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Horizon 2020

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V0.1	22/12/2023	Pre-final draft	The first draft compiled by RegionH was sent to the coordinator and partners in WP7	
V1.0	22/01/2024	Final report	Shared with the Coordination Office to be uploaded to the EU Portal	

Legal Disclaimer

Disclosure Statement

Abbreviations

CEPI	Coalition for Epidemic Preparedness Innovations
CHIP	Center of Excellence for Health, Immunity and Infections
CLEO	Kentro Klinikis Epidimiologias Kai Ekvasis Nosimaton, Greece
ECDC	European Center for Disease Control
EMA	European Medicines Agency
EUC	European University Cyprus
KUH	Karolinska University Hospital
PRQ	Priority question
PHEIC	Public health emergency of international concern
RegionH	Capital Region, Denmark
SERMAS	Servicio Madrileno De Salud
UHC	University Hospital Cologne
UP	Université de Paris
VOCs	Variants of Concern
WHO	World Health Organisation
WP	Work Package

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, RegionH leads the work of task 7.2 in collaboration with several partners (SERMAS, CLEO, KUH, EUC, UHC, UP) focusing on the identification of unanswered research questions in relation to vaccine safety, efficacy and vaccination schemes from a public health perspective. This task aims to assess the gaps and prioritise topics where clinical trials are most urgently needed.

This deliverable (D7.11) is structured as a reflection document complimenting the previously compiled reports produced by task 7.2. The list of previous reports is available below and the documents can be accessed online at https://chip.dk/Research/Studies/VACCELERATE/Report:

- "*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 questions for future trials"* finalised in January 2022,
- "*D7.8 Updated report on unanswered COVID-19 vaccines and vaccination priority questions for future trials"* finalised in July 2022,
- "*D7.9 Updated report on unanswered COVID-19 vaccines and vaccination priority questions for future trials"* finalised in January 2023,
- "*D7.10 Updated report on unanswered COVID-19 vaccines and vaccination priority questions for future trials"* finalised in August 2023.

The current deliverable outlines the work done between August 2023 and January 2024 and serves as a final report on public health priority questions (PRQ) and emerging issues in COVID-19 vaccine development. It aims to summarise our experience in identifying priority questions for COVID-19 vaccination trials throughout the VACCELERATE project.

2 Deliverable content

With the objective to identify and prioritise emerging and unanswered public health and clinical research questions in relation to COVID-19 vaccine safety, efficacy, and vaccination schemes, five reports were developed in the period between March 2021 and August 2023. The key findings of all those reports are described here.

2.1 Utilising survey research for identifying unanswered questions for COVID-19 vaccine trials

Since activities on VACCELERATE projects launched amid the COVID-19 pandemic, online surveys were the most suitable method to collect opinions from a wide range of stakeholders.

- Initial open-ended survey

With the objective to identify and prioritise emerging and unanswered public health and clinical research questions in relation to vaccine safety, efficacy, and vaccination schemes, a stakeholder survey was developed and circulated in the spring of 2021. The received responses were analysed in order to assess the gaps and prioritise topics where clinical trials are most urgently needed.

The initial stakeholder survey was carried out with the public health perspective in mind focusing on eliciting those questions that are relevant for large-scale protection at the population level. Although preliminary knowledge gaps have been anticipated, the specific questions resulting from the stakeholder survey shed further light on the public health needs of the vaccine development. The survey replies have been grouped and compiled into a list of 17 priority questions that are listed below.

Vaccine administration

1. How can immunisation schedule (booster timing and number) and technologies (vaccine dose and type) be optimised to ensure maximum protection?
2. What is the comparative advantage of heterologous vs. homogenic vaccination in terms of efficacy, safety and duration of protection?
3. Can novel vaccines achieve non-inferiority efficacy and safety by non-parenteral route and possibly with only one dose?
4. What should the vaccination strategy be for recovered patients?

