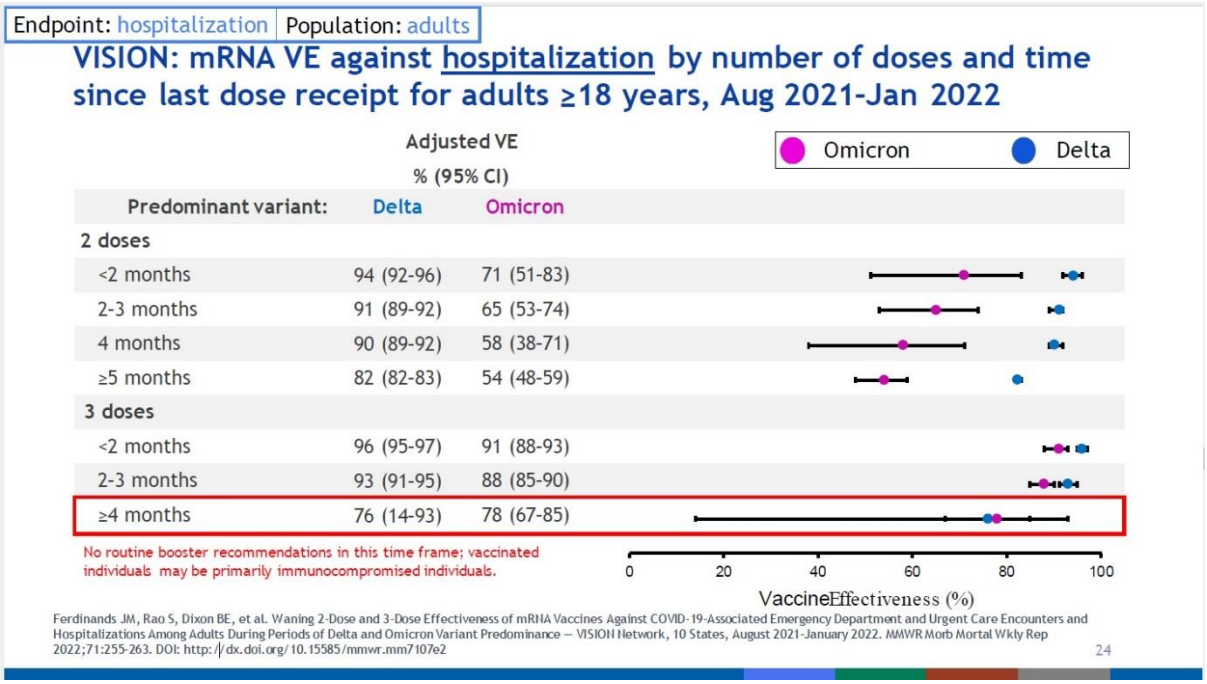
Keywords	**Sleutelwoorden**	**Mots clés**	**Schlüsselwörter**
Prevention	Preventie	Prévention	Verhütung
Booster	Booster	Rappel (dose)	Booster
COVID-19	COVID-19	COVID-19	COVID-19
Vaccination	Vaccinatie	Vaccination	Impfung

List of abbreviations used

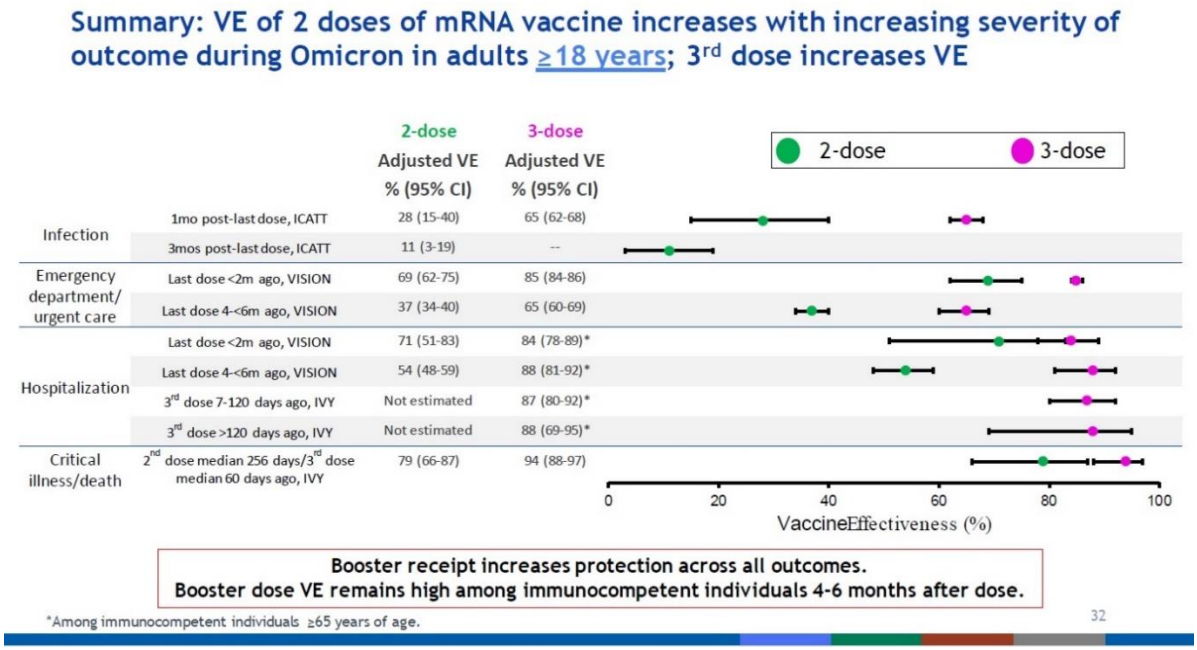
BelSACI	Belgian Society for Allergy and Clinical Immunology
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States)
ICU	Intensive Care Unit
NITAG	National Immunization Technical Advisory Group
SHC	Superior Health Council
SIMID	Simulation Models of Infectious Diseases consortium
VE	Vaccine Effectiveness
VOC	Variants Of Concern

