VACCELERATE – European Corona Vaccine Trial Accelerator Platform

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Co-authors (Work Package/sub-task participants)	CLEO, EUC, KUH, SERMAS, UHC, UP

This deliverable report was approved by all Work Package participants involved in its development and preparation.

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Version	Date	Status	Author(s), Reviewer	Description
V0.1	09/01/2023	Pre-final draft	First draft made by RegionH. Send to the coordinator and partners in WP7	
V1.0	24/01/2023	Final report	Shared with the Coordination Office to be uploaded to EU Portal	

Legal Disclaimer

Disclosure Statement

Abbreviations

CDC	Center for Disease Control
CEPI	Coalition for Epidemic Preparedness Innovations
CHIP	Center of Excellence for Health, Immunity and Infections
CLEO	Kentro Klinikis Epidimiologias Kai Ekvasis Nosimaton, Greece
CPME	Standing Committee of European Doctors
EC	European Commission
ECDC	European Center for Disease Control
ECRIN	Ecrin European Clinical Research Infrastructure Network, France
EMA	European Medicines Agency
EUC	European University Cyprus
KUH	Karolinska University Hospital
NITAG	National Immunization Technical Advisory Group
PRQ	Priority question
PHIRI	Population Health Information Research Infrastructure
REF	Rapid Exchange Forum
RegionH	Capital Region, Denmark
SERMAS	Servicio Madrileno De Salud
SWG	Stakeholder Working Group
UHC	University Hospital Cologne
UP	Université de Paris
VOCs	Variants of Concern
WHO	World Health Organisation
WP	Work Package
REDCap	Research Electronic Data Capture
RCTs	Randomized Controlled Trials
ICTRP	International Clinical Trials Registry Platform

1 Executive summary

Identifying and filling public health knowledge gaps in COVID-19 vaccine development is a key network objective and is included as one of the work streams within VACCELERATE. Within the scope of Work Package (WP) 7 – Public Health Needs under the auspices of VACCELERATE and RegionH, in collaboration with several partners (SERMAS, CLEO, KUH, EUC, UHC, UP) leads the work of task 7.2 focusing on the identification of unanswered research questions in relation to vaccine safety, efficacy and vaccination schemes from a public health perspective. The goal of this task is to assess the gaps and prioritise topics where clinical trials are most urgently needed.

The work of task 7.2 is based on close collaboration with other work streams and partners within VACCELERATE and includes also outreach to other networks and initiatives. It is also anchored in a broad European and international dialogue concerning new COVID-19 vaccine clinical trials aiming to inform both ongoing and future studies through a living document with priority questions that reflects knowledge gaps and emerging priorities from the public health perspective. As such, the main task objective is to *develop and maintain a living document of unanswered priority questions for future COVID-19 vaccine trials from the public health perspective.*

The work of the task includes the following concrete actions:

- Engage with partners from VACCELERATE and synergistic initiatives, including vaccine development stakeholders, through regular meetings in the Stakeholder Working Group (SWG)[1].
- Collect input from a broad stakeholder group regarding knowledge gaps and unanswered questions through a number of channels: open discussions with the relevant stakeholders, online surveys, VACCELARATE webinars (https://vaccelerate.eu/webinars/), collaborating with other initiatives looking into the impact of the COVID-19 pandemic.
- Analyse, categorise, and synthesise survey responses to develop an initial list of unanswered questions; cross-check with Task 7.1. COVID-NMA database (https://covid-nma.com/vaccines/mapping/) to follow up on the existing and changing landscape of ongoing vaccine clinical trials. As of January 12 2023, there are 1016 trials included in the mapping.
- Ensure the continuous relevance of the living document by revising and updating the topics for the COVID-19 vaccine clinical trials regularly (based on discussions with VACCELERATE partners and regular searches on emerging/changing priorities through the official websites and news channels of leading public health agencies (CEPI, ECDC, EMA, WHO Europe, ECRIN, CDC and other key organisations).
- Ensure synergies with WP4 Communication and WP10 Volunteer Registries by using the developed structures to reach the general public and underrepresented groups.
- Assess and re-evaluate the regularity of updates needed as the pandemic progresses.