Vaccination in immunocompromised

5. What is the vaccine efficacy and are there other immunological correlates of protection than antibodies in various immunocompromised groups?
6. How can immunisation schedule (booster timing and number) and technologies (vaccine dose and type) be optimised for the immunocompromised group to ensure maximum protection?

Paediatric vaccination

7. What is the efficacy and the specific immune response to the vaccine in children, including immunocompromised paediatric population?
8. What are the long-term safety considerations of vaccination in children?
9. What is the relationship in terms of protection between vaccination and immuno-mediated diseases such as MIS-C?

Long-term protection and immunity

10. How long does immunity (humoral-cellular) last after vaccination with current vaccines?

11. Are currently available vaccines effective against SARS-CoV-2 variants in the short- and long-term and is there a need to develop new vaccine to protect against the VOCs?
12. What is the best measure of protective immunity after vaccination at the individual level and when after vaccination should it be taken?

Protection against new variants

13. Are currently available vaccines effective against SARS-CoV-2 variants in the short- and long-term and is there a need to develop new vaccine to protect against the VOCs?

Long-term vaccine safety/side effects

14. What are the long-term adverse side effects of vaccination in terms of vaccine-related or vaccine-induced diseases (autoimmune, oncologic, fertility etc.)?

Infection transmission prevention

15. Are current vaccines and vaccine strategies effective in preventing SARS-CoV-2 transmission?

Public health/policy*

16. How can awareness of and confidence in vaccine programmes be improved to address vaccine hesitancy and misinformation with focus on specific population groups?
17. How can wide-scale global vaccination coverage be ensured within reasonable timelines, especially in resource-limited settings?

*Policy questions were later excluded from the list since they cannot be answered by vaccine trial.

- Follow-up prioritisation surveys

In September 2021 and March 2022, we carried out two more surveys attempting to rank the list of questions compiled in the initial survey carried out in spring 2021. The prioritisation surveys asked respondents to identify the top 3 most important unanswered questions for potential upcoming COVID-19 vaccine trials. The surveys also allowed for an option to add new questions to the list.

In total, during the period of spring 2021-2022, 27 priority research questions were identified within task 7.2 via online surveys. The following list includes all those questions in a random order:

1. What are the long-term safety considerations of vaccination in children?
2. Are current vaccines and vaccine strategies effective in preventing SARS-CoV-2 transmission?
3. How can immunisation schedule (booster timing and number) be optimised for the paediatric population to ensure maximum protection?
4. What are the individual or sub-population genetic or metabolic differences in response to vaccines (precision medicine approach)?
5. What is the best measure of protective immunity after vaccination at the individual level and when after vaccination should it be taken?
6. What is the efficacy and specific immune response to the vaccine in children, (incl. immunocompromised paediatric population)?
7. Are currently available vaccines effective against SARS-CoV-2 variants in the short- and long-term?
8. Is there a need to develop new vaccines to protect against the VOCs?
9. Developing vaccines which are protective against a broad range of coronaviruses (e.g., pan-sarbecovirus vaccine).
10. What are the long-term adverse side effects of vaccination in terms of vaccine-related or vaccine-induced diseases (autoimmune, oncologic, fertility etc.)?