1 VE data of the first booster against Omicron – CDC 06/04/2022

https://www.fda.gov/media/157475/download



The table above shows that during the Omicron period, VE against hospitalizations for adults ≥ 18 years, was 91% during the first 2 months following a third dose and decreased to 78% ≥4 months after a third dose (Ferdinands et al., 2022).



The table above shows that administration of a first booster (mRNA) increased VE for infection, hospitalization, ICU admission, critical illness and mortality amongst immunocompetent adults (≥ 18 years).

The overall conclusion from CDC (06/04/2022) are presented in the table below:

Summary: VE during Omicron

	Children 5-11 years	Adolescents, 12-17 years	Adults ≥18 years
2-dose VE against:			
Infection (+/- symptoms)	Limited protection	Limited protection	Limited protection
ED/UC	Higher protection	Higher protection	Higher protection, some waning
Hospitalization	Highest protection, not enough cases to estimate waning	Highest protection, some waning	Highest protection, some waning
3-dose VE against:			
Infection (+/- symptoms)	N/A	Too early to assess	Substantial additional protection for all outcomes; limited waning for hospitalization, especially among immunocompetent
ED/UC			
Hospitalization			

Protection from death: Small numbers of deaths make estimation difficult, but consistently lower rates among vaccinated compared to unvaccinated during Omicron suggest that vaccines protect against deaths in all age groups

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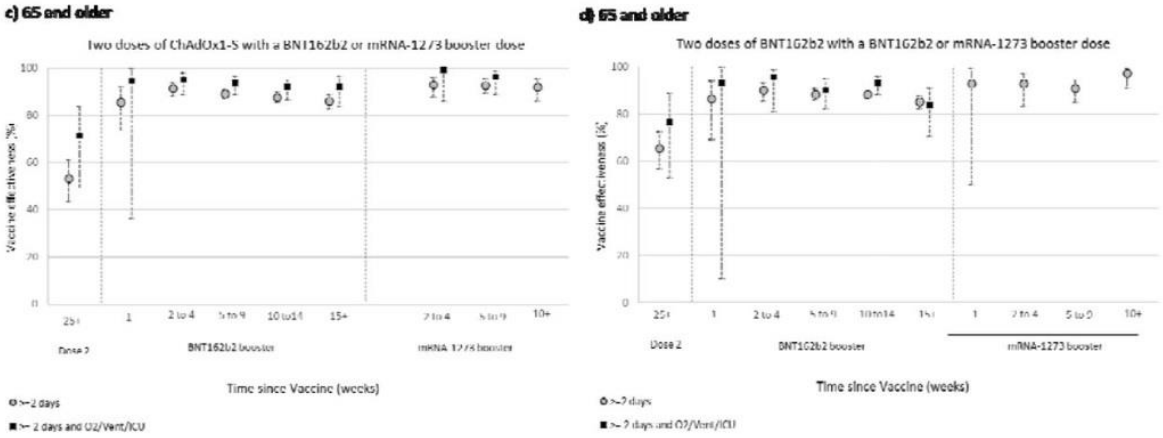
These CDC data are confirmed by Stowe et al. (preprint 01/04/2022) in UK. They investigated the impact of using more specific and more severe hospitalization indicators on VE. With generally milder disease seen with Omicron, in particular in younger adults, "contamination" of hospitalizations with incidental cases is likely to reduce VE estimates against hospitalization. VE estimates improve and waning is more limited **when definitions of hospitalization that are more specific to severe respiratory disease are used**.

