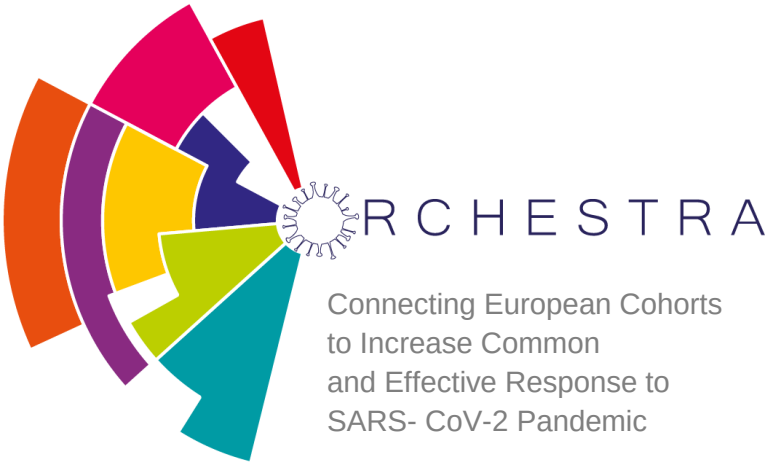


# DELIVERABLE D5.3

## WP5_D5.3

## Report on feasibility of enrolling vaccinated HCWs in phase 4 vaccine trials

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Institutul National de Sanatate Publica (INSP)



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# Executive summary

*The Work Package 5 (WP5) is dedicated to the collection, standardization and harmonization of data related to the effect of COVID-19 pandemic on health care workers (HCW). Given the high risk of exposure to the virus, this occupational group was prioritized in the immunization campaigns all over Europe making the HCW an important population to study the effects of vaccination. This is Deliverable 5.3. The purpose of this document is to describe the activity carried out under Task 5.4: Assessment of feasibility of vaccinated HCWs population-based cohorts for phase-4 vaccine trials (M13-M24). This document is a public report.*

*Lead partners: UNIBO and INSP; other partners involved: all WP5 members (UNIVR, AP-HP, LMU MUENCHEN, RAPH BB, UNIOVI, REG VEN).*

# Abbreviations

HCW=health care workers

ICTRP=International Clinical Trials Portal

RCT=randomized clinical trials

WP=work package



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# Introduction and context

The ORCHESTRA project started in December 2020, and task 5.4 was initially designed to investigate if the uninfected individuals recruited in the HCW cohorts can represent a feasible study group for phase 3 vaccination trials. But the clinical development of COVID-19 vaccines, manufacturing upscale and rolling reviews by regulatory authorities were carried out in parallel and allowed the shortened timescale of bringing COVID-19 vaccines from the laboratories to the populations after only one month from the start of the project.

In Europe, the first conditional marketing authorizations were issued in late December 2020 and early January 2021 for Comirnaty and Spikevax (previously Moderna), allowing the distribution of these vaccines in a short timescale. In the following months, the manufacturer companies have provided detailed information, including data regarding safety, efficacy, and completed all requested studies on the pharmaceutical quality of the vaccines. As a result, the conditional authorizations have been switched to standard ones. By October-November 2022, standard market authorizations were issued for Comirnaty, Spikevax and several others: Vaxzevria (previously Astra-Zeneca), Jcovden (previously Janssen), Valneva. This was an extraordinary achievement in the history of modern vaccination and exceeded by far our project timescale.

All European member states prioritized COVID-19 vaccination of HCW starting with January 2021; as a result, over 95% of ORCHESTRA HCW cohorts received the full vaccination dosage by May- June 2021. The selection of a “control-group” of uninfected and unvaccinated HCWs became impossible.

Given the evolution of the COVID-19 pandemic and the results of the vaccination roll-out, in 2021, the 1st Amendment of the project grant has had to reflect the changing situation and task 5.4 was reformulated to assess whether the pooled cohort of vaccinated HCWs can be used as population for phase-4 (post-marketing) COVID-19 vaccine trials.