The current report outlines the work done between the June 2022 and January 2023 which focused on engaging with public health experts and national institutions in a discussion on the need for future vaccine trials from a public health perspective. This deliverable is intended to be a reflection complimenting the previously compiled lists of priority questions (PRQ) identified through "*D7.4 First report on unanswered COVID-19 vaccines and vaccination priority questions for future trials"* finalised in September 2021, "*D7.6 Updated report on unanswered COVID-19 vaccines and vaccination priority*

[1] The SWG is composed of members of the VACCELERATE Coordination Board (WP leads), VACCELERATE Coordination Office (University Hospital Cologne), VACCELERATE Consortium (National Coordinators and partners) and the TCB & Vaccines Working Group (incl. reps from EC, CEPI, ECDC, EMA, WHO Europe, ECRIN and other organisations)

questions for future trials" finalised in January 2022 and "*D7.8 Updated report on unanswered COVID-19 vaccines and vaccination priority questions for future trials"* finalised in July 2022.

2 Deliverable content

This deliverable is structured as a reflection document complimenting the previously compiled lists of priority questions (PRQ) reported in D7.4, D7.6 and D7.8. It takes point of departure in discussions held in the second half of 2022 with public health experts and national public health institutions on the public health perspective and priorities in relation to vaccine trials.

Identifying unanswered vaccine questions can be complicated, as the development of vaccines and implementation of vaccination programs involves various stakeholders, both national and multinational. The previous deliverables reported on unanswered priority questions for future COVID-19 vaccine trials from the public health perspective in a so-called living document, compiled and prioritised via repeated online surveys to stakeholders. The survey respondents were primarily clinicians and researchers and the compiled list contained limited input from national public health experts and institutions. To counter this bias, this deliverable has been devoted to the perspective of national public health institutions on priorities in future COVID-19 vaccine trials. This was possible due to interactions with national public health experts in the Rapid Exchange Forum (REF) coordinated by the PHIRI Project.

2.1 Methods

To dive deeper into the public health perspective, we reached out to the European Commission funded project on COVID-19 'Population Health Information Research Infrastruture' (PHIRI). The project was launched in November 2020 and includes 41 partners in 30 different countries, and it builds on the BRIDGE Health project and the Joint Action Infact.

Among other objectives, PHIRI seeks to provide a forum for structured exchange between countries on COVID-19 best practices and expertise. Within PHIRI, public health and clinical management information and methodologies identified at national and international level is shared in the so-called 'Rapid Exchange Forum', allowing researchers and policy makers to have access to direct input and inspiration from the other countries.

PHIRI organizes a Rapid Exchange Forum (REF) meeting approximately every two weeks. Meeting participants are representatives of European national public health institutes, Ministries of Health, research institutions and universities as well as EU-level stakeholders. The meetings address current developments in population health during the COVID-19 pandemic and beyond, and allow for exchange of information across countries to learn from each other's challenges and best practices and compare across countries. At each meeting a specific topic or set of topics is addressed. Participants answer questions posed by other participants or externals, both during the meeting as well as in writing immediately before or after the meetings. Examples of topics are: e.g. vaccination-, testing-, and communication strategies, reaction to new virus variants, mortality indicators, long-term pandemic monitoring and surveillance, and beginning impact evaluations of the pandemic.

The summary reports of all the forums are published on the European Health Information Portal https://www.healthinformationportal.eu/rapid-exchange-forum.

The PHIRI project was invited to one of the Task 7.2 meetings where they presented their work and task 7.2 presented the VACCELERATE activities. In this meeting PHIRI invited VACCELERATE to participate in the Rapid Exchange Forum with Task 7.2 members as representatives of the consortium. VACCELERATE was presented at a Rapid Exchange Forum meeting in the spring of 2022, and in October 2022 the focus of this Task was on the agenda. The objective was to better understand the perspective

of different national public health stakeholders on current knowledge gaps and priorities for future COVID-19 vaccine trials.

In October 2022, VACCELERATE WP7 had the possibility to propose the topic for discussion and pose a few questions. The REF participants were asked to provide input to 2 open-ended questions:

1. Which of the following issues have the highest public health priority in your country in relation to future COVID-19 vaccination strategy and vaccine trials:
    a. Vaccine efficacy and safety
    b. Vaccine development
    c. Specific populations
    d. Other topics
2. Is there any example in your country of COVID-19 vaccine trials that are addressing public health needs?

The minutes from the meeting are available in Appendix 1. The summary of this discussion is presented in this report.