The figure below shows that the VE of the first booster (mRNA) against hospitalization (≥2 days) remains high during the Omicron period (Stowe et al., 2022).



Evolving evidence based on early VE data and analysis of antibody levels after the first booster dose suggest there is gradual waning of immunity against the Omicron variant. This is most prominent for VE against symptomatic infection, which declines from 60–75% at 2-4 weeks after a booster dose of either the Pfizer or Moderna vaccine to 25–40% from 15 or more weeks after the booster. VE against COVID-19 hospitalization after the first booster dose is high at 88–95% after an mRNA booster, and appears to wane more slowly than VE against symptomatic infection. VE against hospitalization was 75% by 10–14 weeks for Pfizer vaccine

and 78% ≥4 months after mRNA vaccine (Chemaitelly et al., 2022; Ferdinands et al., 2022, Tseng et al., 2022).

Chemaitelly et al. (Qatar) show that Pfizer vaccine effectiveness against severe, critical, or fatal COVID-19 (Omicron) was maintained at >70% after the second dose and at >90% after the first booster (after 7 weeks) with no evidence for declining effectiveness over time. A limitation of this study is that only a small proportion of Qatar's population is ≥50 years.

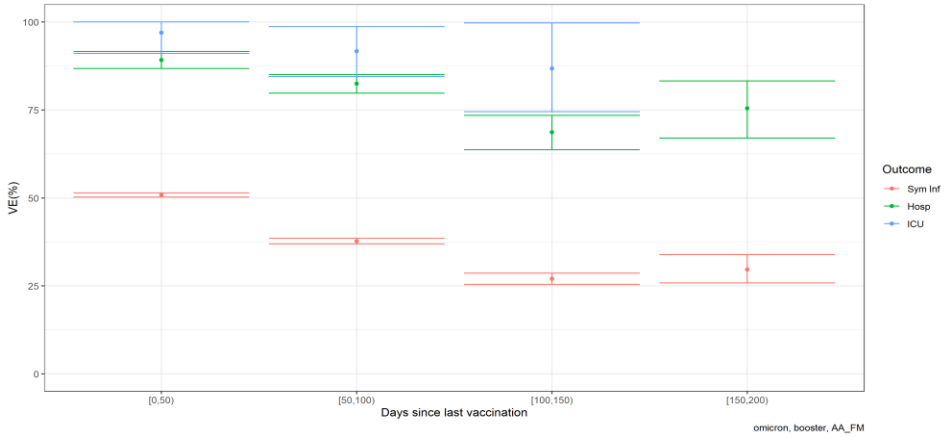
Tartof et al. (22/04/2022 – USA) analyse 11 123 hospital or emergency department admissions. In adjusted analyses, effectiveness of two doses of the Pfizer vaccine against the Omicron variant was 41% (95% Confidence Interval [CI]: 21%-55%) against hospital admission and 31% (95% CI: 16%-43%) against emergency department admission at 9 months or longer after the second dose. **After three doses, effectiveness of the Pfizer vaccine against hospital admission due to the Omicron variant was 85% (95% CI: 80%-89%) at less than 3 months but fell to 55% (95% CI: 28%-71%) at 3 months or longer, although confidence intervals were wide for the latter estimate**. **Against emergency department admission, the effectiveness of three doses of Pfizer vaccine against the Omicron variant was 77% (95% CI: 72%-81%) at less than 3 months but fell to 53% (95% CI: 36%-66%) at 3 months or longer**. Trends in waning against SARS-CoV-2 outcomes due to the delta variant were generally similar, but with higher effectiveness estimates at each timepoint than those seen for the Omicron variant. Three doses of Pfizer vaccine conferred high protection against hospital and emergency department admission due to both the delta and Omicron variants in the first 3 months after vaccination. However, 3 months after receipt of a third dose, waning was apparent against SARS-CoV-2 outcomes due to the Omicron variant, including hospital admission. Additional doses of current, adapted, or novel COVID-19 vaccines might be needed to maintain high levels of protection against subsequent waves of SARS-CoV-2 caused by the Omicron variant or future variants with similar escape potential.

VE against severe outcomes is high following the administration of a first booster dose, with estimates of around 80 to 90% protection against severe disease and hospitalizations up to 3 to 6 months after administration of a booster dose, with a slight decrease after approximately 4 months.

