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

OBS: This deliverable was due end of September but due to the recent amendment process, the report could not be uploaded earlier.

Table of Content

Version	Date	Status	Author(s), Reviewer	Description
V0.1	16/08/2021	Draft for internal review	Reviewed by Task 7.2 partners	First draft version of report (5.2Report_2021AUG16_draft)
V0.2	26/08/2021	Pre-final draft	Send to the coordinator	Final draft (5.2Report_2021AUG26_final)
V1.0	11/11/2021	Final report	Uploaded to EU Portal	Adaptation to new WP umbering

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
EUVAP	European Vaccine Trial Accelerator Platform
KUH	Karolinska University Hospital
MIS-C	Multisystem inflammatory syndrome in children
RegionH	Capital Region, Denmark
SERMAS	Servicio Madrileno De Salud
SWG	Stakeholder Working Group
UHC	University Hospital Cologne
VOCs	Variants of Concern
WP	Work Package
WHO Europe	World Health Organisation Regional Office for Europe

Comprehensive report on public health questions and emerging issues

1 Executive summary

Identifying and filling public health knowledge gaps in COVID-19 vaccine development has been deemed one of key network objectives and included as one of the work streams within VACCELERATE. Within the scope of Work Package 7 – Public Health Needs under the auspices of VACCELERATE, partner RegionH (Capital Region, Denmark), in collaboration with several other partners (SERMAS, CLEO, KUH, EUC, UHC) leads the work of task 7.2 focusing on the identification of unanswered questions for stakeholders. Specifically, task 7.2 aims to identify and prioritise emerging and unanswered public health and clinical research questions in relation to vaccine safety, efficacy, vaccination schemes. 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 within VACCELERATE including general public outreach, among others. It is also anchored in a broad European and international dialogue about new COVID-19 vaccine clinical trials aiming to inform both on-going and future studies through a living document of 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 an open-ended survey; repeat the survey with regular intervals (every 6 months), potentially to more targeted respondent groups, depending on the evolvement of the pandemic.
- Analyse, categorise and synthesise survey responses to develop an initial list of unanswered questions; cross-check with the 7.1. database for ongoing relevant studies addressing these questions.
- Present the prefinal list of priority questions in the SWG for discussion; final list is subsequently made publicly available via the VACCELERATE website
- Ensure the continuous relevance by revising and updating the list of priority questions regularly (every 3 months 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); and every 6 months based on repetitions of the stakeholder survey).
- Ensure synergies with WP2 and WP8 by using the developed structures to reach the general public and underrepresented groups in the repeated stakeholder surveys.
- Assess and re-evaluate the regularity of updates needed as the pandemic progresses.

[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 report outlines the work done between the February and August 2021 focusing on the development of the initial list of priority questions as the initial deliverable due in September 2021.

2 Deliverable content

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

2.1 Methods

- Survey development

Central for this task was the development of a survey targeting a broad range of stakeholders in Europe and beyond to seek input on identifying areas where knowledge gaps in relation to COVID-19 vaccines and vaccination remain. The development of the survey has been supported through discussions during regular meetings of Work Package 7 partners and sub-task meetings with Task 7.1 due to natural synergies between the two tasks. Meetings with partners were an opportunity to seek input on several key parameters of the stakeholder survey, specifically:

  - Survey scope and format
  - Clarification of synergies with other tasks
  - Formulation of survey questions
  - Identification of key stakeholders for the survey

- Input from VACCELERATE Stakeholder Working Group

In addition to regular VACCELERATE partner meetings, the task also received substantial input from the VACCELERATE SWG, which serves as the core advising platform for the consortium in general and for specific activities, including Task 7.2. During one of the monthly SWG meetings on April 15, 2021, following the presentation of scope, objectives and workplan of task 7.2, SWG member provided critical input on the overall direction of task, including:

  - Consideration of the timeline in light of rapidly shifting vaccine priorities and the need for regular updates to the initial list of priorities
  - Suggestions for specific groups to circulate the survey to
  - Stressing the need to clarify the aims and target of the priority list of questions
  - Importance of capitalizing on the National Coordinators and linking to what is happening at the country level

- Stakeholder survey

Once developed the survey was circulated to a broad range of stakeholders in Europe and beyond to seek input on identifying areas where knowledge gaps in relation to COVID-19 vaccines and vaccination remain. The survey has been developed in an open-ended format allowing stakeholders to submit up to three topics that they consider a priority. The respondents were also asked to supply a rationale for

their response explaining why, in their opinion, a particular issue merits to be prioritized for clinical trials. In addition, there was an opportunity to provide additional information including:

- Specific research question and sub-questions to be addressed
- Study design and population to be studied
- Possible outcome measures and/or endpoints

The survey is available in Appendix 1. The survey has been developed in and administered via the RedCap platform and was circulated as an email with a link to the identified stakeholders, specifically:

- VACCELERATE consortium (National Coordinators, Work Package leads and participants, clinical trial sites registered in EUVAP);
- Vaccines Europe (https://www.vaccineseurope.eu/)
- Coalition for Vaccination (https://www.cpme.eu/coalition-for-vaccination/)
- European Federation of Nurses Associations (https://www.efn.be/)
- Standing Committee of European Doctors (https://www.cpme.eu/)
- European Joint Action on Vaccination (https://eu-jav.com/)

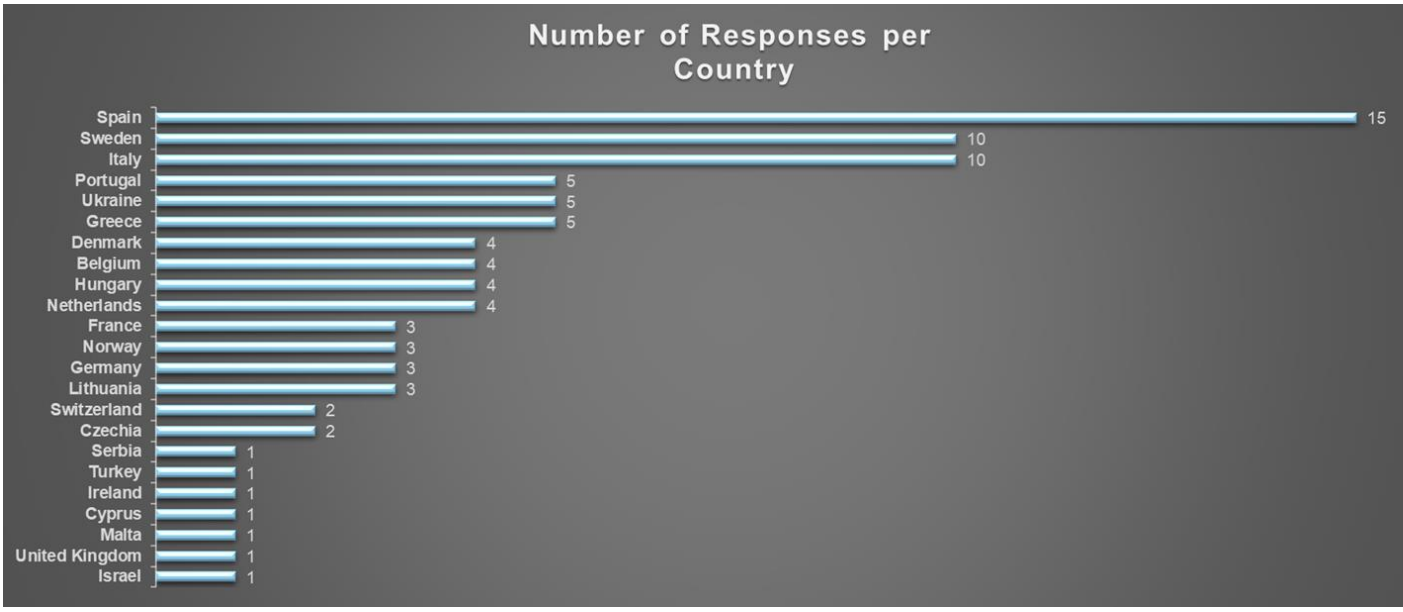
VACCELERATE partners were also asked to further distribute the survey within their networks, and the VACCELERATE National Coordinators distributed to key stakeholders such as Ministry of Health and national public health institutes. The survey responses were collected over a three-week period between May 20 and June 11, 2021.

2.2 Results

- Respondent profile

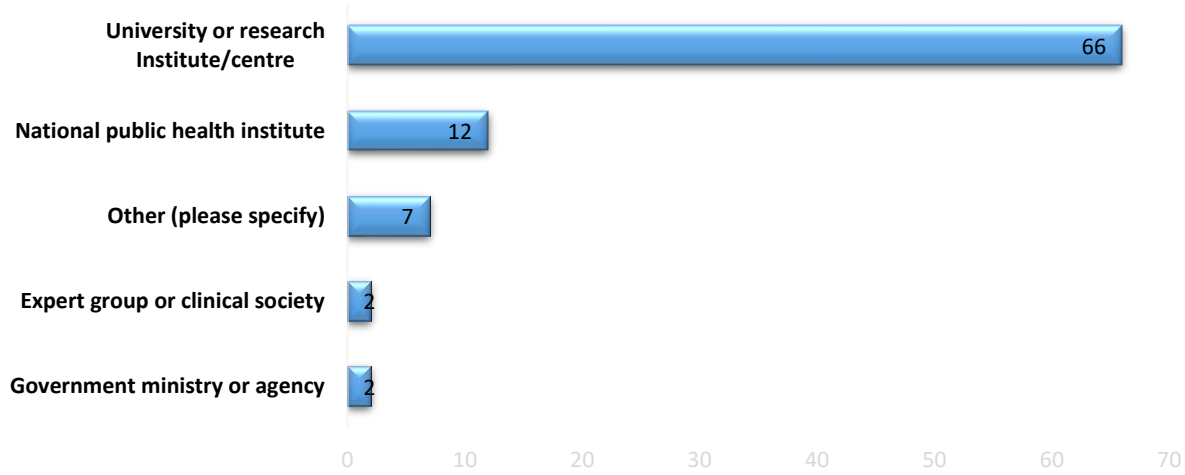
A total of 89 responses to the stakeholder survey have been received resulting in 148 submitted priority topics. Responses have been received from 23 countries across the EU but also from associated countries via clinical sites registered in the EUVAP platform as presented in Figure 1 here:

Figure 1: Responses by country



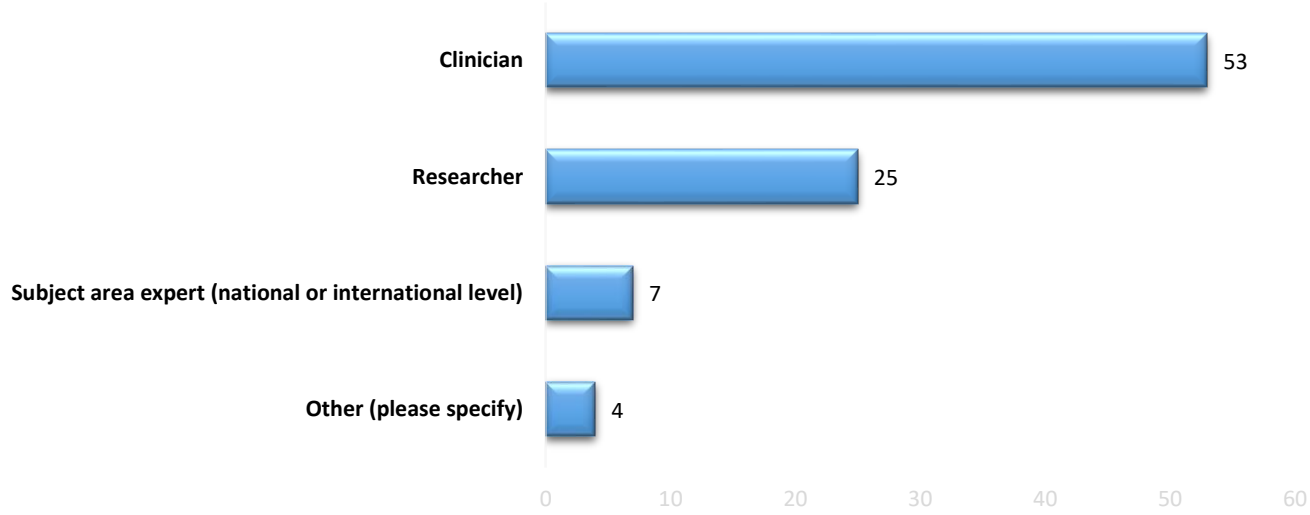
Over half of the respondents represent university research centers, and responses have also been received from government agencies including public health institutes, expert groups, clinical societies, laboratories and non-governmental organizations as listed in Figure 2:

Figure 2: Responses by institutional affiliation



The distribution by professional background included clinicians in over half of the respondents followed by researchers, and subject area experts as shown in Figure 3 below:

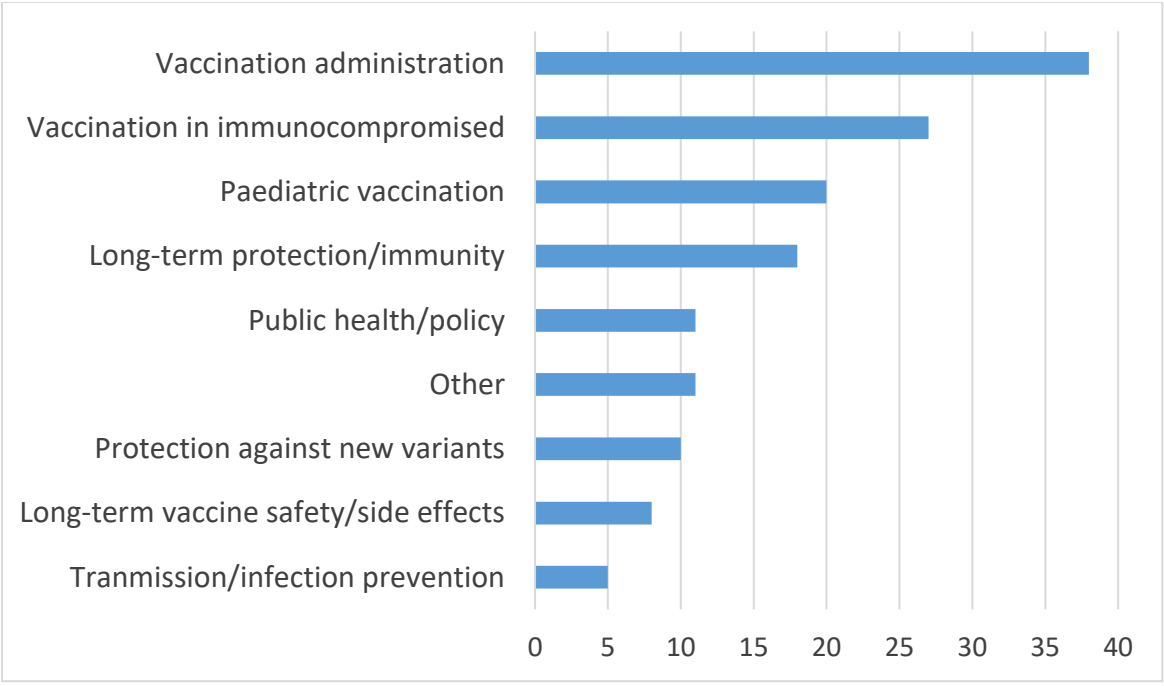
Figure 3: Responses by professional background



- Data analysis

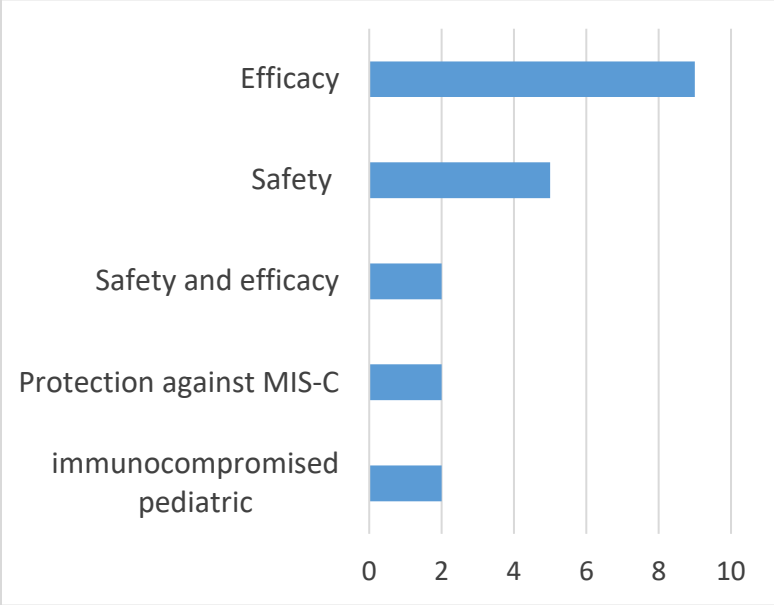
The analysis of the responses has been done internally by RegionH/CHIP as task leader. All the responses have been analyzed thematically and grouped into broader thematic categories resulting in eight thematic and 'Other' categories found in Figure 4 below:

Figure 4: Thematic categories developed from survey responses (by number of responses).



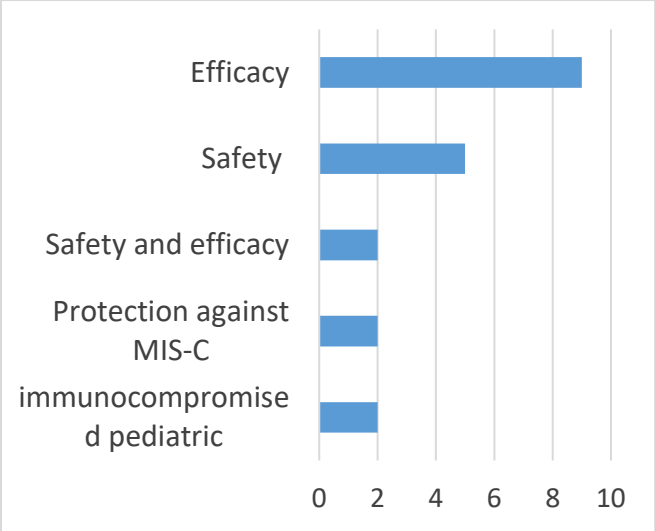
In addition to the development of broad themes, whenever some heterogeneity of responses emerged, further sub-themes have been extrapolated for a more nuanced analysis as per example below of paediatric vaccination in Figure 5.

Figure 5: Paediatric vaccination sub-themes (by number of responses)



Themes and sub-themes have further been formulated into priority questions reflective of the responses as example in Figure 6 below:

Figure 6: Example of sub-categories and corresponding formulated priority questions



Priority question (s):

3a. What is the efficacy and the specific immune response to the vaccine in children, including immunocompromised pediatric population?

3b. What are the long-term safety considerations of vaccination in children?

3c. What is the relationship in terms of protection between vaccination and immuno-mediated diseases such as MIS-C?

For details of the response analysis and charts see Appendices 2 and 3.

- Final list of 17 priority questions

After categorization, the survey replies have been grouped and compiled into a final list of 17 priority questions:

VACCELERATE survey priority questions

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?

Pediatric vaccination

7. What is the efficacy and the specific immune response to the vaccine in children, including immunocompromised pediatric 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?