2.2 Results

In the PHIRI Rapid Exchange Forum (REF) meeting 10th October 2022, the discussion topics proposed by VACCELERATE WP7 were: 1) Which issues have the highest public health priority in your country in relation to future COVID-19 vaccination strategy and vaccine trials?; and 2) Is there any example in your country of COVID-19 vaccine trials that are addressing public health needs?

1) Priority issues

Based on the previous work of listing priority questions for trials, respondents had been given 4 response options for the first question: a) Vaccine efficacy and safety; b) Vaccine development; c) Specific populations; and d) Other topics.

Some country representatives gave their replies in writing, others at the meeting. Across the replies, the following areas were highlighted as important priorities:

- vaccine efficacy and safety
- focus on vulnerable groups of population
- coadministration of vaccinations
- the risk of long COVID in comparison with different vaccination status.

2) Examples of trials

A series of trials were mentioned by the country representatives, but it was stressed that national public health institutions (generally) not part of the national expert groups established to decide on design of vaccine trials and vaccine development. Hence, public health priority questions are not directly covered by the trials. Moreover, it was mentioned that some smaller European countries (e.g. Slovenia, Estonia) have not launched any national vaccination trials but rely on information from bigger countries and European level public health agencies (e.g. ECDC and EMA) in terms of vaccine trial results and vaccination programs recommendations. The limited representation of the EU countries during the meeting places a certain limitation on the results of this discussion.

The discussion and interaction with the PHIRI national representatives helped to shed more light on public health institutions' role and interests in the overall COVID-19 vaccine development and implementation process. One general request was a clearer definition of the VACCELERATE concept "public health priority" – a point we get back to in the discussion below.

The minutes from the meeting are available in Appendix 1.

2.3 Discussion

A very fundamental question arose at the PHIRI REF meeting, namely what is meant by "public health priorities" – and how are these perceived to be different from the priorities of researchers, clinicians, and industry-run vaccine trials – and clear definitions were deemed important. The VACCELERATE WP7 task description has an implied assumption that public health stakeholders have priorities which are different than clinical stakeholders' and industry vaccine producers' priorities in relation to topics for and design of vaccine trials.

It is well recognized that there are many questions which industry-initiated trials most-often cannot answer, and which are better targeted by investigator-initiated or academic clinical trials. Academic clinical trials play a fundamental role in the development of new treatments, the repurposing of

existing treatments and in addressing areas of unmet clinical need[2]. At the same time, academic sponsors and industry partners need to prospectively recognize when the planned collaborative trial could contribute to an application to marketing authorization and plan accordingly[3].

In the following paragraphs, the above mentioned points will be further expanded and connected with other points of reflection that arose from the REF meeting.

- Important public health priority areas in relation to COVID-19 vaccination programmes

The role of national public health institutions in relation to national vaccination programmes varies a lot across the European Union. In a number of EU countries these are not the public health institutes but the NITAGs that make national recommendations, and the sub-national regions that are responsible for the implementation of the national vaccination strategies. A key priority for national public health institutions in times of pandemic is therefore efficient broad vaccine rollout in the population. In practical terms, the concern is to reach as many people for whom the vaccine is recommended as effectively as possible, but also how to counter obstacles such as vaccine hesitancy, which is widespread in some countries or among some population groups. Vaccine trials may not be able to provide direct answers or solutions to these concerns, but indirectly trials can generate evidence on topics raised by vaccine sceptics (e.g., comparative mortality rates vaccination vs infection). However, these concerns may often be better addressed in cohort studies or registry studies than vaccine trials.

It became clear that public health institutions are not regularly involved in the process of defining research question or designing vaccine trials. This typically is in the hands of private vaccine developers.

- Public health issues of priority for COVID-19 vaccine programmes and trials

From the public health perspective unanswered questions in relation to COVID-19 vaccines and vaccinations are first and foremost related to the objective to prevent serious complications, hospitalisations and death by ensuring large, long-term scale immunity for the entire population. Three issues came out as priority from a public health perspective namely: a) vaccine efficacy and safety, b) focus on vulnerable groups of population, and c) coadministration of vaccinations.

a) Clearly, vaccine efficacy and safety are of importance for public health vaccination programmes, but these issues are also of relevance for researchers and vaccine industry developers and probably a natural focus for very many clinical trials. While industry- initiated trials often focus on one product, academic consortia or investigator-driven trials are more prone to launch comparative vaccine trials. The vaccine trials comparing different vaccination schedules, heterologous vaccination, etc., would be of interest not only to academics but also to public health authorities.