For the SHC, the timing of booster administration is more and more crucial and must be adapted to the local epidemiological data and previsions.

2 Belgian epidemiological situation (Sciensano, presentation NITAG 11/04/2022)

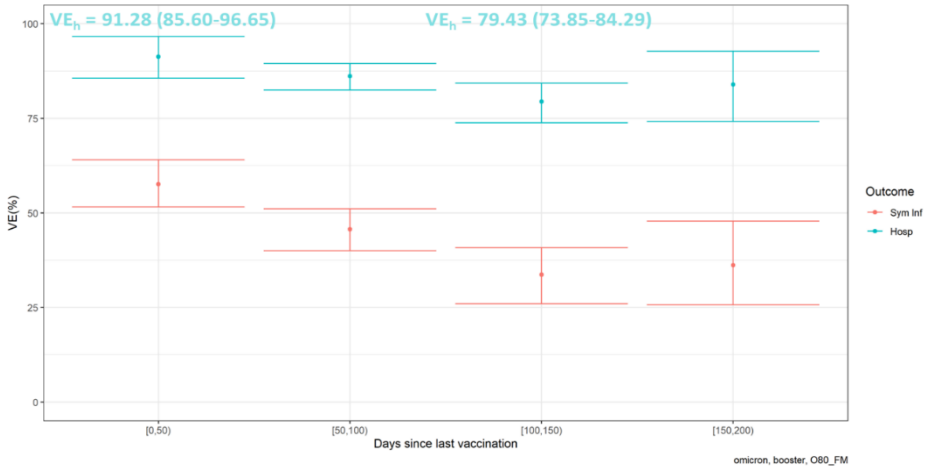
2.1 VE against symptomatic infection, hospitalization and ICU admission caused by Omicron variant, by days since last booster (0 to 200 days) for **the entire adult population**



Profile of hospitalised patients ***100-150 days post-vaccination*** (N = 5 681)

- Median age of 77 years old
- 80% of the hospitalized people is >60 years
- Median number of comorbidities is 2
- Mixed and unmixed vaccine profiles. Majority received 3 vaccine doses

2.2 VE against symptomatic infection and hospitalization caused by Omicron variant, by days since last booster (0 to 200 days) **for the population aged 80 and above**



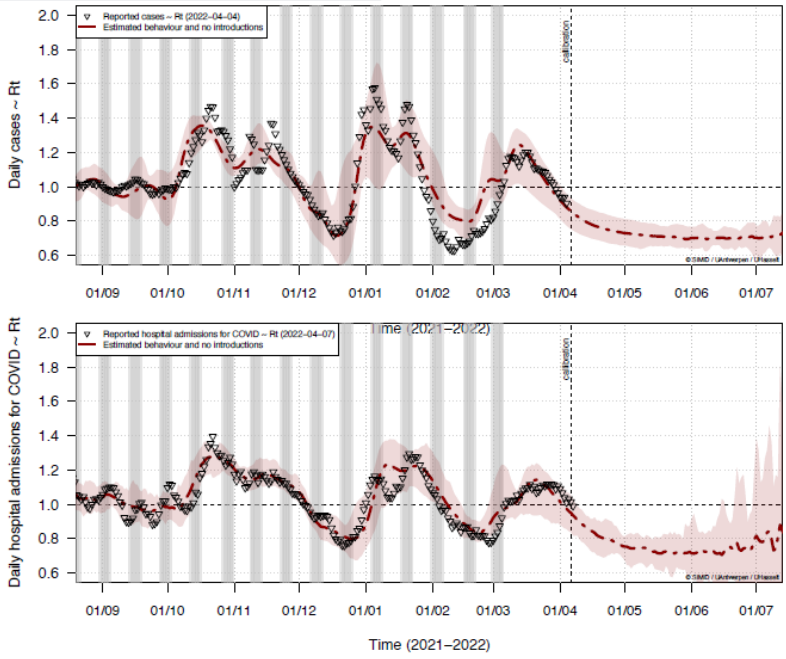
VE of booster vaccination against symptomatic infection by Omicron quickly wanes over time (< 50% after 50 days).

VE of booster vaccination against hospitalization wanes, but was still above ± 80% after 100 to 150 days after last vaccination.

3 Belgian mathematical modelling data (SIMID consortium, presentation NITAG 11/04/2022)

Reproduction number (Rt)

cfr. Daily cases and hospital admissions for COVID-19



At least up until mid-July, the model doesn't show a capacity problem if our set of assumptions hold regarding:

- schedule specific waning of vaccines already administered
- overall age specific contact frequencies for frail elderly in collectivities

What happens until November-December, or when a new VOC arises, will have to be estimated closer to date.