**Topic addressed in the VACCELERATE clinical trials (see Appendix 4)*

2.3 Discussion

Identification of unanswered questions in relation to the vaccine and vaccination is first and foremost motivated by the need to ensure large, long-term scale immunity for the entire population. This means finding answers to the questions not addressed in the initial clinical trials, notably questions related to vaccine efficacy and safety in groups initially underrepresented in the trials such as those with compromised immunity, children, among others. While opinions on the priorities may diverge, the 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.

- Vaccine administration

Priority questions concerning vaccine administration (schedule, technology and vaccine combination) have received the highest number of responses to the survey testifying to the importance this issue holds for the stakeholders. Although many questions concerning the administration of vaccines among specific groups (see below) remain, many of them remain relevant for the population at large. The longevity of protection is thought to depend on vaccination schedule, among other factors, and understanding of both the initial vaccination and subsequent boosters to optimize immune responses will be required. Ongoing discussions regarding administration of 3rd booster dose further underscore the importance of this issue.

- Vaccination in immunocompromised

Because vaccines were initially tested on healthy populations, their efficacy and safety in other demographic groups, particularly immunocompromised, is largely unknown. Knowledge gaps regarding vaccine administration mentioned above are particularly relevant to individuals

with co-morbidities and other health conditions including auto-immune diseases. Although the survey responses resulted in a broad category of vaccination in immunocompromised, specific health conditions such as cancers warrant studies in various demographic groups to fully understand the relationship between specific underlying conditions and COVID-19 vaccination.

- Paediatric vaccination

Despite vaccination of children having been approved in some countries, further studies are needed to determine not only the efficacy of the vaccine but also its safety in the paediatric population including immunocompromised children. Within the context of VACCELERATE a study is planned to elucidate some of these questions by looking at the required vaccination dosage in children and adolescents with prior SARS-CoV-2 infection. The findings of the study will aim to inform vaccination schedule in this group by highlighting whether a single dose is enough.

- Long-term protection and immunity

Although the effectiveness of current vaccines to protect against the disease, developing severe disease outcomes and potentially transmission is known, the duration of the protection remains uncertain. How various factors including demographic and health characteristics influence the immunity will need to be studied to inform future vaccination schedules and the potential need and timing of further boosters or revaccination.

- Protection against new variants

Unknown effectiveness of existing vaccines against current and emerging virus variants warrants further studies to determine if new vaccines will be required to effectively protects again the VOCs.

- Public health/policy

While most priority research questions developed from the survey are suitable for clinical trials, a number of priorities identified fall under the policy and public health umbrella. These include issues of vaccine hesitancy, underrepresented groups, for example, and the need to actively engage with the public to address misinformation, increase public confidence and tackle potential barriers to vaccination, particularly among specific hard-to-reach groups. These issues are covered within VACCELERATE and will be shared with the relevant work packages.

- Long-term vaccine safety and side effects

The need for long-term studies to shed light on any potential long-term side effects of vaccination have also been identified in the survey responses. This relates to general long-term safety as well as specific conditions such as fertility.

- Infection transmission prevention

The effectiveness of current vaccines in reducing transmission in addition to preventing illness is an important public health issue and several responses specifically highlighted this topic encouraging further research efforts to understand the reduction in disease spread.

2.4 Next steps

The survey has been carried out to develop the initial list of knowledge gaps that research and policy stakeholders consider as priorities for clinical trials due to their impact on public health. Nevertheless, other sources such as reports from reputable public health agencies, media, scientific literature and relevant scientific expert organisations must also be considered to ensure continuous relevance and accuracy of the priority questions. A preliminary mapping of the initial priority list against planned VACCELERATE trials has been conducted and can be found in Appendix 4.

In light of the decision to continue Task 7.2 beyond the initial one-off deliverable in August 2021, the activity has been extended until the end of the VACCELERATE project cycle with a view to build on the initial list of questions and update it to reflect changing priorities in line with the public health priorities of the pandemic. The following steps will be the focus of the next phase of the process:

- Repeat the survey with regular intervals (possibly every 6 months), potentially trying to reach respondent groups not covered in the first survey round such as the general public and under-represented groups (in collaboration with WP4 and WP10), depending on the evolvement of the pandemic.
- Conduct a review of the ongoing studies included in the task 7.1. database to assess their linkage to and relevance for providing answers to the identified questions.
- Ensure the continuous relevance by revising and updating the list of priority questions regularly (every 3 months) 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); and every 6 months based on repetitions of the stakeholder survey).
- Ensure synergies with WP4 and WP10 by using the developed structures to reach the general public and underrepresented groups in the repeated stakeholder surveys.
- Assess and re-evaluate the regularity of updates needed as the pandemic progresses.

It is suggested to provide space in the consortium for at discussion of how the list of the identified priority questions is utilized in the process of identifying additional clinical trials to be conducted withing VACCELERATE.

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

This deliverable was due end of September and was delivered to the Coordination Office on time. However, due to the recent amendment process, the report could not be uploaded earlier as the Continuous Reporting was not unlocked.

4 Appendices

Appendix 1: Stakeholder Survey

Appendix 2: Thematic response analysis

Appendix 3: Priority categories charts

Appendix 4: Mapping of priority questions and VACCELERATE Trials

Stakeholder survey to identify public health priority questions for future COVID-19 vaccine trials

The EU funded project VACCELERATE (the European Corona Vaccine Trial Accelerator Platform), aiming to facilitate and accelerate the design and implementation of COVID-19 phase 2 and phase 3 vaccine trials, is conducting a brief survey among key stakeholders. The purpose of the survey is to seek input in identifying public health knowledge gaps in relation to COVID-19 vaccines and vaccination to help prioritise topics where clinical trials/studies are most urgently needed.

The survey is being circulated to a wide range of clinical, public health and other partners across Europe to gather diverse perspectives. We seek your input as individual expert and/or via your institutional affiliation. Please submit your response by June 11, 2021. If you have any questions about the survey, please e-mail vaccelerate.rigshospitalet@regionh.dk.

We thank you in advance for your participation.

Respondent details (please fill in your affiliation details below)

Type of institutional affiliation (check one that applies best):

- ◯ University or research Institute/centre
- ◯ National public health institute
- ◯ Government ministry or agency
- ◯ Expert group or clinical society
- ◯ International organisation or network (expert or policy)
- ◯ Pharmaceutical company/vaccine developer
- ◯ Patient group representative
- ◯ Other (please specify)

If 'other' type of institutional affiliation, please specify: _____

Professional background (check one that reflects best the capacity in which you are responding to this survey):

- ◯ Clinician
- ◯ Researcher
- ◯ Policy advisor
- ◯ Subject area expert (national or international level)
- ◯ Other (please specify)

If 'other' professional background, please specify: _____

Country (please indicate the country where you are currently working):

- ◯ Albania
- ◯ Andorra
- ◯ Armenia
- ◯ Austria
- ◯ Azerbaijan
- ◯ Belarus
- ◯ Belgium
- ◯ Bosnia and Herzegovina
- ◯ Bulgaria
- ◯ Croatia
- ◯ Cyprus
- ◯ Czechia
- ◯ Denmark
- ◯ Estonia
- ◯ Finland
- ◯ France
- ◯ Georgia
- ◯ Germany
- ◯ Greece
- ◯ Hungary
- ◯ Iceland
- ◯ Ireland
- ◯ Israel
- ◯ Italy
- ◯ Kazakhstan
- ◯ Kyrgyzstan
- ◯ Latvia
- ◯ Liechtenstein
- ◯ Lithuania
- ◯ Luxembourg
- ◯ Malta
- ◯ Moldova
- ◯ Monaco
- ◯ Montenegro
- ◯ Netherlands
- ◯ North Macedonia
- ◯ Norway
- ◯ Poland
- ◯ Portugal
- ◯ Romania
- ◯ Russia
- ◯ Serbia
- ◯ Kosovo
- ◯ Slovakia
- ◯ Slovenia
- ◯ Spain
- ◯ Sweden
- ◯ Switzerland
- ◯ Tajikistan
- ◯ Turkey
- ◯ Turkmenistan
- ◯ Ukraine
- ◯ United Kingdom
- ◯ Uzbekistan
- ◯ Other (please specify)

If 'other' country, please specify:

_____

Email address
Your email address will be stored exclusively for the purpose of contacting you in case clarification regarding your survey response is needed. It will not be shared with any other entity or used for any other purpose than stated here.

_____
(By providing my email address, I agree to be contacted in case of validation questions related to my survey responses.)

Top three questions/topics for future COVID-19 vaccine studies

Please include up to three questions/topics from the public health perspective* that you believe should be prioritised at the European level or in your country in future COVID-19 vaccine trials/studies.