[2] Fox L, Toms C, Kernaghan S, Snowdon C, Bliss JM. Conducting non-commercial international clinical trials: the ICR-CTSU experience. *Trials*. 2017;18(1):440. Published 2017 Sep 26. doi:10.1186/s13063-017-2176-0

[3] De Wilde B, Barry E, Fox E, et al. The Critical Role of Academic Clinical Trials in Pediatric Cancer Drug Approvals: Design, Conduct, and Fit for Purpose Data for Positive Regulatory Decisions. *J Clin Oncol*. 2022;40(29):3456. doi:10.1200/JCO.22.00033

b) Trials that focus on vulnerable groups are listed as a second public health priority issue. This includes for example vaccine efficacy and safety in groups initially underrepresented such as those with compromised immunity, and children, among others. These vulnerable groups are typically not addressed in the initial clinical trials conducted for the vaccine development but excluded in order to generate the most generally applicable results. Hence, population groups that are largely underrepresented in existing trials, and which would be important to include in future COVID-19 vaccination trials are:
    - Pregnant and breastfeeding women
    - Immunocompromised patients
    - Patients with comorbidities
    - Elderly population
    - Migrant communities

    It is a key focus area of VACCELERATE to secure better participation of underrepresented groups in future vaccine trials. In one of the workstreams (WP10) the aim is to design an extensive survey addressing the causes of limited access to vaccine trials and participation for individuals from hard-to-reach groups in different countries. Additionally, in WP11, VACCELARTE aims to recruit elderly population into the EU-COVAT-1_AGED vaccine trial evaluating immunogenicity and reactogenicity of different COVID-19 vaccines in adults ≥75 already vaccinated against SARS-CoV-2.

c) The last priority issue is coadministration of vaccinations. For example, simultaneous administration of influenza, pneumococci, and COVID-19 vaccinations in elderly people. A priority question for vaccine trials would be to investigate whether coadministration has implications for effectiveness and adverse event as compared to a single vaccination. Of course, vaccine producers producing several types of vaccines may have an interest in making vaccine trials on coadministration, but most probable this is one of the topics which is best addressed in investigator initiated clinical trials.

- A pan-European approach to vaccine trials

The discussion at the REF meeting clearly reflected the very diverse national situations in relation to COVID-19 vaccine trials. For instance, the national public health representative from Slovenia reported that this country doesn't carry out any COVID-19 vaccine trials but relies on information from other countries and international health authorities when developing the national vaccination program.

This points us towards importance of pan European approach to the issues of prioritizing future vaccine trials. During the conference "Covid-19 lessons learned and looking ahead to ensure a stronger EU Health Security Framework" that took place on 22-23 November 2022 (https://cll-conference.eu/), Irene Norstedt, Director of People Directorate, DG Research and Innovation, spoke about EU level research and innovation priorities. She has pointed out 3 key recommendations in terms research needs for health crisis preparedness:

- Setting up 'ever-warm' Clinical Trial Networks that could be activated in case of a new health emergencies demanding a new therapy or vaccine
- Supporting development of a broad base of science and technologies, including utilising of the personalised medicine approach
- Designing a clear roadmap for the development of new therapies and vaccines

This points to cross-European trials and research activities and networks, rather than individual level country-based trials, and for a continued focus on preparedness and readiness to launch trials on any emerging public health issue.

2.4 Next steps

The focus for the next 6 months will be to continue the dialogue with relevant stakeholders, engage in discussions and disseminate the gathered information to targeted relevant stakeholders (EMA, ECDC, WHO etc.; national expert groups; Global and pan-European health bodies, etc). For the future update of this deliverable, it was suggested to include the research funding agencies into the list of relevant stakeholders.

The issue of defining "public health priorities" and better engagement by public health institutions in setting up research questions could be highlighted even further as a "knowledge gap" and an "infrastructural issue". A possible way to address this could be through further engagement and discussions with the NITAGs and the ECDC.

