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# Pan-European Fragile Populations Cohort for COVID-19: What Worked, What Didn't, and Lessons Learned

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## ABSTRACT

The COVID-19 pandemic exposed the vulnerability of immunocompromised hosts and the scarcity of evidence guiding their management. Within the European Horizon 2020 ORCHESTRA project, a multinational consortium connected existing and new cohorts to harmonize data, laboratory methods, and clinical expertise across fragile populations. The fragile patients' cohort became a model for how collaborative infrastructure can generate actionable evidence during a crisis. Through prospective follow-up and centralized immunologic assessment, ORCHESTRA defined the clinical spectrum of COVID-19 in transplant recipients, identified vaccine-modified disease phenotypes, and clarified the kinetics and correlates of immune protection. The project also demonstrated the feasibility of real-time immunologic monitoring, the value of data interoperability, and the need for adaptive harmonization across health systems. Integrating these results through Delphi consensus, ORCHESTRA translated research into practice, providing pragmatic guidance for clinicians across Europe. This experience underscores that harmonized, multidisciplinary research—rooted in collaboration and flexibility—can transform variability into knowledge and ultimately improve care for the most immunologically fragile patients.

## 1 | Introduction

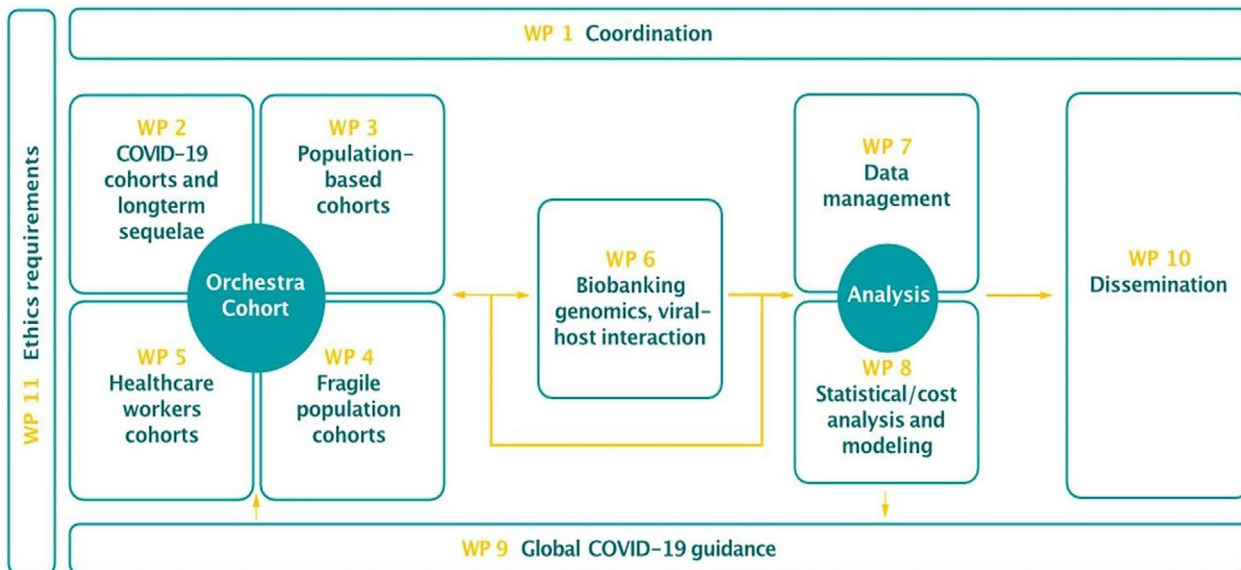
As the COVID-19 pandemic ravaged the globe, it became clear that the complex host-virus interaction led to great heterogeneity of outcomes across different individuals, exposing major evidence gaps especially for fragile populations such as solid

organ transplant (SOT) recipients, patients living with HIV or cancer, pregnant women and children, and those affected by congenital or chronic diseases [1–4]. In these groups, pre-existing immune dysfunction, iatrogenic immunosuppression, or general vulnerability often translated into a higher risk of severe outcomes. Yet, a large part of the early evidence guiding public

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**FIGURE 1** | ORCHESTRA work packages (flow-chart).

health measures and clinical management during the emergency phase of the pandemic was derived from studies that excluded such populations [5].