*** I.e. issues that contribute to maximum societal benefit in terms of health protection and immunity.**

Public health priority question 1 (short title/question) [word limit 30]

_____

1.1 Priority question 1 (please choose a category that the question broadly falls under):

◯ Vaccine efficacy
◯ Vaccine development (e.g. vaccination timing, combination of vaccine technologies etc.)
◯ Specific populations (e.g. chronic conditions, immunodeficiency, age groups etc.)
◯ Other (please specify)

If 'other' category, please specify:

_____

1.2 Please elaborate on the rationale for why you think this question or topic should be a priority [word limit 200]:

_____

1.3 What research question and sub-questions would the study address [word limit 100]?

_____

1.4 Please suggest possible outcome measures or endpoints of the study [word limit 100]:

_____

1.5 Please specify the population to be studied (if not done already):

_____

1.6 Please suggest a possible study design:

_____

Public health priority question 2 (short title/question) [word limit 30]

_____

2.1 Priority question 2 (please choose a category that the question broadly falls under):	◯ Vaccine efficacy ◯ Vaccine development (e.g. vaccination timing, combination of vaccine technologies etc.) ◯ Specific populations (e.g. chronic conditions, immunodeficiency, age groups etc.) ◯ Other (please specify)
If 'other' category, please specify:	_____
2.2 Please elaborate on the rationale for why you think this question or topic should be a priority [word limit 200]:	_____
2.3 What research question and sub-questions would the study address [word limit 100]?	_____
2.4 Please suggest possible outcome measures or endpoints of the study [word limit 100]:	_____
2.5 Please specify the population to be studied (if not done already):	_____
2.6 Please suggest a possible study design:	_____
Public health priority question 3 (short title/question) [word limit 30]	_____
3.1 Priority question 3 (please choose a category that the question broadly falls under):	◯ Vaccine efficacy ◯ Vaccine development (e.g. vaccination timing, combination of vaccine technologies etc.) ◯ Specific populations (e.g. chronic conditions, immunodeficiency, age groups etc.) ◯ Other (please specify)
If 'other' category, please specify:	_____
3.2 Please elaborate on the rationale for why you think this question or topic should be a priority [word limit 200]:	_____
3.3 What research question and sub-questions would the study address [word limit 100]?	_____
3.4 Please suggest possible outcome measures or endpoints of the study [word limit 100]:	_____

3.5 Please specify the population to be studied (if not done already):

_____

3.6 Please suggest a possible study design:

_____

General comments

Please include any other comments you would like to provide:

_____

Respondent #	Categories	Sub-categories	Priority topics	Priority questions
58	Vaccination in immunocompromised	Efficacy	efficacity of vaccines in compromised populations (58)	
1	Vaccination in immunocompromised	Efficacy	Are there substantial differences in different populations or subgroups concerning vaccine efacacy? Oncology etc. (1)	
3	Vaccination in immunocompromised	Efficacy	Vaccine efficacy in each of the target high risk groups (3)	
18	Vaccination in immunocompromised	Efficacy	vaccination of immunosuppressed individuals: need to define if there are other correlates of protection than antibody Effectiveness of boosting / boosting frequency (18)	
47	Vaccination in immunocompromised	Efficacy	Correlates of protection in "X" risk group in "X" COVID19 vaccined patients. Differences in correlates of protection stratified by variants and specific vaccines. (47)	
13	Vaccination in immunocompromised	Efficacy	efficacy in patients with haematological malignancies (13)	
25	Vaccination in immunocompromised	Efficacy	vaccination of immunocompromised pts (25)	
35	Vaccination in immunocompromised	Efficacy	evaluate vaccination in patients with lymphomas (the timing of the vaccination, the antibody response) (35)	
42	Vaccination in immunocompromised	Efficacy	efficacy in heamatological patients (42)	
31	Vaccination in immunocompromised	Efficacy	Protection after vaccination in immunosuppressed individuals (31).	**1. What is the vaccine efficacy and are there other immunological correlates of protection than antibodies in various immunocompromised groups?**
33	Vaccination in immunocompromised	Efficacy	Vaccine efficacy in immune-compromised patients (HIV, steroids, HSCT, SOT recipients etc.) (33)	
41	Vaccination in immunocompromised	Efficacy	coverage of all immunocompromised patients. Epidemiology of infection, seroprevalence of antibodies, frequency of variants of concern, etc (41)	
11	Vaccination in immunocompromised	Efficacy	Neglected populations, Various neglected populations: transplant recipients other immunocompromised, children ...(11)	
14	Vaccination in immunocompromised	Efficacy	Immuniyt pattern in different subpopulations, differences in immunity pattern of general population, immune impaired or comorbid subjetcs (14)	
34	Vaccination in immunocompromised	Efficacy	Vaccine in immunocompromised patients, - immunogenicity (humoral and cellular)? - Number of doses needed? - How long does immune response last? - Does prevent from severe cases? (34)	
54	Vaccination in immunocompromised	Efficacy	vaccine efficacy in global population and in inmunosupressed patients. Density of incidence of new infections in vaccinated population vs non vaccinated. Adverse events detected and severity (54)	
63	Vaccination in immunocompromised	Efficacy	Immunological correlate of protection after COVID-19 vaccination Ideally this would be in different groups stratified by comrobiidties (63)	
66	Vaccination in immunocompromised	Efficacy	How long lasting is the humoral and cell mediated immunogenicity of the mRNA vaccines on SARS CoV2 variants in the general/fragile (oncological/haematological/HIV/rheumatological/cirrhotic...) populations, respecting the	
75	Vaccination in immunocompromised	Efficacy	immunogenicity and safety in immunossupresed patients	
78	Vaccination in immunocompromised	Efficacy	To determine immune response to covod vaccine in some groups of patients such as Immunocompromized children, obese, ...(78)	
47	Vaccination in immunocompromised	Vaccination schedule	Re-vaccination schedules for specific risk groups. 1) Time for revaccination, determined by antibody decay profile or time to SARS-CoV-2 infection 2) Persistency of neutralizing antibodies over time (47)	
43	Vaccination in immunocompromised	Vaccine technologies	Should people with chronic illnesses get the third dose (43)	
88	Vaccination in immunocompromised	Vaccine technologies	Length of immunity after two doses of vaccine in persons with comorbidities. (88)	**2. How can immunisation schedule (booster timing and number) and technologies (vaccine dose and type) be optimised for the immunocompromised group to ensure maximum protection?**
5	Vaccination in immunocompromised	Vaccine technologies	Vaccination of immunocompromised patients to find out which type of vaccines is the most suitable for this population (5)	
79	Vaccination in immunocompromised	Vaccine technologies	evaluation of different vaccination strategies in immunocompromized. (79)	
87	Vaccination in immunocompromised	Vaccine technologies	booster doses in immunocompromised patients. (87)	
7	Vaccination in immunocompromised	Vaccine technologies	Performance of different covid vaccine technologies and combinations in immune suppressed cohorts (7)	
16	Long-term vaccine safety/side effects		Are COVID vaccine strategies safe? Heterologous vaccination or revaccination could harm. Using new life attenuated covid vaccines could give more side effects (16)	
17	Long-term vaccine safety/side effects		lack of long term observational studies/data about possibly vaccine related/induced diseases (autoimmune, oncologic, etc.) (17)	
37	Long-term vaccine safety/side effects		Does vaccination cause any fertility problems (37)	**3. What are the long-term adverse side effects of vaccincation in terms of vaccine-related or vaccine-induced diseases (autoimmunie, oncologoic, fertility etc.)?**
45	Long-term vaccine safety/side effects		Can C 19 Vaccines trigger or unmask an autoimmune hepatitis? Drugs and vaccines are known to trigger auntoimmune hepatitis (45)	
3	Long-term vaccine safety/side effects		Long term adverse effects. Are new vaccines really safety on the long term? (3)	
37	Long-term vaccine safety/side effects		what is the % of side effects and or death after vaccination (37)	
58	Long-term vaccine safety/side effects		population based survey of major side effects after COVID-19 vaccination (58)	
68	Long-term vaccine safety/side effects		Vaccine Safety is a crucial. How to minimise negative effects of the vaccine, at production and administration level is important. (68)	
44	Paediatric vaccination	efficacy	Vaccine efficacy is the most importantn aspect for immunisation of children and adolescents. How long are vaccinated children protected against Covid-19? How probable is a new infection from Covid-19 after completion of the immunisation? - Do all age groups respond to the vaccine in the same potent way? (44)	
2	Paediatric vaccination	efficacy	efficacy, dose, schedule (2)	
41	Paediatric vaccination	efficacy	coverage of children, Epidemiology of infection, seroprevalence of antibodies, frequency of variants of concern, etc (41)	
39	Paediatric vaccination	efficacy	avoid deaths, Avoid deaths and inpatient admissional intensivo care and morbility, children under 12 (39)	**4. What is the efficacy and the specific immune response to the vaccine in children, including immunocompromised pediatric population?**
39	Paediatric vaccination	efficacy	avoid inpatients, children under 12 (39)	
64	Paediatric vaccination	efficacy	Trasmission of SARS-CoV-2 in pediatric population, what is the transission of SARS-CoV-2 in the pediatric population while attending school	