3 Deviations from the Description of the Action (DoA) and/or original deliverable

There are no deviations from the Description of the Action

4 Appendices

Appendix 1: Meeting minutes: 43rd Rapid Exchange Forum: Future vaccination priorities and vaccine trials

The minutes of the Rapid Exchange Forum meeting were compiled by the PHIRI project, the answers to questions discussed during the REF meetings are uploaded to the Health Information Portal and can be accessed online here: https://www.healthinformationportal.eu/rapid-exchange-forum.

Disclaimer: We kindly ask to acknowledge that due to the diverse and heterogeneous nature of the questions and the dynamic pandemic situation some of the information might be incomplete or only correct for the time being. Thus, please consider the date with the below information. All available information was provided by a country representative from the PHIRI network during or in connection to the respective meeting.

Date: 10.10.2022 Updated: 18.10.2022

Table 1: Country responses: Future Vaccine priorities and trials addressing public health needs

Country	Topic: Future vaccine priorities and trials addressing public health needs • **Which of the following issues have the highest public health priority in your country in relation to future COVID-19 vaccine (trials): Vaccine efficacy, Vaccine Development, Specific populations or any other). Please elaborate your choice of max. 2** • **Is there any example in your country of COVID-19 vaccine trials that are addressing public health needs?**
Austria	Currently 42 studies relating to COVID-19 are registered within Austria (https://www.clinicaltrialsregister.eu/ctr-search/search?query=COVID-19&country=at) A couple of trials could be identified that have explicit objectives related to public health needs, mainly focusing on the combination of vaccines, e.g. SPECIFIC POPULATIONS EudraCT Number: 2021-005094-28 Sponsor Protocol Number: VAC3_COVID-19_antibody_study_V1 Sponsor Name: Medical University of Vienna Full Title: Population-based prospective, clinical study on efficacy and safety of a booster COVID-19 vaccination Start Date: 2021-10-25 Link: https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-005094-28/AT EudraCT Number: 2021-001103-32 Sponsor Protocol Number: HEPCOViVac Sponsor Name: Medical University of Graz Full Title: The HEPCOViVac Registry - Immunological response in patients with liver disease vaccinated against COVID-19 Start Date: 2021-04-26 Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-001103-32 EudraCT Number: 2021-001459-15 Sponsor Protocol Number: HS-2021-02 Sponsor Name: Medical University of Graz Full Title: Immune response to COVID-19 Vaccination in people with Diabetes Mellitus - COVAC-DM study Start Date: 2021-04-26 Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-001459-15 EudraCT Number: 2021-001040-10 Sponsor Protocol Number: CoVVac Sponsor Name: Medical University of Graz Full Title: Humoral and cellular immune response to COVID-19 vaccines in immunocompromised and healthy individuals – The CoVVac study Start Date: 2021-04-26

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101018317

Link:	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-001040-10
EudraCT Number:	2021-003277-55
Sponsor Protocol Number:	CAR-CF
Sponsor Name:	Medical University of Innsbruck, University Clinic for Pediatrics III
Full Title:	COVID-19 Antibody Responses in Cystic Fibrosis: CAR-CF
Start Date:	2021-09-01
Link:	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-003277-55
EudraCT Number:	2021-002984-23
Sponsor Protocol Number:	33-391ex20/21
Sponsor Name:	Medical University of Graz
Full Title:	Retrospective quantification of anti-SARS-CoV-2 antibody response after mRNA COVID-19 vaccine in patients treated with peritoneal dialysis
Start Date:	2021-08-01
Link:	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-002984-23
EudraCT Number:	2021-002693-10
Sponsor Protocol Number:	VAC3_SARS-CoV2_seroconversion_study
Sponsor Name:	Medical University of Vienna, Department for Internal Medicine III, Division of Rheumatology
Full Title:	A Phase II Study to Evaluate Safety and Efficacy to a Third Vaccination in Immunocompromised Patients with Inadequate Humoral Response after Primary mRNA SARS-CoV-2 (Covid-19) Vaccination
Start Date:	2021-07-15
Link:	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-002693-10
EudraCT Number:	2021-000291-11
Sponsor Protocol Number:	IMRES
Sponsor Name:	Medical University of Vienna
Full Title:	Characterization of immune responsiveness after SARS-CoV-2 Vaccination in patients with Immunodeficiency or immunosuppressive therapy (COVID-19)
Start Date:	2021-05-30
Link:	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-000291-11
EudraCT Number:	2021-002927-39
Sponsor Protocol Number:	BOOST_TX/RESCUE_TX
Sponsor Name:	Medical University of Vienna
Full Title:	Preventive strategies against SARS-CoV-2 in kidney transplant recipients: Intervention A – vaccination: Single blinded randomized controlled trial on BNT162b2 or mRNA-1273 (mRNA) vs Ad26COVS1 or C...
Start Date:	2021-06-13
Link:	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-002927-39
EFFECTIVENESS/REAL WORLD USE:	
EudraCT Number:	2021-002348-57