From a policy perspective, this paradox—simultaneous prioritization and exclusion—defined one of the most challenging aspects of the pandemic response. Fragile populations were consistently identified as priority groups for early vaccination in national plans due to high morbidity and mortality risk. However, their exclusion from registration trials led to a lack of direct evidence on immunogenicity and protection duration of vaccines, as well as adverse event profiles [6]. This situation delayed the formulation of evidence-based recommendations and led to a fragmented policy landscape in which clinical decisions depended heavily on expert opinion rather than comparative data [7].

In an attempt to overcome this issue, the ORCHESTRA project—Connecting European Cohorts to Increase Common and Effective Response to the SARS-CoV-2 Pandemic—was launched on December 1, 2020, under the European Union’s Horizon 2020 research and innovation framework [8]. The initiative was conceived as one of the largest coordinated international efforts to generate harmonized, high-quality evidence on COVID-19 epidemiology, clinical outcomes, and immunity, based on real-world data collected across various populations. Led by the University of Verona, the consortium brought together 26 partners and multiple third-tier collaborators from 15 European and non-European countries—Argentina, Belgium, Brazil, Congo, France, Gabon, Germany, India, Italy, Luxemburg, Netherlands, Romania, Slovakia, Spain, Venezuela—forming a global research network (Table S1) [9, 10]. The project was structured into 11 work packages (WPs), each addressing a specific objective, including one dedicated to fragile populations (WP4) led by the University of Bologna (see Figure 1 and Table 1). Clinical, epidemiological, and immunological data were integrated into a secure ORCHESTRA database, supporting harmonized analyses and computational modeling. While most cohorts performed routine analyses locally, advanced virological, immunological, and omics

testing was centralized to leverage specialized laboratory capacity. The project also addressed ethical, regulatory, dissemination, and training aspects.

## 2 | Methods

### 2.1 | Cohort Mapping and Protocol Alignment

As mentioned above, WP4, had the scope to understand the impact of COVID-19 among fragile populations. Coordinating more than 35 cohorts and 20 000 participants (Table S2), WP4 included 10 vulnerable groups, namely (1) SOT recipients, (2) people living with HIV, (3) solid and hematological malignancy, (4) hemodialysis patients, (5) pregnant women and their newborns, (6) immunocompromised children, (7) patients with cancer, (8) patients with cystic fibrosis, (9) rheumatologic, and (10) neurological diseases, such as Parkinson’s. The project initiated with comprehensive mapping of fragile cohorts’ data and infrastructure through structured surveys distributed to all WP4 partners [11]. These surveys collected granular information on existing retrospective data, local databases, biobanks, and ongoing prospective data collection efforts. Based on these data, core study variables were defined to harmonize retrospective and prospective cohort protocols across sites, accommodating differences while ensuring comparability of clinical, immunological, and outcome measures.

### 2.2 | Data Architecture and Governance

Centralized data management was established at CINECA, Italy, under WP7, which was meant to provide a secure, General Data Protection Regulation (GDPR)—compliant environment for data harmonization and analysis [12]. Partners were asked to transfer individual-level data when permitted or engaged in federated learning frameworks, preserving local data control yet enabling cross-cohort analyses. Metadata standards and data dictionaries

TABLE 1 | ORCHESTRA work packages.

WP#	Work package title	Leader	Beneficiary (-ies) and partner(s)	Brief description/objective	Main activities/areas
WP1	Coordination	UNIVR		Consortium/project coordination, management, ethics	Coordination, compliance, meetings, ethics, dissemination policies
WP2	COVID-19 cohorts and long-term sequelae	UNIVR	AOUI-VR, INSERM, AP-HP, UNIBO, SAS, UMG	Prospective COVID-19 cohort: acute disease, long-term sequelae, algorithms, predictors	Mapping historical cohorts, standardized protocols, predictive models, algorithms
WP3	Population-based cohorts	INSERM	LMU, LIH, UMG, PENTA, UNIVR	Establish population-based cohorts for epidemiological modeling and risk assessment	Seroprevalence, household transmission, methylation/omics, viral spread
WP4	Fragile population cohorts	UNIBO	UNIVR, REG VEN, SAS, LIH, UBA, CERMEL, ISGLOBAL	Longitudinal cohorts: SOT, HIV, cancer, cystic fibrosis, PD, rheumatology, children	Vaccination studies, mental health, therapeutic algorithms, consensus docs
WP5	Healthcare workers cohorts	UNIBO	UNIVR, RAPH-BB, UNIOVI, INSP, LMU	Large HCW cohort: infection, vaccination, breakthrough, occupational exposure, mental health	Antibody trends, behavioral factors, data harmonization
WP6	Biobanking, genomics, viral-host interaction	UANTWERPEN	UNIBO, INSERM, HMGU, UNIVR, PENTA	Genomics, biobanking, immune response, virology, microbiome	Sequencing, immune phenotyping, virome, microbiome, biomarker discovery
WP7	Data management	CINECA	USTUTT, CINES, CHARITE', HMGU, UNIVR, PENTA	Data harmonization, standards, platform, protection, storage	Data portal, core data dictionary, pseudonymization, interoperability
WP8	Statistical/cost analysis & modeling	HMGU	ISGLOBAL, HMGU, INSERM, UBA, FCRM, CERMEL, UNIVR, UKHD	Statistics, modeling, health economics, socio-economic impact	Individual/population modeling, cost analysis, risk factors, economics
WP9	Global COVID-19 guidance	UMCG	UNIVR, UHC, UNIBO, INSERM, CINECA, UANTWERPEN, HMGU	International networking, collaboration, dissemination of guidance	Collaboration, external cohort integration, global guidance/ext dissemination
WP10	Dissemination	UHC	UNIVR, UMG, SAS, CINECA, RER-ASSR, ISGLOBAL, LMU, UANTWERPEN, CERMEL, CINES, FCRM, USTUTT	Dissemination, stakeholder communication, science challenges	Website, social media, infographics, press releases, science slams, anonymization