11. How can immunisation schedule (booster timing and number) and technologies (vaccine dose and type) be optimised to ensure maximum protection (incl. immunocompromised groups)?
12. What is the relationship in terms of protection between vaccination and immuno-mediated diseases such as MIS-C?
13. What should the vaccination strategy be for recovered patients?
14. Vaccination strategy in pregnant women?
15. What is the vaccine efficacy and are there other immunological correlates of protection than antibodies in various immunocompromised groups?
16. Integration of new types of COVID-19 vaccines (e.g., Nuvaxovid) in EU vaccination programs.
17. How long does immunity (humoral-cellular) last after vaccination with current vaccines?
18. What are the long-term safety considerations of vaccination among different paediatric age groups?
19. What is the vaccine efficacy and are there other immunological correlates of protection than antibodies in various immunocompromised groups?
20. Can novel vaccines achieve non-inferiority efficacy and safety by non-parenteral route (e.g., nasal vaccines) and possibly with only one dose?
21. Longevity of immunity (humoral-cellular) in naturally infected individuals vs vaccinated and vaccinated and naturally infected (vaccination of recovered patients & hybrid immunity).
22. Comparative vaccine studies (incl. booster response of mRNA vaccines against protein-based vaccines).
23. Studies to assess a 5th dose (likely to be provided in the autumn by many if a 4th dose is administered this spring).
24. Co-administration with influenza and pneumococcal vaccines for the elderly and pregnant women.
25. Co-administration with influenza and pneumococcal vaccines for the paediatric populations.
26. Broader vaccines including the new multivalent vaccine candidates possibly even pansarbecovirus vaccines one day.
27. What is the vaccine efficacy and are there any other than immunological correlates outcomes to assess protection including clinical data -symptomatic diseases, severity of diseases and risk of transmission in various immunocompromised groups?

2.2 Role of guidance of international organisations and open public discussion

In parallel with the prioritisation surveys, CHIP/RegionH has been regularly monitoring ongoing public discussion on the official websites, presentations, meetings and press briefings of leading public health agencies (CEPI, ECDC, EMA and WHO) to identify potential new emerging questions.

This has demonstrated that public discussions led by WHO and EMA in particular had a significant impact on the opinions expressed by various stakeholders in our surveys. For the period from January to June 2022, the ongoing public discussion focused on questions similar to the ones posed in the circulated survey. For instance, the main topics discussed at the multistakeholder meetings organised by WHO[1] in 2022 included:

- Advancing the development of pan-sarbecovirus vaccines.
- Developing a framework for evaluating new COVID-19 vaccines.

Altogether, priority questions that were identified as a part of activities within Task 7.2 overlap to a certain degree with the WHO list of research and monitoring activities for addressing the knowledge gap through further research. The recommendations were included in the “Good practice statement

[1] Summary of the meetings are available on the R&D Blueprint and COVID-19 page: https://www.who.int/teams/blueprint/covid-19

on the use of variant-containing COVID-19 vaccines"[2] (First issued on 17 October 2022, Updated on 2 November 2023) and are entered below.

WHO recommends, especially in low- and middle-income country settings, the following monitoring activities and research on:

1) The performance of variant-containing vaccines such as monovalent XBB vaccines doses across all COVID-19 platforms with regards to:

- vaccine effectiveness, immunogenicity and safety;
- vaccine effectiveness stratified by disease outcome (asymptomatic, mild, moderate, severe, death);
- vaccine effectiveness by priority groups;
- the breadth, magnitude and durability of humoral and cell-mediated immune responses to variants;
- the need and timing of further booster doses; and
- hybrid immunity performance against severe disease outcomes.

2) Variant-containing vaccines used as the primary vaccine series across all COVID-19 platforms relating to:

- clinical data on immune responses in humans to the initial series and/or additional/booster dose(s);
- bivalent variant-containing vaccines using platforms other than mRNA platforms;
- data on co-administration of WHO EUL COVID-19 vaccines with other routine vaccines; and
- the performance of heterologous additional doses across all COVID-19 platforms with regard to vaccine effectiveness by disease outcome.

In May 2023, WHO announced that COVID-19 no longer constitutes a public health emergency of international concern (PHEIC)[3] but is now considered an established and ongoing health issue and COVID-19 vaccination was recommended to be integrated into life course vaccination programmes.

Overall, our experience in attempting to identify priority research questions for COVID-19 vaccine trials has demonstrated the significant impact that multinational public health agencies such as WHO, ECDC and EMA play in both guiding and formulating research agendas in response to public health emergencies.

2.3 National public health policies and multinational cooperations in Europe

One of the aims of vaccine trials is to provide scientific evidence for effective public health policies of reaching a population-wide immunity to infectious diseases that can pose a significant risk to the health and well-being at the population level. In Europe, such policies are implemented at the national level based on the existing scientific evidence.