	Sponsor Protocol Number: 2021-002348-57 Sponsor Name: Medical University of Vienna Full Title: A Randomized, Parallel Group, Single-Blind, Phase 2 Study to Evaluate the immune response of two classes of SARS-Cov-2 Vaccines employed as Third Vaccination in Patients under current Rituximab The... Start Date: 2021-05-30 Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-002348-57 EudraCT Number: 2021-002030-16 Sponsor Protocol Number: Shieldvacc2 Sponsor Name: Medizinische Universität Innsbruck, Institut für Virologie Full Title: Immune response and breakthrough infections following an in-label vaccination with Comirnaty against SARS-CoV-2 in the district of Schwaz Start Date: 2021-05-12 Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-002030-16 EudraCT Number: 2021-002171-19 Sponsor Protocol Number: HEVACC Sponsor Name: Medizinische Universität Innsbruck, Institut für Virologie Full Title: Heterologous vaccination with a Vaxzervia (ChAdOx1-S) prime and a Comirnaty (BNT162b2) boost Start Date: 2021-05-12 Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-002171-19
Belgium	Belgian COVID Vaccine trials database: https://databankklinischeproeven.be/fr?title=covid19&medical_condition=&age_range=All&subject_type=All&eudract_number 139 studies in total • 3 studies on children below 11 years old • 11 studies with children and adolescents until 18 years old • 55 studies include volunteers • 114 include vulnerable populations • 71 include safety in their title Focus: vulnerable groups and safety **Recommendations in Belgium** Primary vaccination plus first booster dose remains priority for all adults and for children and adolescents at risk of severe outcomes 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 (ECDC, HAS, UKHSA, JCVI). The SHC reiterates the importance of the timely administration of a first booster dose for all adults and for children and adolescents at risk of severe outcomes and especially for persons aged 65 years or over and for all previously determined comorbidities (SHC 9618, 05/02/2021: level 1, 2 and 3 priority and SHC 9641, April 2021), immunocompromised (SHC 9691, March 2022) and pregnant women (SHC 9622, 22/04/2021). • Vaccination of children aged 5-11 years: Yes, for all children. • Plan to expand primary vaccination to children aged <5 years old: No • Recommendations for a first booster dose for those aged 18 years and above • Recommendations for a second booster for those aged 65 years and above

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101018317

<table>
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Belgium will offer the possibility of a second booster dose for those aged 50 to 64 years as a part of the autumn/winter strategy.
Recommendations a second booster dose for those aged 18 years and above with underlying risk conditions

<table>
<tr><td>Belgium [18]</td><td>Recommendation:
Additional dose for individuals aged 5-11 years (extended primary three-dose vaccination series).
One booster dose (fourth dose) for individuals >12 years (extended primary three-dose vaccination series plus a booster dose). Two booster doses (fifth dose) for individuals >18 years (extended primary three-dose vaccination series plus two booster doses).

Timing:
Additional dose given at least 28 days after second dose followed by a booster dose (fourth dose) at least three months after the third dose.</td><td>Recommendation:
One booster dose for individuals aged ≥18 years (primary two-dose vaccination series plus a booster dose).
Second booster for individuals aged ≥65 years. From September, all staff in the entire healthcare sector, including primary care, residential care centres, hospitals, etc. can receive an autumn booster. After that, the age group from 50 to 64 years is actively invited, in decreasing age. People between 18 and 50 years old can request a second booster.