(Continues)

TABLE 1 | (Continued)

WP#	Work package title	Leader	Beneficiary (-ies) and partner(s)	Brief description/objective	Main activities/areas
WP11	Ethics requirements	UNIVR	All	Ethics oversight for all WPs, compliance management	Supervision, GDPR, engagement, recommendations

Abbreviations: AOUI-VR, Azienda Ospedaliera Universitaria Integrata Verona; AP-HP, Assistance Publique – Hôpitaux de Paris; CERMEL, Centre de Recherches Médicales de Lambaréné; CHARIT, Berlin Institute of Health/Charité – Universitätsmedizin Berlin; CINECA, CINECA Interuniversity Consortium; CINES, Centre Informatique National de l'Enseignement Supérieur; FCRM Fondation Congolaise pour la Recherche Médicale; GDPR, General Data Protection Regulation; HMGU, Helmholtz Zentrum München – Deutsches Forschungszentrum für Gesundheit und Umwelt GmbH; INSERM, Institut National de la Santé et de la Recherche Médicale; INSP, National Institute of Public Health; ISGLOBAL, Fundació privada Institut de Salut Global Barcelona; LIH, Luxembourg Institute of Health; LMU, Ludwig–Maximilians-Universität München; PENTA, Fondazione Penta ONLUS; RAPH-BB, Regional Authority of Public Health Banska Bystrica; REG VEN, Regione del Veneto; RER-ASSR, Regione Emilia-Romagna – Agenzia Sanitaria e Sociale Regionale; SAS, Servicio Andaluz de Salud; UANTWERPEN, University of Antwerp; UBA, Universidad de Buenos Aires; UHC, University Hospital Cologne; UKHD, Universitätsklinikum Heidelberg; UMCG, University Medical Center Groningen; UNIBO, University of Bologna; UNIOVI, University of Oviedo; UNIVR, Università degli Studi di Verona; USTUTT, University of Stuttgart – High Performance Computing Center; WP, work package.

were collaboratively developed to ensure semantic interoperability. Governance procedures included strict access control, audit trails, and compliance checks tailored to multi-jurisdictional data protection frameworks.

### 2.3 | Laboratory and Measurement Logistics

Biological sample processing was performed via combined local and centralized laboratory networks. Local laboratories conducted accessible tests (e.g., PCR, serology) while complex immunological assays (e.g., cytokine/chemokine profiling and cellular immunity assays) were centralized in WP6 reference laboratories to standardize analysis and improve reproducibility. Shipping protocols and cold chain logistics were implemented considering pandemic restrictions. Cohort-specific sampling schedules were synchronized with vaccination timelines and follow-up visits, customized to local epidemiology and vaccine availability.

### 2.4 | Challenges and Variability Across Sites

Variability across participating centers and countries in infrastructure, regulatory approvals, and vaccination schedules posed challenges for data integration and patient enrolment. Some cohorts had well-established electronic databases and biobanks, facilitating integration of retrospective and prospective data, whereas others relied on paper records or had limited capacity to ship biological samples outside local laboratories. Differences in national ethics approvals and vaccination policies also influenced study start times, monitoring schedules, and pediatric cohort enrolment.

