



Summary for policy makers

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About ORCHESTRA: from pandemic response to pandemic preparedness

The COVID-19 pandemic created an urgent demand for evidence-based solutions to advance knowledge on **pandemic control strategies**, to provide **optimized treatment** for COVID-19 patients and to inform on the **longer-term consequences**. Moreover, as the pandemic progressed, the introduction of different **vaccination schemes by population types**, the emergence of **viral variants**, and the development of new **therapeutics** underlined the importance of creating a research infrastructure capable of capturing and adjusting to a constantly varying epidemiological scenario and able to rapidly react to new threats.

Funded by the EU's Horizon 2020 program, the [ORCHESTRA](#) project was tasked with creating such an infrastructure to collect and link data from European and international cohorts representing four broad categories: general population, COVID-19 patients, vulnerable individuals, and healthcare workers. Adopting common electronic data capture tools, standardised variables, and innovative research methods, ORCHESTRA collected demographic and clinical data, biochemical and immunological markers, and patient-reported outcomes from multiple study sites in 16 countries worldwide. On the strength of this multidimensional and harmonized dataset, ORCHESTRA partners were able to formulate evidence-based recommendations supporting the management of the pandemic and contribute to preparedness plans for future public health threats. Recommendations centered around therapeutic effectiveness, patient outcomes, vaccine efficacy, prolonged health effects, and the broader societal and economic consequences of the pandemic, with a particular focus on the underrepresented populations.



[ORCHESTRA Home page](#)



[ORCHESTRA brief video](#)

ORCHESTRA in numbers

34

institutions*

86

**retrospective
and prospective
cohorts**

141

**scientific articles
published in
peer-reviewed
journals**

14

countries

EU: Belgium, France, Germany, Italy, Luxemburg, Netherlands, Romania, Slovak Republic, Spain

International: Argentina, Brasil, Congo, Gabon, India

529,000

patients recruited

7,600 individuals with SARS-CoV-2 infection

448,917 individuals from general population

9,237 individuals from vulnerable populations (pregnant women and new-borns, children, Solid Organ Transplantation (SOT) recipients, persons living with HIV (PWH), patients with rheumatological diseases, oncological diseases (cancer and haematological patients), cystic fibrosis, or Parkinson's disease (PD))

63,516 healthcare workers (HCW)

2,350,000 health records

*The European beneficiaries: Università di Verona, Alma Mater Studiorum – Università di Bologna, CINECA Consorzio Interuniversitario, Fondazione PENTA ETS, Regione Emilia-Romagna, and Regione Veneto from Italy; Institut National de la Santé et de la Recherche Médicale and Assistance Publique – Hôpitaux de Paris from France; Servicio Andaluz de Salud, Fundación Privada Instituto de Salud Global Barcelona, and Universidad de Oviedo from Spain. Germany is strongly represented by: Ludwig-Maximilians-Universität München, Helmholtz Zentrum München, Klinikum der Universität zu Köln, Charité – Universitätsmedizin Berlin, Universitätsklinikum Heidelberg, and Universität Stuttgart. Further European involvement includes: Universiteit Antwerpen from Belgium, Academisch Ziekenhuis Groningen in the Netherlands, Luxembourg Institute of Health, Regionálny úrad verejného zdravotníctva so sídlom v Banskej Bystrici in Slovakia, and Romania's Institutul National de Sanatate Publica. The non-EU partners are: the Centre de Recherches Médicales de Lambaréné in Gabon, Fondation Congolaise pour la Recherche Médicale in Congo, and Universidad de Buenos Aires in Argentina. The five linked third parties to beneficiaries are Azienda Ospedaliera Universitaria Integrata Verona, Azienda Unità Sanitaria Locale di Bologna, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Azienda Unità Sanitaria Locale di Reggio Emilia, and Azienda Zero. Universidade Federal de Sao Paulo in Brasil, Catholics Bishop Conference of India and Transnational Health and Science Technology Institute in India, contribute as international parties.

