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Version	Date	Status	Author(s), Reviewer	Description
V0.1	25/07/2023	Pre-final draft	The first draft compiled by RegionH sent to the coordinator and partners in WP7	
V1.0	09/08/2023	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
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
PRQ	Priority question
PHEIC	Public health emergency of international concern
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

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.

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 anchored in a broad European and international dialogue concerning new COVID-19 vaccine 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 within this task encompass 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 various channels: open discussions with the relevant stakeholders, online surveys, VACCELERATE webinars (https://vaccelerate.eu/webinars/), and collaboration 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 ongoing vaccine trials' existing and changing landscape. As of July 24, 2023, there are 1062 trials included in the mapping.
- Ensure the continuous relevance of the living document by revising and updating the topics for the COVID-19 vaccine 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 in particular underrepresented groups.
- Assess and re-evaluate the regularity of updates needed as the pandemic progresses.

This deliverable is intended to compliment the previously compiled lists of priority questions (PRQ) described in "*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 and "*D7.9 Updated report on unanswered COVID-19 vaccines and vaccination priority questions for future trials"* finalised in January 2023.

[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).

The current deliverable outlines the work done between January and July 2023 and is focused on evaluating which of identified priority questions (PRQ) were addressed by the vaccine trials conducted within the VACCELERATE consortium.

2 Deliverable content

This deliverable is structured as a reflection document complimenting the previously compiled lists of priority questions (PRQ) reported in the deliverables D7.4, D7.6, D7.8 and D7.9. These deliverables listed identified unanswered priority questions for future COVID-19 vaccine trials from the public health perspective, identified and prioritised via repeated online surveys to stakeholders, and compiled these into a so-called living document. The objective was to identify potential knowledge gaps and inform the potential focus of future vaccine trials and the development of phase 2 and phase 3 master protocol templates concerning public health topics.

In May 2023, WHO has announced that COVID-19 no longer constitutes a public health emergency of international concern (PHEIC)[2] but is now considered an established and ongoing health issue and COVID-19 vaccination was recommended to be integrated into life course vaccination programmes. In reflection of this, discussions of the new emerging research questions have mostly transformed into discussions of vaccine trial results, and therefore we deemed it useful to assess which of the previously identified questions were already addressed in the three vaccine trials conducted within the VACCELERATE Consortium.

2.1 Methods

For this report, a list of *all* priority questions regarding vaccine trials that were identified in the previous reports compiled within Task 7.2 was compiled and shared with the partners responsible for VACCELERATE vaccine trial to collect input from each specific trial.

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 template of the questionnaire shared with the partners responsible for the trials is available in Appendix 1. The summary of their answers is presented in this report.

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

[2] 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

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.

2.2 Results

For each trial the responsible partner organisation has submitted their answers to the questionnaire and shared it with CHIP/RegionH. The table below contains an overview of the answers submitted as to whether or not the particular priority question was addressed in the specific trial. The checked tick box in this case represents a positive answer, indicating that the question is addressed in the trial, text of priority questions in *italics* refers to specific questions about vaccination of the paediatric population and in **bold** to specific questions about vaccination of pregnant women.

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 (e.g. 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	WP11 Booster Vaccination in Elderly (EU-COVAT-1 AGED)	WP12 Booster Vaccination in Adults (EU-COVAT-2 BOOSTAVAC)	WP13 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?	☐	☒	☐
What are the long-term adverse side effects of vaccination in terms of vaccine-related or vaccine-induced diseases (autoimmune, oncologic, fertility etc.)?	☐	☐	☐
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?	☐	☐	☒
What is the vaccine efficacy and are there other immunological correlates of protection than antibodies in various immunocompromised groups?	☐	☐	☐
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 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?	☐	☐	☐
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)?	☐	☐	☒
How can immunisation schedule (booster timing and number) be optimised for the paediatric population to ensure maximum protection?	☐	☐	☐
What are the long-term safety considerations of vaccination among different paediatric age groups?	☐	☐	☐

Co-administration with influenza and pneumococcal vaccines for the paediatric populations.	☐	☐	☐
Vaccination strategy in pregnant women?	☐	☐	☐
Co-administration with influenza and pneumococcal vaccines for the elderly and pregnant women.	☐	☐	☐
Are current vaccines and vaccine strategies effective in preventing SARS-CoV-2 transmission?	☐	☐	☐
What are the individual or sub-population genetic or metabolic differences in response to vaccines (precision medicine approach)?	☐	☐	☐
Developing vaccines which are protective against a broad range of coronaviruses (e.g., pan-sarbecovirus vaccine).	☐	☐	☐
Integration of new types of COVID-19 vaccines (e.g., Nuvaxovid) in EU vaccination programs.	☐	☐	☐
Can novel vaccines achieve non-inferiority efficacy and safety by non-parenteral route (e.g., nasal vaccines) and possibly with only one dose?	☐	☐	☐

2.3 Discussion

Overall, it became evident that several identified PRQs were addressed in the VACCELERATE-led trials, 2 of them were addressed in all 3 trials, those being:

- ***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?***

And 3 priority questions were reported to be addressed to some degree by at least 2 VACCELERATE-led trials:

- ***Is there a need to develop new vaccines to protect against the VOCs?***
  (partially addressed EU-COVAT-1 AGED (booster vaccination in elderly) and addressed by EU-COVPT-1 COVACC (vaccination in children)).
- ***Longevity of immunity (humoral-cellular) in naturally infected individuals vs vaccinated and vaccinated and naturally infected (vaccination of recovered patients & hybrid immunity).***
  (partially addressed EU-COVAT-2 BOOSTAVAC (booster vaccination in adults) and addressed by EU-COVPT-1 COVACC (vaccination in children)).
- ***Comparative vaccine studies (incl. booster response of mRNA vaccines against protein-based vaccines).***
  (partially addressed EU-COVAT-1 AGED (booster vaccination in elderly) and addressed by EU-COVPT-1 COVACC (vaccination in children)).