The epidemiology of the SARS-Cov-2 virus also changed over the first two years of the project and several subvariants emerged and replaced the original variant, prompting the manufacturing companies to adapt the original formulas of the vaccines. Some of these adapted vaccines were later authorized for use in particular high-risk populations, as primary or booster dose. In some European member states booster were recommended for HCW, considered as an occupational high-risk group. Meantime, the review of the scientific evidence showed that extensive phase-4 clinical trials for COVID-19 authorized vaccines had already been on-going and even finalized. To add a real value with our dataset from different HCW cohorts in Europe, we proposed to facilitate the link between our cohorts and other clinical trials initiatives by facilitating the enrollment of HCW as volunteer’s in COVID-19 vaccine studies.


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# Objectives

For task 5.4 the main objective was to determine whether the post-market vaccine trial is appropriate for further testing in a pooled cohorts of HCW and to enable the interested researchers to assess whether or not the ideas and findings can be shaped to be relevant and sustainable.

Phase-4 clinical trials include post market requirement and commitment studies that are required of or agreed to by the study sponsor. For example, after a new drug is approved, the authorizing bodies or agencies often requires that the pharmaceutical company continue to monitor the effectiveness and safety of the drug. These trials gather additional information about a drug's safety, efficacy, or optimal use. Phase-4 studies should follow general and specific guidelines, with respect to the selection of the study population, study design (observational or interventional), sample size calculations, ethics clearance, consideration of other governance issues, confounding factors and the training and supervision of study staff.

In a vaccine safety surveillance program, the aim is to collect and analyze information from reports of adverse events (side effects) that occur after the administration of licensed vaccines. Reports are welcome from medical community and all concerned individuals and are submitted in highly standardized format.

ClinicalTrials.gov currently lists 13 studies on COVID-19 vaccination in Europe (Belgium, Denmark, France, Germany, Greece, Netherlands, Spain, Sweden, Switzerland) classified as phase-4 trials. Another international initiative aimed to collect data on clinical trial is COVID-NMA, led by the Centre of Research in Epidemiology and StatisticS (METHODS Team) and Cochrane France. As of February 08, 2023, the COVID-19 - living NMA initiative collected 709 RCTs and 313 non-randomised studies of vaccines from the ICTRP. 72 of these are on-going phase-4 trials and 38 are recruiting patients in Europe. The HCW represents the study population in four of them, based in The Netherlands (2) and Belgium (2), and their focus is on:

- the difference in immune response of breakthrough infection and booster vaccination;
- the effect of time between breakthrough infection and booster vaccination on humoral immune response;
- impact of the immune response on the incidence of COVID19 infections among hospital staff, on nosocomial transmission to patients, and on hospital outbreaks;
- COVID-19 illness, both primo as reinfection, up to one year following booster vaccination.

In this context, the feasibility of pooling the vaccinated HCW cohorts and to use this population in phase-4 vaccine trials was assesed by the WP5 members with focus on acceptability, demand, implementation, practicality, adaptation to the requirements and context of the COVID-19 pandemic.

The valuable characteristics of our cohorts including size (tens of thousands of participants), high participation/retention rate, high rate of adherence to primary COVID-19 vaccination, health-consciousness and regular occupational health surveillance made possible to observe and track several facets of the immune response to vaccines such as temporal trends of


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COVID-19 antibodies in vaccinated HCW[1], the determinants of Anti-S immune response[2] and the breakthrough infections[3]. Moreover, it was possible to investigate factors predictive for the breakthrough infection after booster dose in a subsample of participants (manuscript submitted for publication).

However, our group discussions questioned the manner in which an interventional phase-4 trial can be truly implemented in a highly heterogenous pooled-group of HCW, with different characteristics of the source cohort: design, source of data collected, and status. The relevant characteristics of the HCW cohorts are presented in Table 1. Several others important barriers were identified: the strict national ethical rules for clinical trials issued by regulatory national bodies, the resources, the time and study staff constraints.