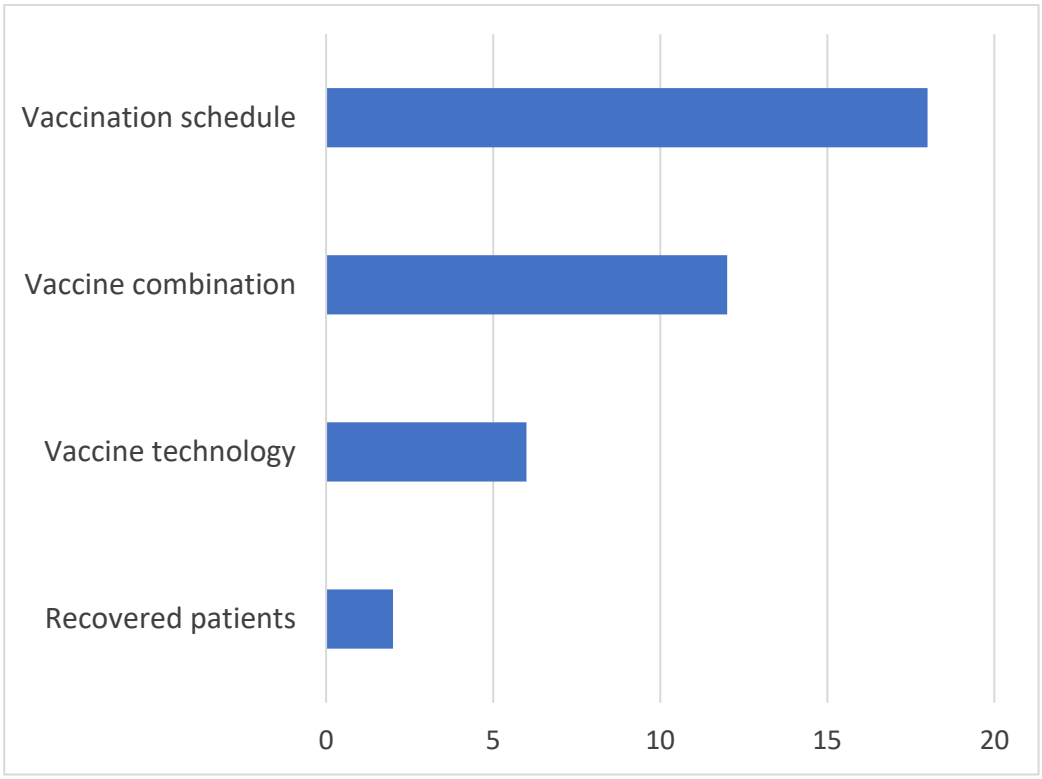
78	Paediatric vaccination	efficacy	To identify pediatric spécifities of immune response to the COVID vaccine in children (immunomonitoring). (78)	
78	Paediatric vaccination	efficacy	To study immune response towards new covid variants in already vaccinated children	
89	Paediatric vaccination	efficacy	The vaccine efficacy in Children and adolescents. (89)	
45	Paediatric vaccination	immunocompromised pediatric	Response in immunocompromised pediatric population to know whether the efficacy and immunogenicity response of C19 VACCINE in immunocompromised pediatric population is similar to other children and adults (45).	
67	Paediatric vaccination	immunocompromised pediatric	COVID-19 immunization of immunocompromised children/adolescents. Immunogenicity of various COVID19 vaccine dosing regimens in immunocompromised children. (67)	
27	Paediatric vaccination	Protection against MIS-C	Children, vaccination and reduction of MIS-C (27)	**5. What is the relationship in terms of protection between vaccination and immunomediated diseases such as MIS-C?**
74	Paediatric vaccination	Protection against MIS-C	Covid-vaccination in children and risk of PIMS/MISC-T. Children can have PIMS/MISC-T after/during an acute covid-19 episode. Are they more prone after vaccination or does the vaccine also protect for this immunemediated disease? (74)	
29	Paediatric vaccination	safety	safety aspects in pediatrics (29)	
37	Paediatric vaccination	safety	How safe is the vaccination for kids (37)	
44	Paediatric vaccination	safety	Is it safe in longterm to apply a Covid-19 vaccination in children and adolescents? - Are there side effects connected to the vaccine in short-term or longterm?	
59	Paediatric vaccination	safety	vaccine safety in children (59)	**6. What are the long-term safetry considerations of vaccination in children?**
67	Paediatric vaccination	safety	for children and adolescents: safety and reactogenicity of co-administering COVID19 vaccine with routine childhood immunizations (67)	
10	Paediatric vaccination	safety and efficacy	vaccine efficacy and safety in paediatric population (vaccination regimen, timing) (10)	
18	Paediatric vaccination	safety and efficacy	vaccination of children, Identify effective and not least safe vaccines for children (18)	
2	Vaccination administration	Recovered patients	Vaccination of people that had COVID (2) (recovered patients)	
65	Vaccination administration	Recovered patients	Long term effects of (vaccination in) patients who experience severe healty issues after a COVID-19 infection, comparison with non-vaccinated. (65)	**7. What should the vaccination strategy be for recovered patients?**
2	Vaccination administration	Vaccination schedule	Need of further booster doses. Duration of vaccine protection Identification of biomarkers of protection (2)	
11	Vaccination administration	Vaccination schedule	Vaccination schedule (timing and number of boosters. Optimization of the timing of any booster doses (after the 1st dose) and how many booster doses will be needed. (11)	
30	Vaccination administration	Vaccination schedule	Vaccine revaccination strategies (30)	
11	Vaccination administration	Vaccination schedule	Vaccination dose. Can we safely reduce booster doses (to save money and limited vaccines) (11)	
13	Vaccination administration	Vaccination schedule	role of booster vaccination after 6 months, can we provide increased protection with a booster vaccination following the initial dosis (13)	
31	Vaccination administration	Vaccination schedule	Booster vaccination, How long time after vaccination does the protection seem to vanish (31)	
15	Vaccination administration	Vaccination schedule	A vaccine that can fit the immunization schedule. Safety. Efficacy. (15)	
55	Vaccination administration	Vaccination schedule	When is next booster? (55)	
61	Vaccination administration	Vaccination schedule	Compare the duration of immunity achieved by the different licensed vaccines administered according to the protocol or with an increase in the interval between doses, when applicable	**8. How can immunisation schedule (booster timing and number) and technologies (vaccine dose and type) be optimised to ensure maximum protection?**
63	Vaccination administration	Vaccination schedule	Prime boost studies, need to understand when one dose of vaccine is sufficient and which vaccines prime or boost best, along with appropairtae timing interval (63).	
66	Vaccination administration	Vaccination schedule	Does administration of a booster mRNA vaccine affect humoral/cellular response to SARS CoV2 after schedule completion with the same vaccine? at what time is the booster more effective in generalpopulation. (66)	
76	Vaccination administration	Vaccination schedule	Frequency of regularly needed vaccinations? (76)	
79	Vaccination administration	Vaccination schedule	evaluation of correlates of protection. (79)	
79	Vaccination administration	Vaccination schedule	boost evaluation and dose interval. (79)	
80	Vaccination administration	Vaccination schedule	booster studies, adress the safety and efficacy of booster studies. (80)	
82	Vaccination administration	Vaccination schedule	What is the need for future booster doses and when should they be given? (82)	
87	Vaccination administration	Vaccination schedule	Booster SARS-CoV2 vaccine doses in Healthcareworkers. (87)	
6	Vaccination administration	Vaccination schedule	Whom vaccinate, when third vaccination (6)	
5	Vaccination administration	Vaccine combination	Mix-and-match COVID vaccines trigger potent immune response. To evaluate the advantage of combining the vaccines. To find out how to continue with re-vaccination with the different types of vaccine. (5)	
7	Vaccination administration	Vaccine combination	performance of varient vaccines in different schedules. how often booster vaccines are required and which vaccines should be used, in which combinations. (7)	

12	Vaccination administration	Vaccine combination	vaccine switch for the future dose. different vaccines will be available at the same time. no efficacy data regarding cross-over from viral vector-base vaccine vs DNA/RNA-based ones in terms of both amount and duration of antibodies response (12)	
52	Vaccination administration	Vaccine combination	Which vaccine to use for re-vaccination. Would a new type of vaccine induce a different type the immune response that would confer long-lasting immunity against COVID? (52)	
55	Vaccination administration	Vaccine combination	Should the vaccine programme be heterogenous? (55)	
57	Vaccination administration	Vaccine combination	Duration and levels of protective vaccine induced immunity after heterologous vs homogenic vaccine administration, eg mRNA vaccine followed by viral vector vaccine or 2 doses of the same type (57).	**9. What is the comparative advantage of heterologous vs. homogenic vaccination in terms of efficacy, safety and duration of protection.**
65	Vaccination administration	Vaccine combination	Can current vaccines give greater benefit/efficacy when combined. (65)	
69	Vaccination administration	Vaccine combination	Second generation of vaccines and understand vaccine efficiency with good correlates of protection using standardized immunological assays. Effectiveness and safety of heterologous prime boost strategies. Effectivness of boosting with 2nd gen vaccines. reliable immunological comparisons across studies. (69)	
74	Vaccination administration	Vaccine combination	Is it possible to combine 2 vaccines of different technology (for example a first dose with a vector vaccine and a second dose with a RNA vaccine)? (74)	
83	Vaccination administration	Vaccine combination	booster studies, safety and eficacy of booster dose with a vaccine different from the one adminitered during primary vaccination. (83)	
84	Vaccination administration	Vaccine combination	Trials of different vaccine combinations for 1st ,2nd and booster doses to obtain the best variant coverage and duration of response eg mRNA first dose , protein based second dose,etc. (84)	
88	Vaccination administration	Vaccine combination	COVID-19 vaccine boosters; combining different vaccines. The combination of two different vaccines might be more valuable than one. (88)	
40	Vaccination administration	Vaccine technology	Which vaccination routes can be used leading to dose sparing and non-inferior efficacy creating the possibility to vaccinate many more people. (40)	
54	Vaccination administration	Vaccine technology	Number of vaccine doses, how to achieve a safe and efficacy vaccine with only one dose (54)	
13	Vaccination administration	Vaccine technology	efficacy of novel avccines in patients failing to respond to first-genration vaccines (13)	
61	Vaccination administration	Vaccine technology	To develop and evaluate the efficacy of using vaccines administered by the non-parenteral route, namely by the nasal route (61)	**10. Can novel vaccines achieve non-inferiority efficacy and safety by non-parenteral route and possibly with only one dose?**
4	Vaccination administration	Vaccine technology	What is the best possible technology and focus on vaccine development with that technology, preferably requiring a single dose. (4)	
54	Vaccination administration	Vaccine technology	Monodosis vial COVID-19 vaccine, economic evaluation of monodose vaccine, costs of fabrication and costs or adverse events comparison (54). - move	
14	Tranmission/infection prevention		How many transmissions could be prevented by vaccination (14)	
16	Tranmission/infection prevention		Are COVID vaccine strategies reducing further spread? (16)	
51	Tranmission/infection prevention		assess infection effectiveness, the effectiveness in preventing the infection is unknown. How many neutralizing antibodies are produced in increasing doses of vaccine? How long are they here for? What is the minimum number of effective neutralizing antibodies on the infection?	**11. Are current vaccines and vaccine strategies effective in preventing SARS-COV-2 transmission?**
16	Tranmission/infection prevention		Are COVID vaccine strategies reducing further spread? (16)	
75	Tranmission/infection prevention		Protection to the infection, not only the disease.	
17	Long-term protection/immunity	immunity duration	How long does immunity last after COVID-19 vaccination? (17)	
31	Long-term protection/immunity	immunity duration	Duration of protection: How long does the protection last after the two prime-prime doses? (31)	
33	Long-term protection/immunity	immunity duration	Duration of protection after vaccination: determine the need for revaccination and isolation precaution duration after achieving herd immunity (33)	
34	Long-term protection/immunity	immunity duration	Durability of vaccine protection:How long does immunity last (humoral-cellular)? - How long does vaccine protect from COVID disease? - How long does vaccine protect from severe COVID-19? - Of the commercialized vaccines, which one offer a better long-term immunity? (34)	
38	Long-term protection/immunity	immunity duration	long-lasting protection: duration of vaccine efficacy (38)	
52	Long-term protection/immunity	immunity duration	The time scale of effectiveness of every type of vaccines. It is of utmost importance to have a clear idea of how long the current vaccines confer immunity against SARS-CoV-2 and to define cut-off values that would indicate need for re-vaccination. (52)	**12. How long does immunity (humoral-cellular) last after vaccination with current vaccines?**
43	Long-term protection/immunity	immunity duration	How long does immunity after Covid vaccination last? Do we need vaccination every year? (43)	
46	Long-term protection/immunity	immunity duration	Duration of immunity (46)	
48	Long-term protection/immunity	immunity duration	long-term clinical trials to determine duration of immunity to determine in the long term if we will have to revaccinate and also if it will be necessary to do it only in certain groups (48)	
52	Long-term protection/immunity	immunity duration	Does the individual immune response correlate with effectiveness of vaccines? Is there a surrogate marker that would indicate when a given person is no longer safe after being	
56	Long-term protection/immunity	immunity duration	Long term immunity with current vaccines (56)	