4 FDA Authorizes Second Booster Dose for Older and Immunocompromised Individuals (March 29, 2022)

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-second-booster-dose-two-covid-19-vaccines-older-and

"The Food and Drug Administration (FDA) amended the emergency use authorizations as follows:

- ***A second booster dose of the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine may be administered to individuals 50 years of age and older at least 4 months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine.***
- *A second booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be administered to individuals 12 years of age and older with certain kinds of immunocompromise at least 4 months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine. These are people who have undergone solid organ transplantation, or who are living with conditions that are considered to have an equivalent level of immunocompromise.*
- *A second booster dose of the Moderna COVID-19 Vaccine may be administered at least 4 months after the first booster dose of any authorized or approved COVID-19 vaccine to individuals 18 years of age and older with the same certain kinds of immunocompromise.*

Information to Support Authorization of a Second COVID-19 Booster Dose

The FDA has determined that the known and potential benefits of a second COVID-19 vaccine booster dose with either of these vaccines outweigh their known and potential risks in these populations. The evidence considered for authorization of a second booster dose following primary vaccination and first booster dose included safety and immune response information provided to the agency as well as additional information on effectiveness submitted by the companies.

A summary of safety surveillance data provided to the FDA by the Ministry of Health of Israel on the administration of approximately 700,000 fourth (second booster) doses of the Pfizer-BioNTech COVID-19 Vaccine given at least 4 months after the third dose in adults 18 years of age and older (approximately 600,000 of whom were 60 years of age or older) revealed no new safety concerns.

The safety of Moderna COVID-19 Vaccine, when administered as a second booster dose, is informed by experience with the Pfizer-BioNTech COVID-19 Vaccine and safety information reported from an independently conducted study in which the Moderna COVID-19 Vaccine was administered as a second booster dose to 120 participants 18 years of age and older who had received a two-dose primary series and a first booster dose of Pfizer-BioNTech COVID-19 Vaccine at least 4 months prior. No new safety concerns were reported during up to three weeks of follow up after the second booster dose.

Immunogenicity data from an ongoing, open-label, non-randomized clinical study in healthcare workers at a single center in Israel were reported in a publication provided to the FDA. In this study, individuals 18 years of age and older who had received primary vaccination and a first booster dose with Pfizer-BioNTech COVID-19 Vaccine were administered a second booster dose of Pfizer-BioNTech COVID-19 Vaccine (154 individuals) or Moderna COVID-19 Vaccine (120 individuals) at least four months after the first booster dose. Among these individuals, increases in neutralizing antibody levels against SARS-CoV-2 virus, including delta and

Omicron variants were reported two weeks after the second booster as compared to 5 months after the first booster dose."

FDA authorized a second booster for people 50 years of age and older. The second booster may be administered to these individuals. Conclusion were taken mainly based on Israelian data[2].

This position is actually challenged by the Advisory Committee on Immunization Practices (ACIP) https://www.cnbc.com/2022/04/21/cdc-panel-skeptical-of-fourth-covid-shots-for-broader-population-says-us-needs-clear-vaccine-strategy.html
"Long criticized the CDC for clearing fourth shots for older adults without consulting the committee, saying the decision has created public confusion and could lead to booster fatigue. She said having a full public discussion in the committee about vaccine recommendations would help restore public trust."

5 Joint EMA and ECDC statement (April 6, 2022)

COVID-19: Joint statement from ECDC and EMA on the administration of a fourth dose of mRNA vaccines (europa.eu)

"This statement is based on the currently available scientific evidence and, as such, is preliminary and may be subject to change as more data become available. This statement should not be interpreted as a regulatory decision in terms of changes to the product information. National recommendations regarding COVID-19 vaccines policies are made by National Immunization Technical Advisory Groups.

Administration of a fourth dose of mRNA vaccines to immunocompromised individuals whose immune system may have mounted a suboptimal response to earlier vaccination is already recommended and should be part of current vaccination campaigns. There are currently no data on immunogenicity, safety or effectiveness of additional further doses in this population. Additionally, in severely immunocompromised subjects, passive immunization with monoclonal antibodies should be considered as an additional shield to protect against infection and disease.

The main source of empirical evidence on the potential public health impact of a fourth dose of mRNA vaccines as a second booster in immunocompetent individuals comes from data from Israel. These data indicate that a fourth dose of an mRNA vaccine given to immunocompetent individuals at least 4 months after the third dose is able to restore humoral immunity to the level seen after the third dose without raising any new safety concerns. Immunogenicity data are available for a follow-up period of 3 weeks. No longer-term data are available on the duration of the achieved antibody levels however available data indicate that protection against Omicron infection may wane at a similar rate to that observed following the receipt of a third dose. Only preliminary data from Israel with respect to vaccine effectiveness against severe disease following a fourth dose are currently available.