Table 1. Characteristics of the cohorts included in the feasibility analysis

| | Source of data (Health surveillance records, prospective protocols) | Cohort type (legacy=before Dec. 2020/prospective=after Dec 2020) |
|---|---|---|
| **Barcelona (Northern)** | health surveillance records | legacy |
| **Bari** | health surveillance records | legacy |
| **Bologna** | health surveillance records | legacy |
| **Brescia** | health surveillance records | legacy |
| **Munich** | prospective protocols | prospective |
| **Oviedo** | health surveillance records | prospective |
| **Paris** | prospective protocols | legacy |
| **Romania** | prospective protocols | prospective |
| **Slovakia** | prospective protocols | prospective |
| **Turin** | health surveillance records | legacy |
| **Verona** | health surveillance records | legacy |

Although HCW are well characterized participants and documented in earlier response to COVID-19 vaccination, the experienced SARS-CoV2 infections after vaccination is difficult to prove retrospectively, by measuring N-specific antibodies in the pre boost sample from all participants. In general, HCW have a high socio-economic status and a good health, they can

[1] Collatuzzo G, De Palma G, Violante FS, Porru S, Larese Filon F, Fabianova E, Violán C, Vimercati L, Leustean M, Rodriguez-Suarez MM, Sansone E, Sala E, Zunarelli C, Lodi V, Monaco MGL, Spiteri G, Negro C, Beresova J, Carrasco-Ribelles LA, Tafuri S, Asafo SS, Ditano G, Abedini M, Boffetta P. Temporal trends of COVID-19 antibodies in vaccinated healthcare workers undergoing repeated serological sampling: An individual-level analysis within 13 months in

the ORCHESTRA cohort. Front Immunol. 2023 Jan 11;13:1079884. doi: 10.3389/fimmu.2022.1079884. PMID: 36713452; PMCID: PMC9875291

[2] Collatuzzo G, Lodi V, Feola D, De Palma G, Sansone E, Sala E, Janke C, Castelletti N, Porru S, Spiteri G, Monaco MGL, Larese Filon F, Negro C, Cegolon L, Beresova J, Fabianova E, Carrasco-Ribelles LA, Toràn-Monserrat P, Rodriguez-Suarez MM, Fernandez-Tardon G, Asafo SS, Ditano G, Abedini M, Boffetta P. Determinants of Anti-S Immune Response at 9 Months after COVID-19 Vaccination in a Multicentric European Cohort of Healthcare Workers-ORCHESTRA Project. Viruses. 2022 Nov 28;14(12):2657. doi: 10.3390/v14122657. PMID: 36560660; PMCID:

PMC978 1450

[3] Porru S, Monaco MGL, Spiteri G, Carta A, Pezzani MD, Lippi G, Gibellini D, Tacconelli E, Dalla Vecchia I, Sala E, Sansone E, De Palma G, Bonfanti C, Lombardo M, Terlenghi L, Pira E, Mansour I, Coggiola M, Ciocan C, Godono A, Tardon A, Rodriguez-Suarez MM, Fernandez-Tardon G, Jimeno-Demuth FJ, Castro-Delgado RV, Iglesias Cabo T, Scapellato ML, Liviero F, Moretto A, Mason P, Pavanello S, Volpin A, Vimercati L, Tafuri S, De Maria L, Sponselli S, Stefanizzi P, Caputi A, Gobba F, Modenese A, Casolari L, Garavini D, D'Elia C, Mariani S, Filon FL, Cegolon L, Negro C, Ronchese F, Rui F, De Michieli P, Murgia N, Dell'Omo M, Muzi G, Fiordi T, Gambelunghe A, Folletti I, Mates D, Calota VC, Neamtu A, Perseca O, Staicu CA, Voinoiu A, Fabiánová E, Bérešová J, Adamčáková ZK, Nedela R, Lesňáková A, Holčíková J, Boffetta P, Abedini M, Ditano G, Asafo SS, Visci G, Violante FS, Zunarelli C, Verlato G. SARS-CoV-2 Breakthrough Infections: Incidence and Risk Factors in a Large European Multicentric Cohort of Health Workers. Vaccines (Basel). 2022 Jul 27;10(8):1193. doi: 10.3390/vaccines10081193. PMID: 36016081; PMCID: PMC9415790



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easily access the medical services; these aspects were judged as important limitations of the expansion/generalization of vaccination adverse effects to the general population.

Finally, the group concluded that a pooled cohort of HCW may not be a suitable study population for phase-4 vaccine trials but individuals interested in volunteering for such studies (and in particular for COVID-19 vaccines studies) can and should be informed about the on-going or planned trials recruiting participants.