Timing:
Booster given at least four months after primary vaccination with mRNA-based vaccines; four months after primary vaccination with Vaxzevria; two months after single dose of COVID-19 vaccine Jcovden.
An interval of at least three months, and ideally six months must be maintained between the two boosters.</td></tr>
<tr><td>Belgium</td><td colspan="2">The Belgian Superior Health Council has published recommendations that all risk groups should be vaccinated with an additional booster by the end of September 2022 at the latest and that the campaign should be ‘as compact as possible’ to maximise the benefits of vaccinating against COVID-19 (the interval should be at least three months, but preferably six months for the administration of an additional booster dose). For the autumn/winter season 2022-2023, a proactive mass vaccination campaign will target adults aged 65 years and above, any patient with immune suppression due to disease or treatment, any patient with at least one comorbidity, all pregnant women, all ‘persons active in the care sector’ in and outside care institutions, and people living in the same household as those at high risk of severe disease. After that, the age group from 50 to 64 years will be invited. People aged between 18 and 50 years can volunteer [55].</td></tr>
</table>
References

1. https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/20220706_shc-9721_covid-19_booster_automn-winter_2022-2023_vweb.pdf
2. https://www.ecdc.europa.eu/sites/default/files/documents/Overview-vaccination-strategies-COVID-19-8-September-2022.pdf
3. https://databankklinischeproeven.be/fr?title=covid-19+AND+safety&medical_condition=&age_range=All&subject_type=All&eudract_number=
4. https://www.afmps.be/fr/humain/medicaments/medicaments/covid_19/vaccins

</td></tr>
<tr><td>Czech Republic</td><td>Reply will follow in written.</td></tr>
<tr><td>Denmark</td><td>Plan for this winter to give people 65+ booster shot and sme interest in how immune system reacts when you got 2 or 3 boosters on the same day. Stine Jakokbsen ganz am LSchluss nochmals abhören.</td></tr>
</table>

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101018317

Estonia	At the moment there is no information about ongoing trails available. Further reply will follow after a request to the MoH.
Italy	• As part of the COVID-19 epidemiological emergency, the Italian medicine Agency (AIFA) was entrusted with the task of evaluating all clinical trials on medicines for patients with COVID-19 (Decree Law "Cura Italia" Art. 17). Italy is participating in several multicentric trials, still ongoing, on development, safety and immunogenicity of SARS-CoV-2 vaccines (just to name the most recent trial: 'HIPRA-HH-5 - HIPRA SCIENTIFIC', a Phase III, open-label, single-arm, multicenter study to evaluate the safety and immunogenicity of a booster vaccination with candidate recombinant heterodimeric RBD fusion protein (PHH-1V) against SARS-CoV-2 in vaccinated adults). • To my knowledge, COVID-19 vaccine trials specifically addressing public health needs are not currently ongoing. For upcoming winter season, for COVID-19 vaccination, priority has been given to 60 years and older and, from the 5th of September, recommendation has been extended to 12 years and older.
Ireland	Reply will follow in written.
Moldowa	At the moment there is no information available. Further reply will follow after investigation.
Poland	The National Immunization Program against COVID-19 (approved in December 2020) is designed to plan activities that are to guarantee safe and effective vaccinations among Polish citizens. It includes not only the purchase of an appropriate number of vaccines, their distribution, but also monitoring of the course and effectiveness of vaccination and the safety of Poles. https://www.gov.pl/web/szczepimysie/narodowy-program-szczepien-przeciw-covid-19 The main goal presented in the program is the delivery of vaccines: - safe and effective, - in sufficient quantity, - in the shortest time, - free, - voluntary, - easily accessible. The document consists of 9 chapters describing, among others vaccine effectiveness and safety, purchasing and financing, distribution and logistics, medical recommendations and organization of vaccination points, or the order of vaccination. The European Commission is responsible for approving COVID-19 vaccines. First, the European Commission must obtain a positive recommendation from the Committee for Medicinal Products for Human Use operating within the European Medicines Agency (EMA). Intensive cooperation with national agencies is also carried out. Opinions on the vaccine are issued, among others, by experts from the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (https://urpl.gov.pl/en) working for scientific committees and EMA working groups. Polish specialists also take part in the meetings of the special EMA group dedicated to COVID-19.
Portugal	Portugal runs a trail to access the safety and emergency of Covid-19 vaccination in cooperation with Italy and Spain: https://covid19.trackvaccines.org/country/portugal/
Serbia	An adaptive phase I/II/III trial to evaluate the efficacy and safety of a combination of monoclonal antibodies against SARS-CoV-2 (SCTA01C and SCTA01) for the outpatient treatment of patients with COVID-19 https://www.alims.gov.rs/humani-lekovi/pretrazivanje-odobrenih-klinickih-ispitivanja/?id=177
Slovenia	Slovenia relies on information from other countries.

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