Key findings

Clinical

- ➔ **Study:** A Systematic Review of COVID-19 Prognostic Scores, including Predictor Composition, Outcomes, Risk of Bias, and Validation. **Main results and recommendation:** The application and translation of most existing COVID-19 scores appear unreliable. Guided development and predictor selection could improve the generalizability of the scores and may enhance pandemic preparedness in the future.
- ➔ **Study:** Machine learning to predict antibody response to SARS-CoV-2 vaccination in solid organ transplant recipients. **Main results and recommendation:** Almost a quarter of solid organ transplant recipients showed a negative antibody response after the first booster dosage.
- ➔ **Study:** SARS-CoV-2 mRNA vaccination and short-term changes in viral load and CD4/CD8 T-cell counts in people living with HIV. **Main results and recommendation:** SARS-CoV-2 mRNA vaccine can activate a proper immunological response through specific CD4 T cells, even in people living with HIV.
- ➔ **Study:** Quasi-species prevalence and clinical impact of evolving SARS-CoV-2 lineages in European COVID-19 cohorts, January 2020 to February 2022. **Main results and recommendation:** Specific mutations correlate with COVID-19 severity. Quasi-species potentially shaping VOCs' emergence are relevant to be considered.
- ➔ **Study:** Host immunological responses facilitate development of SARS-CoV-2 mutations in patients receiving monoclonal antibody treatments. **Main results and recommendation:** Host-driven immune and nonimmune responses are essential for development of mutant SARS-CoV-2. These data also support point-of-care decision making in reducing the risk of mAb treatment failure and improving mitigation strategies for possible dissemination of escape SARS-CoV-2 mutants.
- ➔ **Study:** Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort. **Main results and recommendation:** Long COVID can be classified by clinical phenotypes with different impact on quality of life, underlying possible different pathogenic mechanisms. These results might help in selecting patients for inclusion in clinical trials.
- ➔ **Study:** Chemosensory assessment and impact on quality of life in neurosensorial cluster of Long COVID. **Main results and recommendation:** Quantifying and characterizing COVID-19-related chemosensory impairment is key to understand underlying mechanisms and to develop preventive and therapeutic treatment.
- ➔ **Study:** Epigenome-wide association study (EWAS) results of population-based cohorts identified possible Long COVID markers. **Main results and recommendation:** Persistent changes in DNA methylation patterns are present up to four months after SARS-CoV-2 infection. This may lead to a possible development of epigenetic tests for Long COVID.
- ➔ **Study:** Learning from Long COVID for epidemic preparedness: a variable catalogue for future post-acute infection syndromes. **Main results and recommendation:** A standardised catalogue of variables representing different aspects of Long COVID based on the ORCHESTRA dataset was adopted to build a standardised electronic Case Report Form (eCRF) for immediate use in the design of future observational studies and clinical trials assessing post-acute viral infectious syndromes.

Socioeconomics

- ➔ **Study:** Impact on mental health on exposure to the COVID-19 pandemic in HCWs. **Main results and recommendation:** Emotional exhaustion, occupational burnout, and PTSD represent a high burden of stress in HCWs, especially among females, younger HCWs, those affected by PCC, workers in shift schedules, and those who have direct contact with patients. The findings of these studies highlight significant concerns related to PCC and the psychosocial health of HCWs.
- ➔ **Study:** Relationship between the COVID-19 pandemic and early retirement. **Main results and recommendation:** Early retirement has decreased across all age groups, potentially due to the uncertainties and economic disruptions caused by the COVID-19 pandemic.
- ➔ **Study:** Pandemic healthcare service disruptions. **Main results and recommendation:** Socio-economic factors played a role in healthcare disruptions, such as experiencing financial hardship, being female, and having higher education level. Disruptions significantly increased the risk of patients being lost to follow-up.
- ➔ **Study:** Psychological distress among vulnerable populations. **Main results and recommendation:** Increased disputes among family members or sleep disorders augmented the risk of worsened mental health. Self-perceived loneliness and resilience play a more crucial role in the variation of psychological distress than demographic and socio-economic factors.

Long COVID in ORCHESTRA

Long COVID, also known as Post-Covid Condition (PCC) has proven a difficult syndrome to identify, characterise, and treat. Even if this condition was not contemplated during the first months of the pandemic, ORCHESTRA focused on studying the long-term effects of COVID-19, becoming the largest European Long COVID cohort with active follow-up. In ORCHESTRA, Long COVID was described for the first time as having different and specific clinical presentations (or phenotypes), that probably represent different diseases with the same cause, i.e., previous SARS-CoV-2 exposure. Moreover, ORCHESTRA defined severe Long COVID as the presence of chronic pain, chronic fatigue, and respiratory symptoms, with an impact on Quality of Life (QoL). Over the course of the project, the description of Long COVID evolved to include a model to predict the temporal evolution of Long COVID symptoms, starting from common descriptors, such as age, sex, and COVID-19 severity. The description of common blood test in Long COVID showed, in line with the experience of the scientific community, poor discrimination ability; however, subtle changes hinted at inflammation as a possible mediator in the pathology of Long COVID. Neurosensorial symptoms, even if less impactful on QoL, were proven common with the use of dedicated tests. These results provided solid foundation for the exploration of possible treatments. ORCHESTRA data consistently demonstrated the disproportionate impact of Long COVID on females, highlighting this group as a priority for targeted support and management protocols to mitigate long-term effects. The findings also suggested that patients, and therefore women in particular, may benefit from early interventions during acute infection. Furthermore, ORCHESTRA data strongly supported the effectiveness of vaccination in reducing Long COVID risk. ORCHESTRA also demonstrated that Long COVID has an important impact on QoL, labour outcomes, and risk-related behaviours, highlighting the need to investigate the underlying drivers of work incapacity and to develop strategies that address employment challenges linked to Long COVID.