## 3 | Results

### 3.1 | Clinical Manifestations of COVID-19 in Immunocompromised Host

Within the ORCHESTRA consortium, the SOT cohort offered an opportunity to observe COVID-19 progression in one of the most

controlled and well-characterized immunocompromised groups of fragile populations.

Early multicenter analyses revealed that the disease course in SOT was characterized not only by increased severity but also by unique patterns of presentation that differed subtly from those observed in immunocompetent individuals. The first comprehensive meta-analysis, encompassing over 1000 SOT hospitalized with COVID-19 across multiple European centers, demonstrated that the majority presented with bilateral pneumonia (85%), and approximately one-third required oxygen supplementation at admission. Despite, SOT patients affected by COVID-19 compared with the general population, showed a higher risk of intensive care unit (ICU) admission and acute kidney injury, they were not associated with an increased risk of mortality when appropriate adjustment for demographic and clinical features, including comorbidities and COVID-19 severity, were made at baseline [13].

The umbrella meta-analysis of comorbid conditions conducted by ORCHESTRA investigators further contextualized these findings by highlighting the interplay between chronic organ diseases and COVID-19 severity [14]. Cardiovascular disease, chronic kidney disease, and diabetes—conditions highly prevalent in transplant recipients—were the leading predictors of severe outcomes across fragile populations.

A subsequent ORCHESTRA study moved beyond binary outcomes to identify distinct clinical phenotypes among transplant recipients [15]. Using 16 demographic, clinical, and laboratory variables, a clustering model was already proposed in the general population [16]. It was applied to SOT into three phenotypic groups with progressively increasing severity: phenotype A (mild, 30%), B (intermediate, 38%), and C (severe, 32%). Mortality followed a gradient across these clusters—8.7%, 16.6%, and 40.1%, respectively. Strikingly, vaccination reduced mortality in the most severe cluster (C) from 52.0% to 17.3%, confirming that vaccine-induced immunity not only mitigated severity but also altered the natural trajectory of disease phenotypes [15].

Finally, a longitudinal cluster analysis from the broader ORCHESTRA cohort extended this lens to the post-acute phase. In a multinational study of 1796 patients, including

transplant recipients, four major post-COVID phenotypes were identified—fatigue-dominant, respiratory, pain-related, and neuro-sensorial—each associated with different impacts on health-related quality of life [17]. Persistent symptoms affected over half of survivors (57%), with vaccination and early antiviral therapy significantly reducing long-term sequelae.

### 3.1.1 | Immunologic Monitoring and Antibody Response (AbR) in Immunocompromised Hosts

Immunologic monitoring was a cornerstone of ORCHESTRA's approach to fragile populations. Serial assessments of humoral and cellular immunity provided unique insight into vaccine responsiveness among SOT. In the first multicenter analysis, 1062 SOT were evaluated after mRNA vaccination. Only 9.8% developed detectable antibodies after two doses, increasing to 52.3% at  $3 \pm 1$  months [18]. Factors associated with seroconversion included liver transplantation (OR 2.71), time more than 3 years since transplant (OR 4.92), and mRNA-1273 vaccination (OR 3.57), while mycophenolate, steroids, and renal dysfunction independently predicted non-response. Antibody kinetics showed a slower, prolonged increase up to 110 days, suggesting that early testing may underestimate response. Follow-up analyses extended observation to 1 year. After a third dose, 75% achieved seroconversion, but titers declined faster than in immunocompetent controls, particularly in heart and lung recipients, justifying additional boosters and individualized monitoring.

Another study established the clinical significance of antibody levels. Among more than 600 SOTR, 18%–20% developed breakthrough infections despite three vaccine doses. Low anti-RBD titers predicted BI (OR 0.67), with a protective threshold of  $\approx 185$  U/mL. Heart transplant recipients, the poorest responders, had the highest infection rates [19].

A complementary machine-learning analysis of 1615 SOTR explored predictive modeling of vaccine response [20]. Using logistic regression and k-nearest-neighbor algorithms, the study identified older age, antimetabolite and steroid use, transplant less than 3 years, and non-hepatic graft as the strongest predictors of negative AbR. Machine-learning models achieved moderate accuracy (AUROC  $\approx 0.72$ ), suggesting that clinical data alone are insufficient and should be integrated with immunologic biomarkers within the ORCHESTRA digital infrastructure.

To evaluate cell-mediated immunity (CMI), a sub-cohort of 73 SOTR underwent parallel T-cell testing. Overall, 83.6% were antibody-positive, 54.8% had detectable CMI, and no patient was AbR-negative but CMI-positive [21]. Roughly 30% experienced BI, but CMI did not correlate with infection risk (OR 1.01,  $p = 0.79$ ), confirming that both humoral and cellular immunity are key to protection.