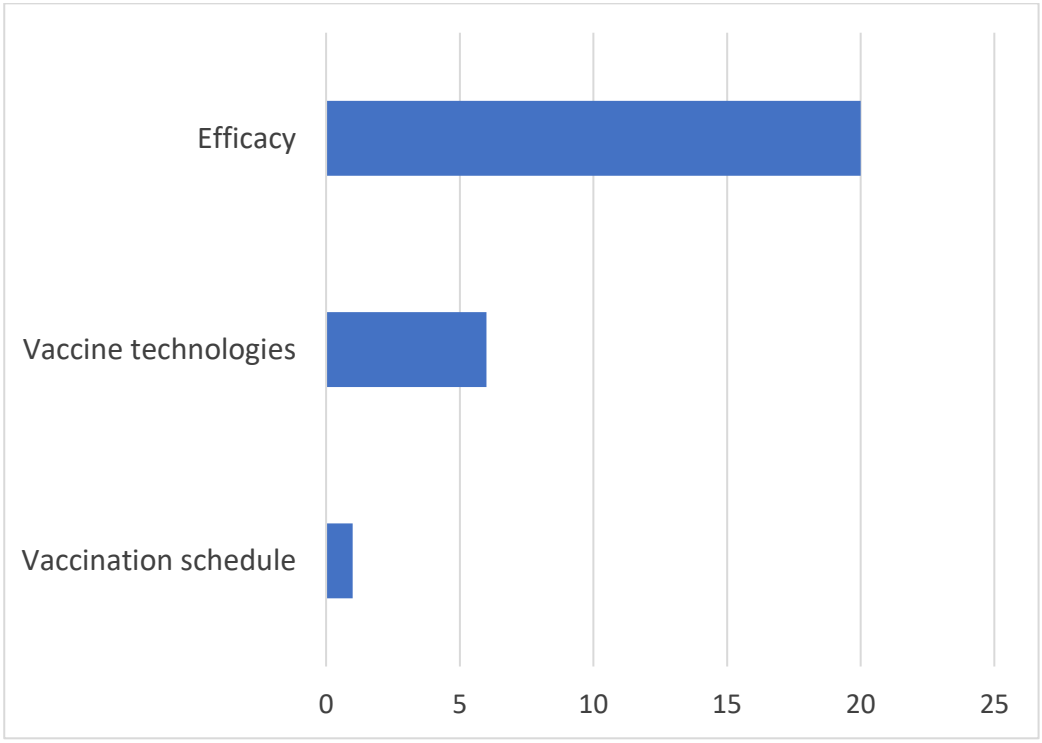
86	Long-term protection/immunity	immunity duration	Its the essence of vaccination. Type and long-lasting of immunity. (86)	
32	Long-term protection/immunity	immunity duration	Evaluation of the effectiveness of the vaccine in controlling the disease and the duration of that protection. Comparison with the immunity produced by the disease. (32)	
58	Long-term protection/immunity	immunity duration/VOCs	Durability of protection (duration and variants) (58)	**13. Are currently available vaccines effective against SARScoV2 variants in the short- and long-term and is there a need to develop new vaccine to protect against the VOCs?**
62	Long-term protection/immunity	immunity duration/VOCs	Vaccine immune response duration and immune response to different variants (62)	
63	Long-term protection/immunity	immunity duration/VOCs	Long term protection after vaccination by age group and cross-protection agains VOCs (63)	
57	Long-term protection/immunity	immunity measurment	Methods that are possible to implement in clinical routine labs to measure levels of protective immunity after vaccination (57)	**14. What is the best measure of protective immunity after vaccination at the individual level and when after vaccination should it be taken?**
84	Long-term protection/immunity	immunity measurment	What is the best measure of vaccine effectiveness at individual level - antibodies , neutralisation ,T cells and at what time point post vaccination .	
28	Public health/policy	public outreach	How do we better target immigrant populations with information concerning vaccines? Which approaches to immigrant populations has had most effect with regards to informations? (28)	**15. How can awareness of and confidence in vaccine programmes be improved to address vaccine hesitancy and misinformation with focus on specific population groups?**
53	Public health/policy	public outreach	How can we increase confidence in COVID-19 vaccines? What are the root causes of low confidence in COVID-19 vaccines? What are the insights to not accepting the COVID-19 vaccines in different populations? Which populations are more hesitant about having the	
28	Public health/policy	public outreach	How does government and trusted information become more accessible on all media platforms? How can we generate automated response systems to counter false information	
68	Public health/policy	public outreach	Compliance, We need to persuade people to trust in the vaccine program. (68)	
70	Public health/policy	public outreach	Wide availability of vaccine, to be effective vaccination should be delivered to the whole population, including	
84	Public health/policy	public outreach	Overcoming vaccine hesitancy /resistance in sub populations. (84)	
81	Public health/policy	public outreach	Engagement of specific population adherence to vaccine +AE collection.	
72	Public health/policy	vaccine access/coverage	Impact of HCWs' Vaccination coverage to lost workdays due to infection. to understand what is the minimum coverage that needs to be achieved as soon as possible in order to achieve	**16. How can wide-scale global vaccinaton coverage be ensured within reasonable timelines, especially in resource-limited settings?**
73	Public health/policy	vaccine access/coverage	How can a sufficiently large part of the world population be vaccinated within a reasonable time? How can we reach resource limited settings with effective COVID19 vaccines? (73)	
36	Public health/policy	vaccine access/coverage	The expansion to the whole population of the word to the to vaccine. Phase 2/Phase 3 (36)	
41	Public health/policy	vaccine access/coverage	Increase the vaccine coverage of the population to the maximum. Epidemiology of infection, seroprevalence of antibodies, frequency of variants of concern, etc (41)	
55	Other	development	How could new vaccine candidates be developed in shortest time? (55)	
68	Other		Vaccine efficacy will directly influence how we are going to deal with the pandemic, both time and actions. (68)	
5	Other	pregnant and breasfeeding	Vaccination of pregnant and breastfeeding women. The establishment of the safety profiles of vaccines in pregnant women and infant outcomes is critical to inform recommendations on maternal vaccination against Covid-19. (5)	
77	Other	vaccine ethics	Ethics of vaccines and vaccine strategy as related to the European Economy, How the different vaccine strategy could prevent the disparities of European Countries. (77)	
14	Other	prevention	Covid-19 prevention: To assess the different efficycy profiles of SARS-CoV-2 vaccines to avoid severe disease and/or hospitalization (14)	
44	Other	cost effectivness	In order to be available in large quantities, cont efficacy and cost effectiveness studies need to be performed (44)	
15	Other	testing in schools	Adequate testing services Viral spread at school (15)	
28	Other	trial participation	How do we increase awareness about the importance of participating or supporting vaccine trials? How do we build public support for participation in vaccine trials? (28)	
39	Other	schools closures	Avoid closing schools, Its essencial children go to school because of learning socializing and social problems (39)	
87	Other	vaccine interaction	Interaction of SARS-CoV2 vaccines with systhemathic vaccines. (87)	
17	Other	vaccine comparison	comparison of several vaccines using the same conditions (17)	
19	Protection against new variants		access to new vaccines (new mutations) (19)	**same as #13 (Are currently available vaccines effective against SARScoV2 variants in the short- and long-term and is there a need to develop new vaccine to protect agains the VOCs?)**
3	Protection against new variants		Are the vaccine effective to prevent infection with putative escape variants? ¿Are the vaccine effective to prevent severe disease aftar infection with potential escape variants? (3)	
34	Protection against new variants		Does commercialized vaccines protect against SARScoV2 variants? Does COVID-19 vaccine protect against COVID 19 cause new variants of SARScoV2? (34)	
57	Protection against new variants		Measure protective immunity by surveillance of re-infections in society and aspects of protective immunity in relation to emerging new viral variants. To study the aspects of protective immunity in relation to emerging new viral variants. (57)	
61	Protection against new variants		Assess to what extent the reduction of neutralizing antibodies against variants of Concern (VOCs) will impact vaccine effectiveness and disease severity in vaccinated population (61)	
56	Protection against new variants		It is needed the development of new vaccines against new variants; ideally vaccines which includes the most prevalent/aggresive strains (56)	
65	Protection against new variants		Are current vacccines effective against all variants. (65)	
73	Protection against new variants		The ability of present vaccines and new vaccine candidates to protect against SARS-CoV-2 variants. (73)	
75	Protection against new variants		universal COVID-19 vaccine to offer protection agains different variants (75)	
85	Protection against new variants		impact of virus variants. (85)	