Innovation in ORCHESTRA

- ➔ **Harmonization of more than one thousand variables across several existing cohorts and studies to ensure data interoperability.** Cohorts often used site-specific data dictionaries, developed in different national languages or designed at the start of the pandemic. ORCHESTRA was able to map the variables to the corresponding international terminology codes provided by standard development organisations such as SNOMED CT and LOINC. Over 3700 coded variables were published on the [ART-DECOR platform](#) to facilitate their reuse in external COVID-19 studies and support interoperability and data integration.
- ➔ **Development of a Latent Transition Analysis model to describe the evolution over time of Long COVID symptoms.** This model was integrated into a [public interactive visualisation website](#), that includes the visualisation of the model as well as the prediction of the symptoms in the future based on the past symptoms and most relevant covariates such as age and comorbidities.
- ➔ **Development of an [interactive dashboard](#) for tracking serological response to vaccination in fragile populations.** Such tools can support real-time monitoring, personalised care, and policy adjustments in future health emergencies.
- ➔ **Use of dried blood spot testing** has been proven to be a fast and cost-effective method to enable large-scale sample collection in compressed timeframes.
- ➔ **Development of an emotional exhaustion screening questionnaire** to explore the psychological consequences of the pandemic on HCWs. This is a psychometric tool that can be used to screen for emotional exhaustion among HCWs during public health crises.
- ➔ **Development of recommendations for the management of COVID-19 patients** with pre-existing conditions, covering risk assessment, vaccination, diagnosis, early COVID-19 therapy, interaction between COVID-19 and pre-existing conditions, and Long COVID. Five Delphi consensus documents were developed to guide clinical management of COVID-19 and Long COVID in vulnerable populations, addressing key gaps in treatment strategies for high-risk patient groups.

The Orchestra Data Portal

The [ORCHESTRA Data Portal](#) is the top-level component in the ORCHESTRA architecture with the main role of providing a centralised point of access for ORCHESTRA data. In line with the principles of Open Science, the ORCHESTRA Portal is open to the public for the benefits of science and society as a whole. Through the Portal, users can have immediate access to public data and request access to specific cohort data of the project that will be made available for analysis through Question Oriented Data Export or Federated Learning Data Analysis. The Portal also provides details on all the biobanked samples from COVID-19 patients, which is highly relevant for future research as it provides a valuable resource for ongoing and future analyses. This biobank enables deeper insights into COVID-19 long-term effects and lays the groundwork for discovering biomarkers, understanding disease progression, and developing targeted interventions.

Pandemic preparedness: recommendations for future research

Data interoperability

Data interoperability was achieved in ORCHESTRA thanks to the harmonization of variables across existing cohorts and adoption of common data collection tools. However, this task was complex, time-consuming and resource intensive in an emergency context where time and resources were already strained.

1

Recommendation: Mandate international standard terminologies and classifications as well as reference eCRFs in grant proposal to ensure interoperability of results and secondary analysis of data.

Flexibility in research design

The ORCHESTRA project provided valuable insights into the challenges of conducting research during a public health emergency. In the context of novel diseases like COVID-19, where the clinical landscape shifts rapidly due to innovations in treatment, prevention, and our understanding of the disease itself, traditional research designs may struggle to keep pace.

2

Recommendation: Foresee flexibility in research designs that allow to identify and respond to emerging clinical needs and redirect focus as new questions arise. In particular, adaptive designs such as adaptive clinical trials that allow for modifications to the study plan based on interim data analysis should be embraced.

Inclusion of under-represented groups

ORCHESTRA highlighted how fragile populations, particularly individuals with underlying health conditions (e.g., cardiovascular diseases, obesity, diabetes, chronic respiratory diseases, solid and hematologic malignancies, transplant recipients, and immunocompromised individuals) were disproportionally affected by the pandemic.

3

Recommendation: Prioritize observational studies such perpetual cohort studies in interpandemic times. Availability of running cohorts in under-represented populations would greatly facilitate detection of cases and inclusion into relevant studies of such patients at the start of pandemics, to estimate related risk factors, treatment responses, and outcomes.

Innovative data sharing solutions

ORCHESTRA successfully adopted the federated learning model to address the challenges associated with sharing of data due to GDPR restrictions. Federated learning allowed participant-level analysis without exchanging the participant-level data and allowed ORCHESTRA to access and analyse data that otherwise would not have been possible to share.

4

Recommendation: Support and explore further federated learning and other innovative data-sharing solutions, in particular during interpandemic times. This includes establishing “good practice” for implementing federated learning in multicentric research networks and investigating advancements in federated learning, such as differential privacy and secure multi-party computation.

Research infrastructures and capacity building

ORCHESTRA successfully established a robust research infrastructure but its set-up and implementation highlighted the significant time and resources required to launch such an infrastructure and to navigate complex data protection and privacy legislation.

5

Recommendation: Support permanent research infrastructures that continue to collect data in interpandemic times and invest in capacity building, particularly within academic institutions, as regards legal expertise to navigate data protection and privacy norms.

Targeted scientific dissemination

The COVID-19 pandemic saw an unprecedented volume of publications making it difficult to navigate the emerging evidence. To address this challenge, ORCHESTRA created an external expert evaluation mechanism, the COVID-19 Global Guidance Group (CGGG), to evaluate the ORCHESTRA scientific publications in order to support targeted dissemination of the most relevant results to different stakeholders.

6

Recommendation: Broaden the adoption of external evaluation of research messages, to enhance the integrity and reliability of scientific dissemination to the appropriate target audiences, especially during times of crises.