The influence of immunosuppression intensity emerged from a study in 268 heart transplant recipients. After a fourth mRNA dose, infection-free survival rose to 85.9% versus 72.5% in three-dose recipients ( $p = 0.03$ ). MMF exposure more than or equal to 2000 mg/day doubled the risk of BI (HR 2.22), while time less than 5 years from transplant further increased susceptibility [22].

### 3.1.2 | Gathering Evidence Together With Clinical Experience

Despite substantial efforts, complete harmonization of data across multiple centers was not always achievable, as datasets sometimes contained thousands of highly heterogeneous variables. To address the resulting gap—and the urgent need for standardized clinical guidance in fragile populations—consensus-based approaches were undertaken by leveraging the established international network. Hence, Delphi consensus exercises were carried out to develop evidence- and expert-based recommendations for the diagnostic management, prevention, and treatment of COVID-19 across diverse fragile patient populations, including SOT, hematologic, rheumatologic, and HIV patients [23–26]. A dedicated consensus was also produced for the management of post-COVID syndrome in these vulnerable groups [27]. Together, these initiatives integrated the project's scientific findings with practical guidance, translating complex data into a coherent, adaptable clinical framework for everyday practice.

## 4 | Discussion

The ORCHESTRA project exemplified how large-scale collaboration and shared data architecture can generate meaningful evidence for fragile populations during a global health emergency. Its experience demonstrated that harmonization and adaptability are not opposing forces but complementary enablers of rapid, high-quality research.

Harmonizing laboratory methods and datasets across multiple countries proved both essential and challenging. ORCHESTRA adopted a hybrid model in which local laboratories performed baseline diagnostics while reference centers standardized advanced immunologic assays. Despite inevitable variability in timing, calibration, and logistics, this structure allowed broad participation and data comparability. Integrating heterogeneous clinical and immunologic datasets required extensive validation and curation across centers, but ultimately achieved genuine interoperability within the federated ORCHESTRA database.

These achievements were possible thanks to intense collaboration and constant communication among clinical, laboratory, and data teams. Pre-existing networks of transplant and infectious disease specialists, weekly coordination meetings, and transparent data-sharing policies fostered trust and momentum across 18 countries. Challenges linked to asynchronous enrolment, diverse infrastructures, and evolving vaccine policies were mitigated through pragmatic, context-sensitive analytics rather than rigid standardization.

The ORCHESTRA experience illustrates that harmonization is as much a human process as a technical one. Overcoming variability required not only shared protocols and digital tools but also sustained dialogue, flexibility, and mutual confidence. This collaborative model transformed diversity into analytical strength, demonstrating that rigorous, inclusive research on fragile populations is feasible even under the constraints of a pandemic.

## 5 | Conclusion

In conclusion, the ORCHESTRA experience among fragile patients demonstrated that harmonized, multinational research can produce actionable evidence even under crisis conditions. By integrating clinical, immunologic, and operational perspectives, the consortium revealed both the fragility and the resilience of this population, transforming variability into insight. Despite inevitable heterogeneity, logistical challenges, and data complexity, the project established a sustainable framework for real-time surveillance and evidence translation. Its legacy lies not only in the knowledge generated, but in the collaborative infrastructure and culture it built—an enduring model for studying and protecting fragile populations in future health emergencies.

### Author Contributions

**Beatrice Tazza:** conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft preparation, writing – review and editing. **Cecilia Bonazzetti:** conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft preparation, writing – review and editing. **Natascia Caroccia:** conceptualization, methodology, writing – review and editing. **Michela Di Chiara:** conceptualization, methodology, writing – review and editing. **Lorenzo Maria Canziani:** conceptualization, methodology, review and editing. **Anna Maria Azzini:** conceptualization, methodology, review and editing. **Zaira R. Palacios Baena:** conceptualization, methodology, review and editing. **Paula Olivares-Navarro:** conceptualization, methodology, review and editing. **Jesús Rodríguez-Baño:** conceptualization, methodology, supervision. **Evelina Tacconelli:** conceptualization, methodology, supervision. **Pierluigi Viale:** conceptualization, methodology, supervision. **Maddalena Giannella:** conceptualization, methodology, writing – original draft preparation, supervision, writing – review and editing. All the authors have validated and approved the final submission.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section.

**Supporting File 1:** tid70145-sup-0001-tableS1.docx **Supporting File 2:** tid70145-sup-0001-tableS2.docx