There are currently no data with respect to a second booster dose of an mRNA vaccines in people who have received a primary series with another type of vaccine, e.g. a viral vector vaccine.

Although data on the rate of waning protection among the very elderly (adults above 80 years of age) following the first booster dose are still limited, due to the fragility of this population, the lower immune response to vaccination and the higher risk of severe COVID-19 a second booster could be administered. Data on safety and efficacy are only available for a fourth dose administered at least 4 months after a third dose, and this interval, together with local epidemiological data, should be taken into account when deciding on vaccination strategies.

In the context of continued high SARS-CoV-2 incidence, rates of severe outcomes and deaths remain low. For immunocompetent individuals between 60 and 80 years of age, there are currently no clear epidemiological signals from the European region of substantial waning of vaccine protection against severe COVID-19. Therefore there is no indication of an imminent need for a second booster dose in this population. However, continued close epidemiological and vaccine effectiveness monitoring is essential in order to rapidly detect signals indicating the emergence of an increasing risk of severe COVID-19 among vaccinated individuals. If such signals emerge, a fourth dose may be considered for adults between the ages of 60 and 80 years. Furthermore, local data on the epidemiological profile of severe COVID-19 cases may warrant a tailored use of a second booster dose in population groups identified as being at particular risk. If made available, vaccines adapted to better match recently circulating variants would be in principle preferable for additional boosters.

For immunocompetent individuals below 60 years of age, the administration of a second booster dose is not supported by the available data on continued level of vaccine protection against severe disease or death.

While seasonality is not yet established for SARS-COV-2, it is known that respiratory viruses tend to spread more consistently during the cold season. Therefore, plans for catch-up and re-vaccination campaigns should take this into account. In addition, in view of the possibility of new variants of concern (VOCs) emerging rapidly, the need to increase immunological breadth from available vaccines is a priority warranting the investigation of updated vaccine composition. However, it is still unclear when data on such updated vaccines will be available for a possible approval during the summer. Depending on whether waning protection against severe outcomes is observed in the coming months and on the evolving epidemiological situation, additional booster doses in anticipation of future waves or in advance of the next autumn/winter season may be needed in some or all age groups. Such additional doses will be of greatest value if administered closer to expected periods of increased viral circulation.

It must also be emphasized that, based on current evidence from longitudinal studies, routine surveillance and observational vaccine effectiveness studies, a primary course of vaccination remains the most efficient way to limit the disease burden and impact of COVID-19. COVID-19 vaccines continue to be very protective against severe disease, hospitalization and death after completion of primary series and administration of the first booster dose. With vaccine uptake stagnating and in view of the significant variation in uptake across countries (only 63.5% of subjects aged 18 years and above in EU/EEA countries had received the first booster as of the end of March 2022), additional efforts are needed to increase vaccination uptake with a focus on the first booster dose as a public health priority.

ECDC and EMA will continue to closely follow vaccine effectiveness and epidemiological data, along with the progress in the development of adapted vaccines and will update advice accordingly. In addition, as more data are generated and submitted by marketing authorization holders, these data may be reflected in the relevant product information where applicable."

At this moment and according to the limited available data, EMA and ECDC:

- Do not support the administration of a second booster in the general immunocompetent population below 60 years of age;
- Found no indication of an imminent need for a second booster dose for immunocompetent individuals between 60 and 80 years of age, there are currently no clear epidemiological signals from the European region of substantial waning of vaccine protection against severe COVID-19;
- Stated that a second booster could be administered among the very elderly (adults above 80 years of age), however local epidemiological should be taken into account.

6 Immunogenicity, efficacy and safety of the second booster (international publications and preprints)

Preliminary finding show that a fourth dose of mRNA vaccine is immunogenic, safe, and somewhat efficacious (primarily against symptomatic disease). A comparison of the initial response to the fourth dose with the peak response to a third dose did not show substantial differences in humoral response or in levels of Omicron-specific neutralizing antibodies. Along with previous data showing the superiority of a third dose to a second dose, these results suggest that maximal immunogenicity of mRNA vaccines is achieved after three doses and that antibody levels can be restored by a fourth dose (Regev-Yochay et al, 2022).