Communications with representatives of national public health authorities in Europe have revealed significant differences in relation to funding and organising COVID-19 vaccine trials. For instance, the national public health representative from Slovenia reported[4] that their country doesn't carry out any

[2] https://www.who.int/publications/i/item/WHO-2019-nCoV-Vaccines-SAGE-Variants-2022.1
[3] https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic
[4] https://www.healthinformationportal.eu/rapid-exchange-forum/49th-rapid-exchange-forum-vision-resilience-indicators

COVID-19 vaccine trials but relies on information from other countries and international health authorities when developing the national vaccination program. This demonstrates the importance of pan European approach to the issue 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 of research needs for health crisis preparedness:

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

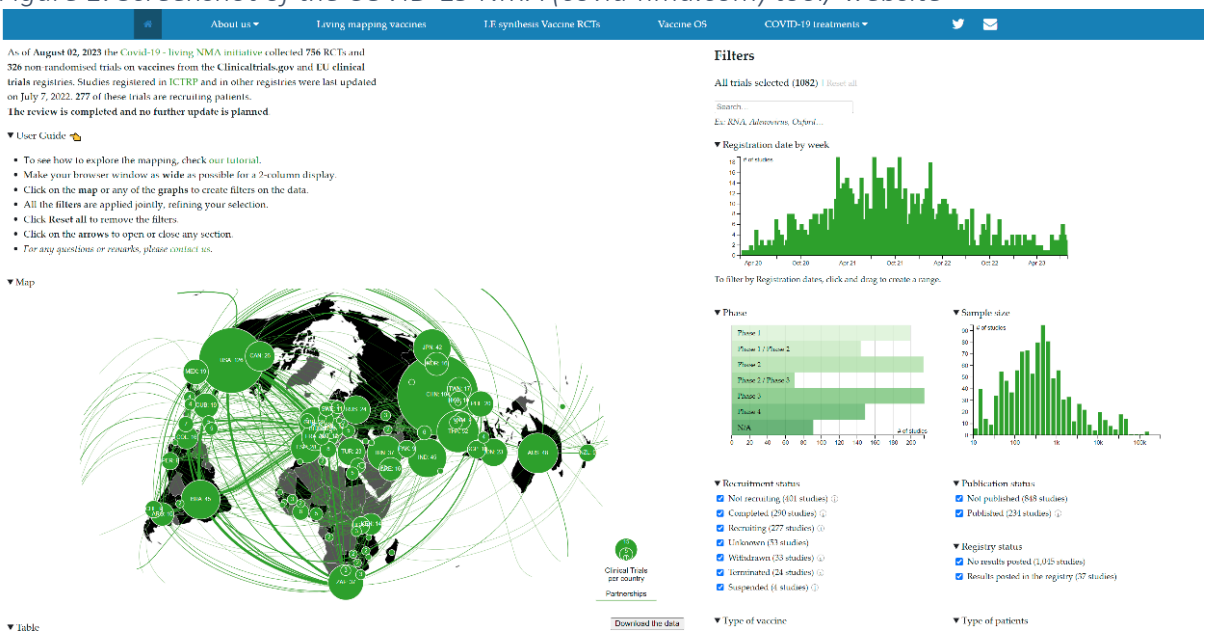
In general, we support the notion that effective pandemic preparedness and readiness to launch trials on any emerging public health issue can only benefit from cross-European trials and research activities and networks.

2.4 Monitoring and incorporation of priority topics into the COVID-NMA mapping

Efficient planning of future COVID-19 vaccine trials requires an ongoing monitoring of previous and ongoing vaccine trials. The up-to-date living mapping of planned, active, completed and published registered trials assessing COVID-19 vaccines is conducted in task 7.1 of the VACCELERATE project. The COVID-NMA mapping was developed with the purpose of helping stakeholders plan future trials.

The data are made available on a platform through interactive data visualisation (https://covid-nma.com/vaccines/mapping/). Studies can be filtered by several variables such as the country in which they are taking place, study design, type of participants and type of vaccine, among others. The screenshot of the homepage of the COVID-NMA mapping is included below.