Appendix 4: Priority category charts

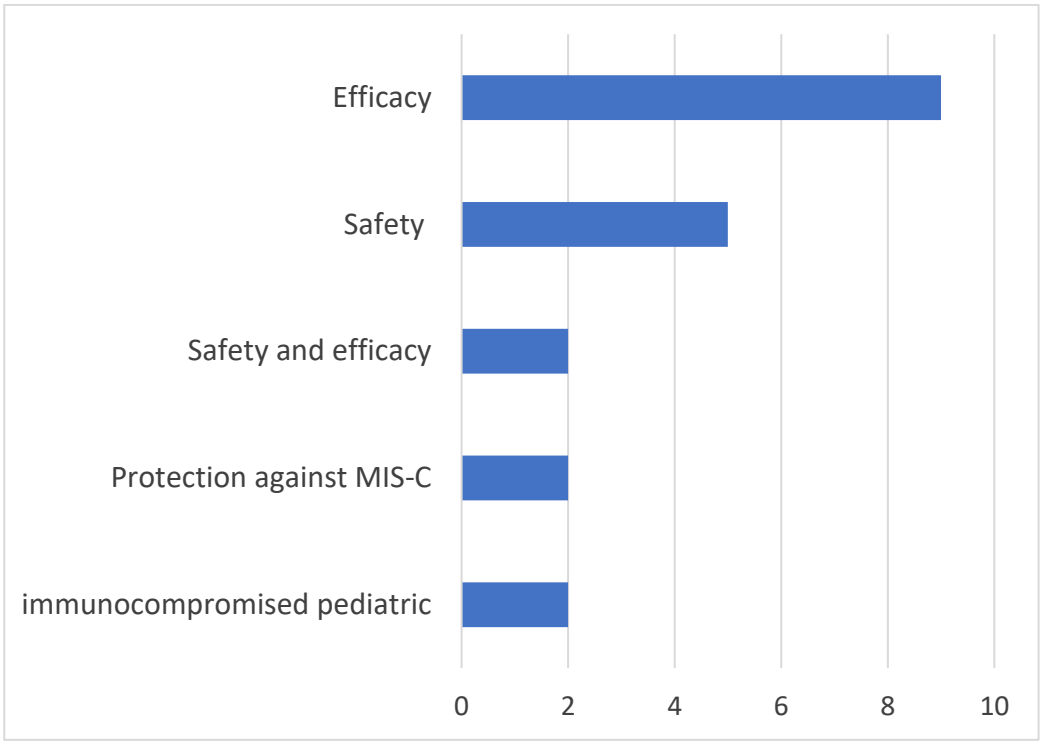
1. Vaccine administration (schedule, technology, combination) (N=38)



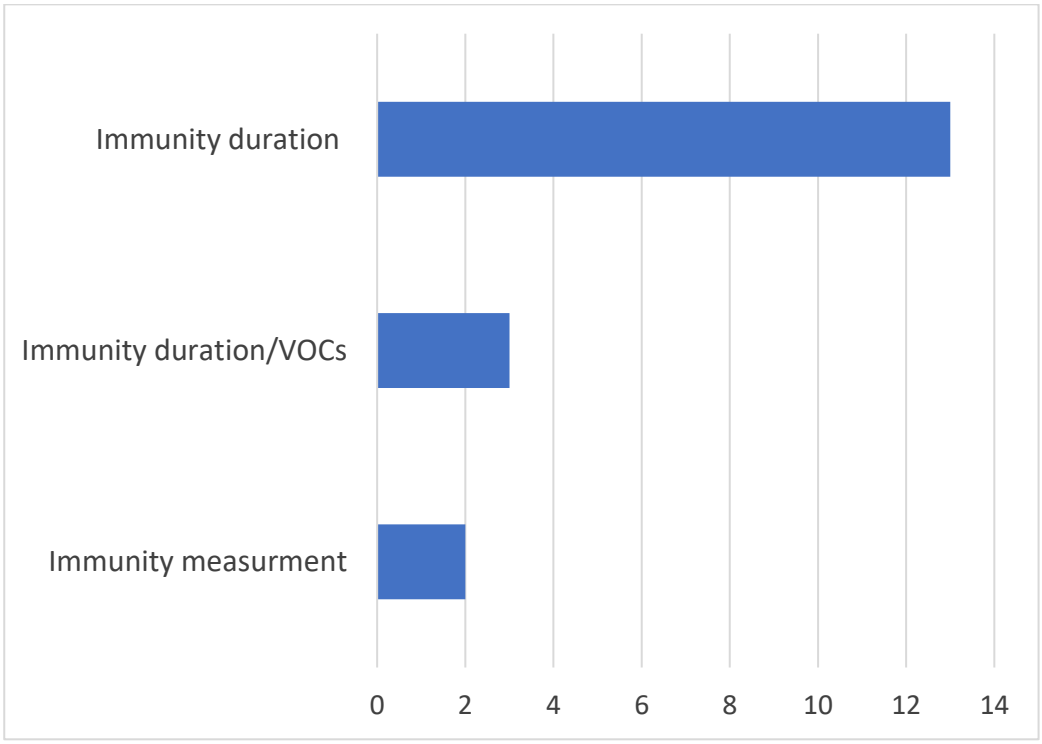
2. Vaccination in immunocompromised (n=27)



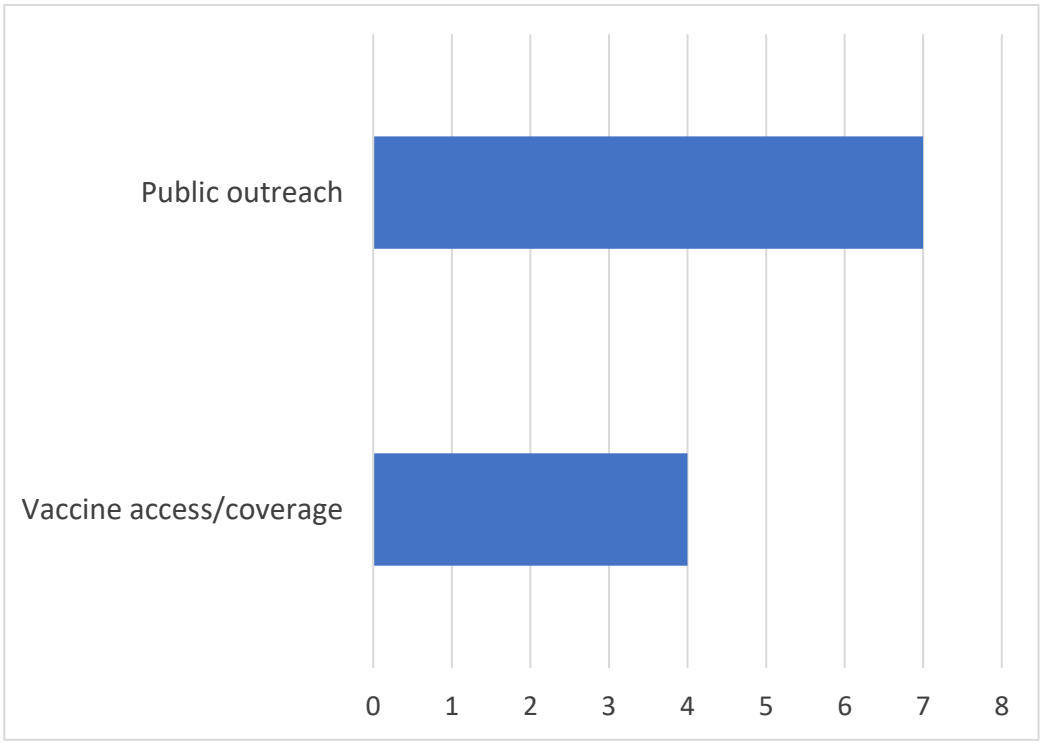
3. Pediatric vaccination (n=20)



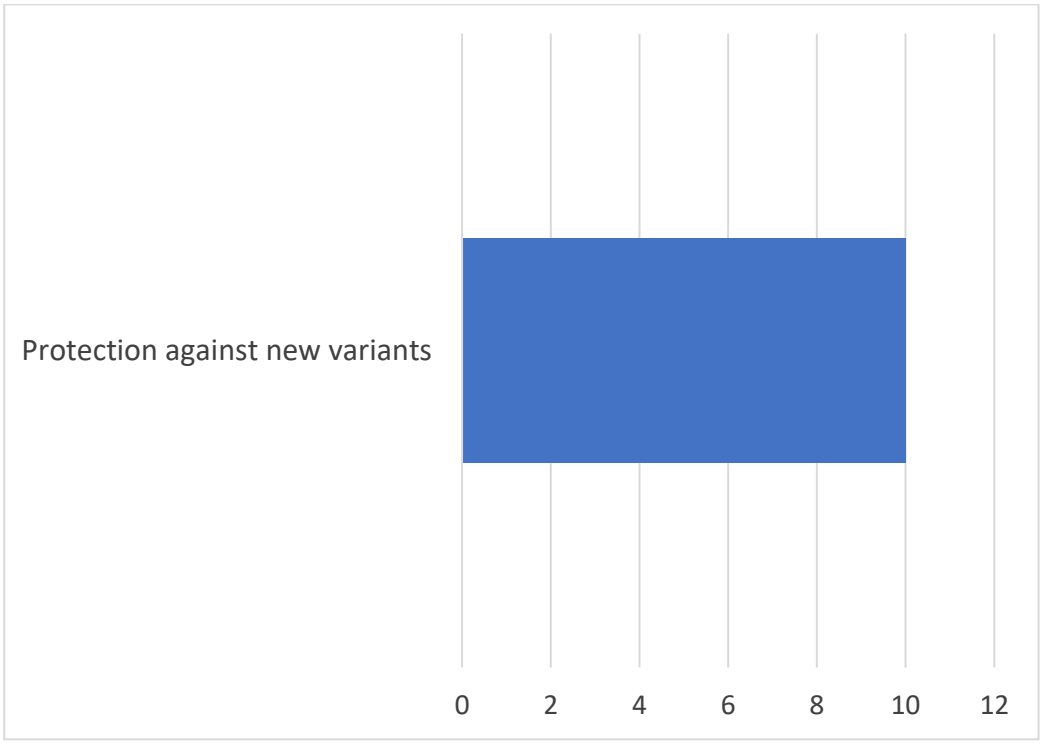
4. Long-term protection and immunity (n=18)