Of course, some questions were not relevant for a particular trial due to the focus on a specific age group.

- Need for evidence synthesis on a global level

The exercise in identifying knowledge gaps could be useful on different levels. On the level of the VACCELERATE Consortium, it could help us ensure that our research activities remain relevant to the current epidemiological situation and can thus contribute to the synthesis of evidence on a global level.

In general, 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 list was included as part of the "Good practice statement on the use of variant-containing COVID-19 vaccines"[3] (First issued on 17 October 2022, Updated on 20 February 2023) and is included below:

- performance of variant-containing vaccines as booster doses across all COVID-19 platforms about:
    - vaccine effectiveness, immunogenicity and safety,
    - vaccine effectiveness stratified by disease outcome (asymptomatic, mild, moderate, severe, death),
    - vaccine effectiveness by priority groups,
    - breadth, magnitude and durability of humoral and cell-mediated immune responses to variants,
    - need and timing of further booster doses,
- hybrid immunity performance against severe disease outcomes;
- data on variant-containing vaccines as primary vaccine series across all COVID-19 platforms relating to:
- clinical data on immune responses in humans to a primary series and/or booster dose;
- bivalent variant-containing vaccines using platforms other than mRNA platforms;
- data on co-administration of WHO EUL COVID-19 vaccines with other routine vaccines;
- performance of heterologous boosters across all COVID-19 platforms about vaccine effectiveness by disease outcome;
- development of pan-SARS-CoV-2 or pan-sarbecovirus vaccines;
- development of vaccines with the ability to decrease transmission.

2.4 Next steps

In the upcoming final report on public health questions and emerging issues, we plan to summarise our experience in identifying priority questions for COVID-19 vaccination trials and compare the list against the latest version of vaccine trials listed in the COVID-NMA mapping tool (Task 7.1). The data are made available on a platform through interactive data visualisation (https://covid-nma.com/vaccines/mapping/).

[3] https://www.who.int/publications/i/item/WHO-2019-nCoV-Vaccines-SAGE-Variants-2022.1

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: Questionnaire to identify unanswered COVID-19 vaccines and vaccination priority questions for future trials that were addressed in VACCELERATE clinical trials

Please indicate your name, institution and contact details:

Name:

Institution:

Contact email:

Indicate your VACCELERATE Trial*:

- ☐ WP11 Booster Vaccination in Elderly (EU-COVAT-1 AGED)
- ☐ WP12 Booster Vaccination in Adults (EU-COVAT-2 BOOSTAVAC)
- ☐ WP13 Vaccination in Children (EU-COVPT-1 COVACC)

**Please submit only 1 response per trial and send it back to CHIP/RegionH at vaccelerate.rigshospitalet@regionh.dk*

Priority Questions for COVID-19 vaccine research	Addressed	Not addressed	Comments (e.g. PRQ not relevant for the trial/protocol)
What are the long-term safety considerations of vaccination in children?	☐	☐	
Are current vaccines and vaccine strategies effective in preventing SARS-CoV-2 transmission?	☐	☐	
How can immunisation schedule (booster timing and number) be optimised for the paediatric population to ensure maximum protection?	☐	☐	
What are the individual or sub-population genetic or metabolic differences in response to vaccines (precision medicine approach)?	☐	☐	
What is the best measure of protective immunity after vaccination at the individual level and when after vaccination should it be taken?	☐	☐	
What is the efficacy and specific immune response to the vaccine in children, (incl. immunocompromised paediatric population)?	☐	☐	
Are currently available vaccines effective against SARS-CoV-2 variants in the short- and long-term?	☐	☐	
Is there a need to develop new vaccines to protect against the VOCs?	☐	☐	
Developing vaccines which are protective against a broad range of coronaviruses (e.g., pan-sarbecovirus vaccine).	☐	☐	
What are the long-term adverse side effects of vaccination in terms of vaccine-related or vaccine-induced diseases (autoimmune, oncologic, fertility etc.)?	☐	☐	

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?	☐	☐	
Vaccination strategy in pregnant women?	☐	☐	
What is the vaccine efficacy and are there other immunological correlates of protection than antibodies in various immunocompromised groups?	☐	☐	
Integration of new types of COVID-19 vaccines (e.g., Nuvaxovid) in EU vaccination programs.	☐	☐	
How long does immunity (humoral-cellular) last after vaccination with current vaccines?	☐	☐	
What are the long-term safety considerations of vaccination among different paediatric age groups?	☐	☐	
Can novel vaccines achieve non-inferiority efficacy and safety by non-parenteral route (e.g., nasal vaccines) and possibly with only one dose?	☐	☐	
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).	☐	☐	
Studies to assess a 5th dose (likely to be provided in the autumn by many if a 4th dose is administered this spring).	☐	☐	
Co-administration with influenza and pneumococcal vaccines for the elderly and pregnant women.	☐	☐	
Co-administration with influenza and pneumococcal vaccines for the paediatric populations.	☐	☐	
Broader vaccines including the new multivalent vaccine candidates possibly even pansarbecovirus vaccines one day.	☐	☐	
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?	☐	☐	