Figure 1: Screenshot of the COVID-19 NMA (covid-nma.com) tool/ website



Throughout the VACCELERATE project, the list of the identified priority research questions for COVID-19 vaccine trials has been shared and discussed with the leads of task 7.1. The discussion has enabled us to address the best way of using the COVID-19 NMA (covid-nma.com) tool/ website to explore and identify registered clinical trials that potentially can answer some of the questions and knowledge gaps.

2.5 VACCELERATE Consortium experience

The VACCELERATE Consortium has set up 3 different vaccine trials looking into 3 different population groups, each trial was organised into a separate work package with a dedicated lead partner that served as trial sponsor and can be seen in the table below.

Table 1. COVID-19 vaccine trial conducted by VACCELERATE

VACCELERATE Trials	Sponsor
WP11 Booster Vaccination in Elderly (EU-COVAT-1 AGED)	University Hospital Cologne (UHC), Germany
WP12 Booster Vaccination in Adults (EU-COVAT-2 BOOSTAVAC)	University College Dublin (UCD), Ireland
WP13 Vaccination in Children (EU-COVPT-1 COVACC)	University Medical Centre Utrecht (UMCU), Netherlands

The 3 VACCELERATE trials focus on the following population groups:

- **Booster Vaccination in Elderly:** EU-COVAT-1 AGED is a multinational, phase 2, randomised, adaptive protocol to assess immune response and side effects of different COVID-19 vaccines given **in older adults (75 years and older) already vaccinated** against SARS-CoV-2
- **Booster Vaccination in Adults**: EU-COVAT-2 BOOSTAVAC is an international multicentre, phase 2, randomised, adaptive protocol to determine the need for, optimal timing of and immunogenicity of administering a 4th homologous mRNA vaccination dose against SARS-CoV-2 in the **general population (18+ years) already vaccinated** against SARS-CoV-2.
- **Vaccination in Children:** EU-COVPT-1 COVACC is phase 2, comparative randomised trial to evaluate the impact of reduced COVID-19 mRNA vaccination regimens on immunological responses and reactogenicity in **paediatric subjects** with and without prior SARS-CoV-2 infection.

In the previous deliverable D7.10, we have identified which of the priority questions for vaccine trials are addressed in the VACCELERATE trials. The table below contains the list of priority questions that were addressed in the specific trial. The priority questions in ***bold italics*** refer to specific questions about vaccination of the paediatric.

To further discern between the different submitted answers, the responses are highlighted in the following colours:

Colour	Explanation
Green	The question is addressed by the trial.
Yellow	The question is partially addressed by the trials
Grey	The question is not relevant to the trial (different study population, endpoints etc.)
White/Blank	The question is not addressed by the trial

Table 2. Overview of the PRQ addressed in the VACCELERATE COVID-19 vaccine trials

Priority Questions for COVID-19 Vaccine Research	Booster Vaccination in Elderly **(EU-COVAT-1 AGED)**	Booster Vaccination in Adults **(EU-COVAT-2 BOOSTAVAC)**	Vaccination in Children **(EU-COVPT-1 COVACC)**
Are currently available vaccines effective against SARS-CoV-2 variants in the short- and long-term?	☒	☒	☒
How long does immunity (humoral-cellular) last after vaccination with current vaccines?	☒	☒	☒
Is there a need to develop new vaccines to protect against the VOCs?	☒	☐	☒
Longevity of immunity (humoral-cellular) in naturally infected individuals vs vaccinated and vaccinated and naturally infected (vaccination of recovered patients & hybrid immunity).	☐	☒	☒
Comparative vaccine studies (incl. booster response of mRNA vaccines against protein-based vaccines).	☒	☐	☒
What is the best measure of protective immunity after vaccination at the individual level and when after vaccination should it be taken?	☐	☒	☐
How can immunisation schedule (booster timing and number) and technologies (vaccine dose and type) be optimised to ensure maximum protection (incl. immunocompromised groups)?	☐	☒	☐
What is the relationship in terms of protection between vaccination and immuno-mediated diseases such as MIS-C?	☐	☒	☐
What should the vaccination strategy be for recovered patients?	☐	☐	☒
Studies to assess a 5th dose (likely to be provided in the autumn by many if a 4th dose is administered this spring).	☐	☒	☐
Broader vaccines including the new multivalent vaccine candidates possibly even pansarbecovirus vaccines one day.	☐	☐	☒
What are the long-term safety considerations of vaccination in children?	☐	☐	☒
What is the efficacy and specific immune response to the vaccine in children, (incl. immunocompromised paediatric population)?	☐	☐	☒