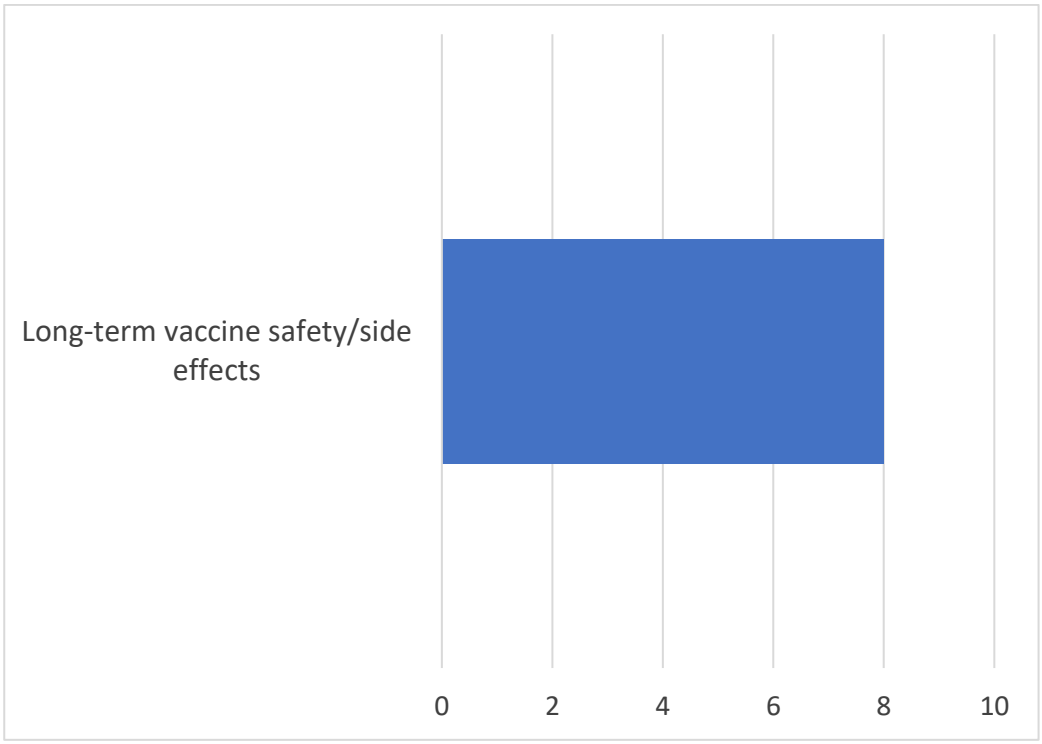
5. Public health/policy (n=11)



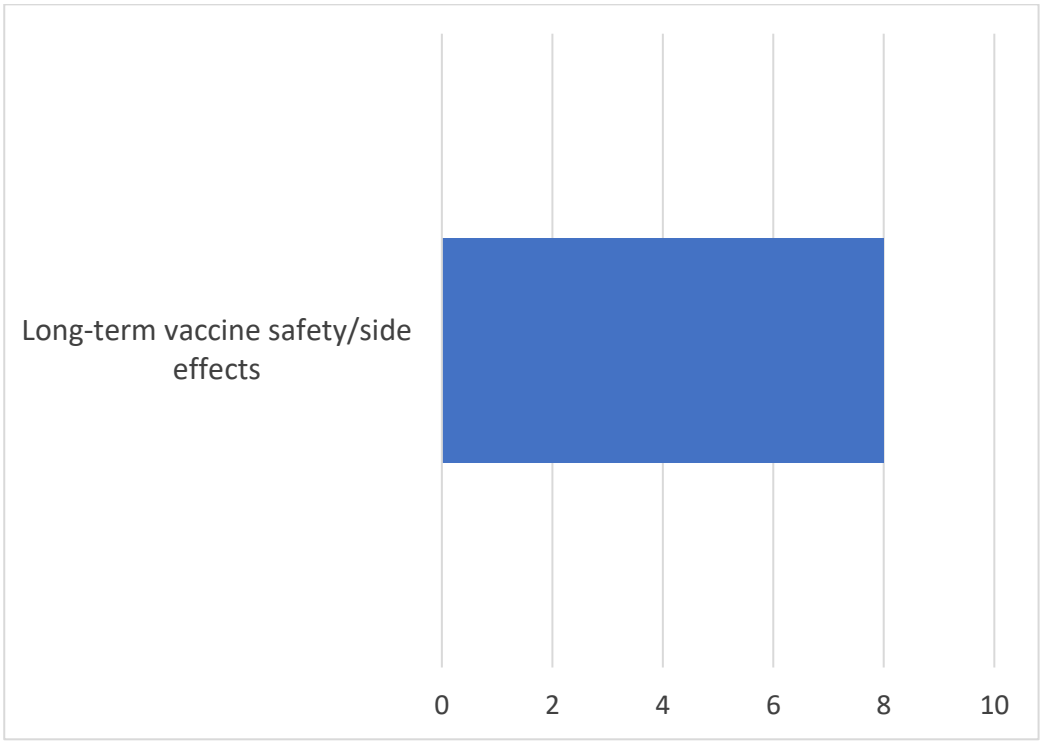
6. Protection against new variants (n=10)



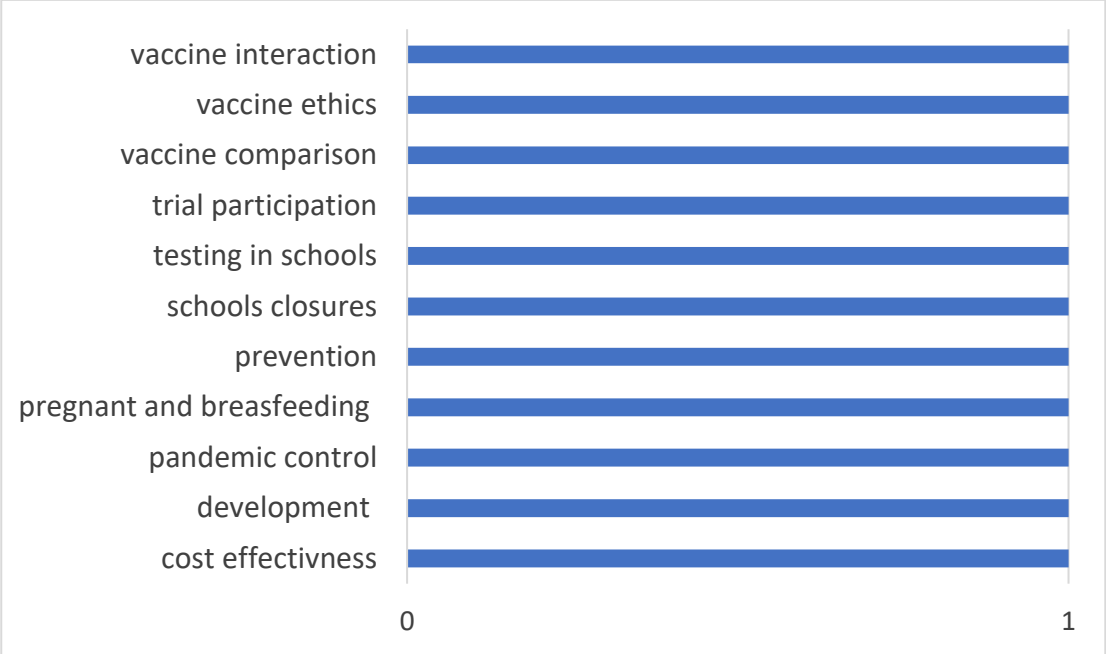
7. Long-term vaccine safety/side effects (n=8)



8. Infection transmission prevention (n=5)



9. Other (single responses/n=11)



Appendix 4 Mapping of priority questions addressed in planned VACCELERATE trials

Vaccelerate trials	Priority questions addressed
A Multinational, Phase 2, Randomised, Evaluator-Blinded, Adaptive Master Protocol to Evaluate the Impact of Different COVID-19 Vaccine Booster Strategies in Adults Already Vaccinated Against SARS-CoV-2 • **subprotocol 1: objective: To assess the Impact of heterologous prime-boost strategies on immunological responses against common strain and variants** • **subprotocol 2: objective: To assess the impact of dose spacing on long-term immune response**	1a. How can immunisation schedule (booster timing and number) and technologies (vaccine dose and type) be optimised to ensure maximum protection? 1b. What is the comparative advantage of heterologous vs. homogenic vaccination in terms of efficacy, safety and duration of protection? 4b. Are currently available vaccines effective against SARSCoV2 variants in the short- and long-term and is there a need to develop new vaccine to protect against the VOCs?
A Phase 2, Comparative, Randomized, double Blinded Trial to Evaluate the impact of reduced COVID-19 mRNA vaccination regimens on Immunological Responses and reactogenicity in children aged 12-16 years with history of prior SARS-CoV-2 infection. - **Objective: To study direct and indirect SARS-CoV-2 vaccination effects in children/ mucosal and systemic immune responses following vaccination in children** **OBS: Focus is on adolescents (i.e. not children) with either good health or stable health conditions.**	3a. What is the efficacy and the specific immune response to the vaccine in children, including immunocompromised pediatric population?