Therefore, in reply to our task and in line with the general goal of HORIZON research and innovation programme to enhance collaboration, complementary research actions and to foster data interoperability among EU scientific consortia, we explored the feasibility of linking the ORCHESTRA cohorts of HCW with other EU initiatives, sharing the objective of COVID-19 vaccine development and clinical research excellence.

In 2022, we have contacted VACCELERATE, a clinical research network for the coordination and conduct of COVID-19 vaccine trials (https://vaccelerate.eu/ ). The network is comprised of academic institutions from all over Europe: the consortium is led by the University Hospital Cologne, Germany, and currently includes 29 national partners in 18 EU-member states and 5 countries associated to the EU Horizon 2020 research programme. VACCELERATE is funded by the European Commission's activities for future pandemic preparedness, the HERA Incubator, an instrument that was created in analogy to the United States' BARDA.

VACCELERATE main scope is to speeding up the vaccine trials and, in particular, WP10 is aiming to bring together stakeholders in the development of vaccines against the coronavirus (SARS-CoV2) with citizens who want to participate in vaccine research or other research projects on COVID-19. An electronic Volunteer Registry (https://vaccelerate.eu/volunteer-registry-2/) was created to provide access to on-going COVID-19 vaccine clinical trials to individuals interested to enroll as volunteers. Currently the Volunteer's registry is active in 16 countries and the total numbers of registered volunteers is 107 022.

During the preparatory phase of the collaboration, we invited the VACCELERATE coordination board to explore how the two projects can collaborate by linking HCW ORCHESTRA cohorts with the Volunteer's Registry. Prof. Oliver Cornely (project coordinator) and Dr. Zoi_Dorothea Pana (WP10 leader) presented VACCELERATE project and the Volunteer's Registry concept during our regular WP5 meetings. Another complementary action presented was the by VACCELERATE willingness survey questionnaire, designed to test the interest for clinical trials, which was recommended for use, with some adaptations, in ORCHESTRA HCW cohorts. The PIs interested in this collaboration were invited to participate in several separate meetings with VACCELERATE researchers.

Finally, the WP5 established the followings common actions:

- Activation of Volunteer's Registry in interested countries where it is inactive, followed by an active promotion of the registry among the cohorts' participants;
- Communication and dissemination activities to promote the Volunteer's Registry among the HCW cohorts, in the centers where the registry is active (France, Germany, Italy, Spain);


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# Results

1. activation and promotion of the Volunteer's Registry in Romania.

The VACCELERATE coordination board issued the procedure to be followed by the INSP team who was in charged with the translation of the Registry content and introductory messages in Romanian. VACCELERATE communication team insured the translation of the promo and educational materials.

At this moment, the Volunteer's registry is activated in Romanian and can be easily accessed by anyone interested. More information on the Registry concept and the link to the registry webpage were posted on the INSP website.

2. communication and dissemination activities

In Romania, where the register was newly activated, several actions are going-on

- In the letter inviting participants to the third follow-up of ORCHESTRA cohort we will include an explanatory message and the link to the Volunteer's Registry
- On the official website of the INSP, in the section dedicated to the ORCHESTRA project we have posted information about the VACCELERATE and the Volunteer's Registry
- Promotion materials translated in Romanian will also be available on our website

Similar activities are carried out in different cohorts/study centers as described in Table 2.

Table 2. ORCHESTRA linkage with VACCELERATE Volunteer's registry

| | Volunteer's registry available in local languages | Dissemination of Volunteer's registry information among the HCW | Means of dissemination (w=website, e=email, 0=other) |
|---|---|---|---|
| **Barcelona (Northern)** | yes | yes | e |
| **Bari** | yes | no | - |
| **Bologna** | yes | yes | w, o |
| **Brescia** | yes | No | - |
| **Munich** | yes | yes | e |
| **Oviedo** | yes | yes | w, e |
| **Paris** | yes | yes | w |
| **Romania** | yes | yes | w, e, o |
| **Slovakia** | no | no | - |
| **Turin** | yes | no | - |
| **Verona** | yes | yes | w, o |


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# References

*e.g. Journal articles, book chapter, scientific publication, scientific report, websites, etc*.

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*e.g Acknowledge contribution of advisory board members or other external stakeholders*



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