2.6 Future perspectives of COVID-19 vaccine research

For this final section on future perspectives of COVID-19 vaccine research and the remaining knowledge gaps where future trials ought to focus, we have asked the VACCELEREATE National Coordinators for input. In an email send out early December 2023 the NCs were asked to provide the top three questions/topics for future COVID-19 vaccine studies that they believe - from a public heath perspective (i.e. issues that contribute to maximum societal benefit in terms of health protection)- still ought to be prioritised in coming COVID-19 vaccine trials/studies:

Replies were received from 7 NCs and can be group into these four interrelated and overlapping topics for future studies (in no particular order):

a) What is the most appropriate and effective vaccine/booster schedule for specific groups?
- Studies on vulnerable groups: frail subjects/ subjects with (multiple) comorbidities/ newborns /no responders to previous vaccines/immunocompromised host and infants
- Studies on general population: highly vaccinated and post-infected population

b) Safety and effectiveness of vaccine administration schedules:
- Studies on administration schedules: co-administration (e.g. with influenza for higher compliance)/adapted schedules/mixed schedules
- Studies on adverse events in recipients of multiple doses and related to different vaccines/co-administration/schedules

c) Studies on new COVID-19 vaccine technologies
- intranasal vaccines especially for the pediatric population

d) Studies on the vaccines' effectiveness on transmission and correlates of protection

Clearly, while the world has come a long way in understanding the COVID-19 virus, and how best vaccinate populations, there are still unanswered questions of outmost importance for the public health and which warrants further study.

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: List of National Coordinators

Country	Organisation		Contact
Austria	MUW	Prof.	Markus Zeitlinger
Belgium	UA	Prof.	Pierre van Damme
Cyprus	EUC	MD, MSc, PhD	Zoi-Dorothea Pana
Czech Republic	MUNI	Prof.	Petr Husa
Czech Republic	MUNI	Assoc. prof.	Regina Demlova
Denmark	REGIONH	Prof.	Jens Lundgren
France	INSERM	Prof.	Odile Launay
Germany	UHC	Dr.	Sibylle Mellinghoff
Greece	CLEO	Prof.	Theoklis E. Zaoutis
Hungary	OKPI	Dr.	Krisztina Tóth
Ireland	NUID UCD	Prof.	Patrick Mallon
Italy	UNIVR	Prof.	Evelina Tacconelli
Italy	UNIVR		Anna Maria Azzini
Lithuania	VUH	Prof.	Ligita Jancoriene
Netherlands	UMCU	Prof.	Peter W.M. Hermans
Poland	MUB	Dr.	Robert Flisiak
Portugal	CHUSA	Dr.	Laura Marques
Slovakia	BMC SAS	Dr.	Alena Koscalova
Spain	ISCIII	Dr.	Jordi Cano Ochando
Sweden	KUH	Dr.	Pontus Nauclér
Associated EU-countries, membership candidates & other neighbouring countries			
Israel	MOH	Dr.	Miriam Cohen- Kandli
Norway	UIB	Prof.	Rebecca Jane Cox
Serbia	MFUB	Prof.	Ljiljana Markovic-Denic
Switzerland	UBERN	Dr.	Cornelia Stahelin
Turkey	HU	Prof.	Murat Akova