A study from Israel by Bar-on et al., published on 5 April 2022, used the Israeli Ministry of Health database and extracted data on 1,252,331 persons who were 60 years of age or older and eligible for the fourth dose during a period in which the B.1.1.529 (Omicron) variant of SARS-CoV-2 was predominant (January 10 through March 2, 2022). For persons in the fourth week after receipt of the fourth dose, the adjusted rate of severe illness was lower by a factor of 3.5 (95% CI, 2.7 to 4.6) than that in the three-dose group and was lower by a factor of 2.3 (95% CI, 1.7 to 3.3) than that in the internal control group. Severe illness continued to occur at lower rates in the four-dose groups than in the control groups in later weeks after receipt of the fourth dose, and no signs of waning were evident by the sixth week after receipt of the fourth dose. (Bar-On et al., 2022). However, the SHC notes large confidence intervals for severe illness and a very short time of evaluation. After 6 weeks the adjusted rate difference compared with the three dose group was 4.9 (CI, 2.6-7.1).

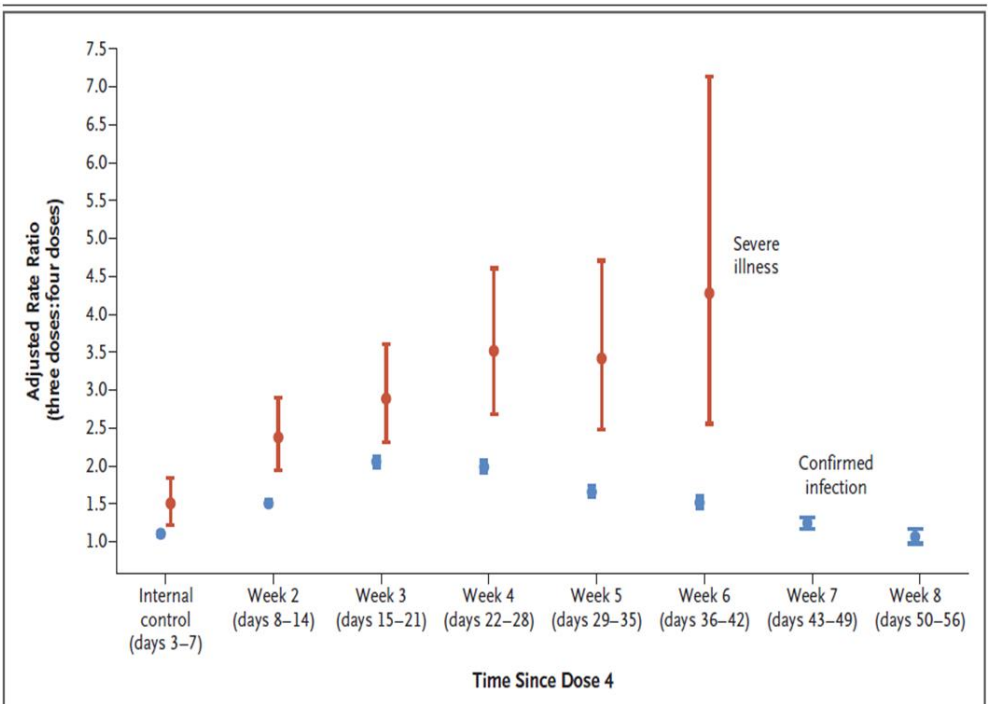


Figure 2. Adjusted Rate Ratios for Confirmed Infection and Severe Illness.

Shown are adjusted rate ratios for confirmed SARS-CoV-2 infection and severe Covid-19 in the group of persons eligible for a fourth dose who had not yet received it (three-dose group) as compared with those who had received a fourth dose, as a function of time since the fourth dose (the higher the rate ratio, the greater the protection conferred by the fourth dose of vaccine). Persons in the internal control group had received a fourth dose 3 to 7 days earlier (a period in which the fourth dose was not expected to affect the rate of confirmed infection or severe illness). Because of the 14-day follow-up period for severe Covid-19, the study period for this outcome was 2 weeks shorter than that for confirmed infection, and therefore the estimates of the adjusted rate ratio for severe illness end at week 6 instead of week 8.

A retrospective study by Arbel et al. investigated the second Booster vaccine and Covid-19 mortality in 563,465 adults 60 to 100 years old (Israel). During the study, death due to Covid-19 occurred in 92 of the second-booster recipients and 232 participants in the first-booster group. The adjusted hazard ratio for death due to Covid-19 in the second booster group compared with the first-booster group was 0.22 (95% CI: 0.17-0.28). In the Cox regression model, higher age group, male sex, ultra-orthodox Jewish, chronic heart failure, chronic obstructive pulmonary disease, and diabetes were confounding variables that had a significant association with death due to Covid-19:

Variable	Hazard Ratio for Death Due to Covid-19 (95% CI)
Second booster received	0.22 (0.17-0.28)
Age group	
60-69	Reference
70-79	2.24 (1.51-3.34)
≥ 80	9.95 (6.93-14.28)
Male sex	1.59 (1.26-1.99)
Population sector	
General Jewish	Reference
Ultra-Orthodox Jewish	1.61 (1.00-2.59)
BMI	0.96 (0.94-0.98)
Chronic Heart Failure	4.11 (3.22-5.25)
Chronic obstructive pulmonary disease	1.82 (1.35-2.43)
Diabetes	2.06 (1.64-2.58)
History of stroke	1.84 (1.44-2.37)

- **Data after a second booster are still limited.**
- **Effectiveness in preventing infection is observed for a few weeks after the administration of the fourth dose but decreases quickly over time. Early data from Israel indicate that the risk of severe infection and/or death due to COVID-19 is decreased for up to 10 weeks after the administration of a fourth dose as compared to those receiving only the third dose.**
- **The maximum duration of this protection is not yet known due to short follow-up times in the studies available.**
- **Despite the relatively small size of the safety database, no major safety issues have emerged following administration of the second booster dose.**

7 Safety of the second booster and repeated doses (EMA/ECDC, 06/04/2022)

At this stage of post-vaccination side effect surveillance, **there are no additional safety issues related to the administration of a second booster**.

- As with any allergen, repeated injection involves a risk (small) of inducing an allergy. This is true for all allergens (drugs, venoms, etc.).
- At this stage of our knowledge, there are no examples of the immune system being "overloaded" by too many repeated doses of vaccines.

These two statements (personal communication of Prof. Antoine Froidure - BelSACI - 55024973C) are possible theoretical risks but there is no scientific evidence for it in the real life context concerning COVID-19 vaccination and other vaccination campaigns.

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VI COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

Based on the discussions and conclusions of the NITAG meeting on April 11 2022, this advisory report was drafted. The following experts participated at the NITAG meeting and approved the conclusions or send their approval by mail on 22 April 2022. The NITAG meeting was chaired by **Yves VAN LAETHEM**; the scientific secretariat were Veerle MERTENS, Fabrice PETERS and Jean-Jacques DUBOIS.

BEUTELS Philippe	Health Economics	UAntwerpen
BOIY Tine	Pediatrics	UZA
BRASSEUR Daniel	Pediatrics	CEPI
CALLENS Steven	Infectiology, Internal medicine	UZ Gent
CARILLO Paloma	General medicine, vaccination	ONE
CORNELISSEN Laura	Epidemiology, Obstetrics, Gynaecology	Sciensano
DE LOOF Geert	General medicine	BCFI
DOGNE Jean- Michel	Pharmacovigilance	UNamur, EMA
DONDERS Gilbert	Gynaecology	UZA / RZ Tienen
FLAMAING Johan	Geriatry	UZ Leuven
FRERE Julie	Pediatrics, Infectiology	CHU Liège
GOVAERTS Frans	General medicine, Prevention and health promotion	Domus Medica
HULSTAERT Frank	Epidemiology, Health Economics	KCE
LEROUX-ROELS Isabel	Vaccinology, Infection prevention, Microbiology	UZ Gent
MAERTENS Kristen	Vaccinology	UAntwerpen
MICHIELS Barbara	General medicine	UAntwerpen
PELEMAN Renaat	Infectiology, Vaccinology	UZ Gent
ROSSI Camelia	Infectiology, internal medicine	CHU Ambroise Paré
SWENNEN Béatrice	Epidemiology, Vaccinology	ULB
VAN DAMME Pierre	Epidemiology, Vaccinology	UAntwerpen
VAN LAETHEM Yves	Infectiology, Vaccinology, Travel medicine, HIV	CHU Saint-Pierre, ULB
VEKEMAN Veerle	General medicine	Kind en Gezin

The following experts or administrations were heard but did not take part in endorsing the advisory report.

DAEMS Joël	Directorate Drugs	RIZIV-INAMI
JESPERS Vicky	Expert KCE, translational infectious disease researcher	KCE
MAHIEU Romain	General medicine	CCC-GGC, Directorate for Health
STOUTEN Veerle	Epidemiology of infectious diseases	Sciensano
THEETEN Heidi	Vaccinology	VAZG
TOP Geert	Manager vaccination program	VAZG
WILLEM Lander	Epidemiology, Health economics, Transmission dynamics	SIMID Consortium
WUILLAUME Françoise	Vaccine vigilance	AFMPS-FAGG

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.shc-belgium.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organizations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.fgov.be.

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