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The INfectious DIsease REgistry BIObank (INDI-REBIO): protocol for the design and implementation of a single-centre, prospective registry and biobank in a tertiary care centre in Italy for advancing infectious disease research

Marco Ripa ,[1,2] Laura Galli,[1] Paola Cinque,[1] Silvia Nozza ,[1,2] Vincenzo Spagnuolo,[1,2] Chiara Tassan Din,[1] Monica Guffanti,[1] Riccardo Lolatto,[1] Girolamo Piromalli,[1] Silvia Carletti,[3] Massimo Locatelli,[3] Francesca Sanvito,[4] Maurilio Ponzoni,[2,4] Elisa Cantarelli,[5] Cristina Tresoldi,[5] Antonella Castagna,[1,2] on behalf of the INDI-REBIO Study Group

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For numbered affiliations see end of article.

Correspondence to
Dr Marco Ripa;
ripa.marco@hsr.it

ABSTRACT

Introduction Infectious diseases are a major global health concern, responsible for significant morbidity and mortality. To advance the understanding and treatment of these diseases, biobanks and biorepositories play a crucial role in guaranteeing sample traceability through their entire life cycle (collection, acquisition and registration, processing, storage, distribution) and future analysis of clinical and biological data.

Methods and analysis The INfectious DIsease REgistry BIObank (INDI-REBIO) is an observational, prospective, monocentric, open-ended registry with ad hoc procedures and a systematic collection of uniform clinical, laboratory, imaging and therapeutic data of patients with suspected or microbiologically documented bacterial, viral, fungal and parasitic infectious diseases from the IRCCS San Raffaele Hospital (Milan, Italy). The study aims to collect both uniform data and biological samples such as blood and other relevant specimens. The registry aims to include significant patient numbers across various conditions (among others: bloodstream infections, endovascular infections as infective endocarditis, central nervous system infections, bone and joint infections, multidrug-resistant organisms (MDROs) colonisation, sexually transmitted infections, HIV infection, emerging and re-emerging infectious diseases), enabling comprehensive research on disease evolution, treatment outcomes and the identification of biomarkers.

Ethics and dissemination The study adheres to ethical principles outlined by the Helsinki Declaration and Good Clinical Practice guidelines. It has received ethical approval (Comitato Etico CET Lombardia 1, CET 138–2023) and is registered on clinicaltrials.gov (NCT06418048). Participants will provide informed consent and can withdraw at any time. The study results will be disseminated through major international conferences and submitted to peer-reviewed research journals.

Trial registration number ClinicalTrials.gov, NCT06418048.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective design with continuous collection of uniform data, linking clinical data with biological samples.
⇒ Inclusion of a wide spectrum of infectious diseases.
⇒ Biological samples stored in the institutional biorepository (bbmri-eric:ID:IT_1383758011993577).
⇒ Monocentric design limits the generalisability of findings.
⇒ Enrolment will potentially be limited by late referrals, patient frailty, consent issues or lack of follow-up.

INTRODUCTION

Infectious diseases are globally recognised as a leading cause of death and health loss and constitute a public health priority. Among the leading causes of death globally, communicable diseases (especially lower respiratory tract infections, with around 500 000 incident cases in 2019 and 2.5 million deaths[1]) still pose a significant burden,[2] and in 2017 alone, an estimated 11.0 million sepsis-related deaths were reported, representing 19.7% of all global deaths.[3] Bacterial infections constitute a major health burden, and in 2019 alone, 33 pathogens were associated with 7.7 million deaths, accounting for 13.6% of global deaths

due to level 3 Global Burden of Diseases (GBD) underlying causes of death[4] (ranking second behind ischaemic heart disease[5]). More than half of these deaths were associated with five pathogens: *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.[4] Even more concerning is the impact of bacterial antimicrobial resistance (AMR), as 4.71 million deaths were associated with bacterial AMR in 2019 (among which 1.14 were directly attributable to bacterial AMR), with an estimated increase to 8.22 million deaths associated with AMR and 1.91 million deaths attributable to AMR.[6 7 7] Among European countries, the mortality burden was highest in Italy, with more than 10 000 attributable deaths, about 30% of all deaths in the European Union and European Economic Area in 2015.[8] When comparing pre- and post-COVID periods (2019 vs 2023), a significant increase of multidrug-resistant pathogens was reported (namely third-generation cephalosporin-resistant and carbapenem-resistant *Klebsiella pneumoniae*, carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* and vancomycin-resistant *Enterococcus faecium*), underscoring the growing challenge of AMR even in the post-pandemic era.[9] While the impact of non-bacterial pathogens is generally less pronounced, fungal, viral and parasitic infections are nevertheless relevant, especially in vulnerable populations. Fungal diseases are estimated to cause over 1,5 million deaths annually, and among acute invasive diseases, the incidence of candidiasis (about 750 000), invasive aspergillosis (about 300 000), *Pneumocystis jirovecii* pneumonia (about 500 000) and cryptococcosis (>2 00 000) is particularly relevant.[10] Notably, in recent years, there has been a growing emergence of resistant non-albicans *Candida* species, with pathogens such as *Candida auris* and *Candida parapsilosis* increasingly contributing to significant morbidity and mortality.[11 12]

Viruses are also responsible for a significant burden of morbidity and mortality. HIV infection is a chronic viral infection that targets CD4+T cells and impairs the immune system, leading to AIDS. According to the latest global statistics from 2021, there were an estimated 38.4 million people living with HIV worldwide, of whom 28.7 million were receiving antiretroviral therapy.[13] The impact of HIV infection on patients' health is multifaceted and depends on several factors such as stage of disease, access to care, comorbidities and psychosocial issues. People living with HIV face increased risks of morbidity and mortality from various co-infections and HIV-associated conditions; moreover, HIV infection affects patients' mental health, quality of life, sexual and reproductive health, social support networks and economic status.[14] Therefore, HIV infection remains a major public health challenge that requires comprehensive and patient-centred care.

Viral respiratory infections, as demonstrated by influenza and the COVID-19 pandemic, are potentially associated with severe outcomes also in immunocompetent patients, while other viruses such as respiratory syncytial virus mainly cause severe disease in immunocompromised patients.[15] Nevertheless, the role of viruses in the aetiology of lower respiratory tract infections is becoming increasingly relevant, especially thanks to the use of molecular diagnostic techniques, accounting for up to 1/3 of all documented causes of community-acquired pneumonia.[16] Other viral infections are particularly relevant for immunocompromised patients, such as herpes viruses (Herpes Simplex Virus 1 and 2, Cytomegalovirus, Epstein-Barr virus, Human Herpesvirus 6 and 8), BK virus, Adenovirus and Parvovirus B19, among others.[17]

Finally, several parasites, such as *Toxoplasma gondii*, *Leishmania* spp and *Strongyloides stercoralis*, are frequently encountered in immunocompromised patients and are associated with potential severe outcomes.[18]

Biobanks and biorepositories are of fundamental importance to infectious disease research, given the rapid evolution of diagnostic techniques and therapeutic approaches, and the European Commission already recognised the pivotal role of these infrastructures for medical research.[19]

In the field of infectious diseases, it is frequently difficult to have access to uniform data and an adequate amount of biological samples of patients with specific infectious conditions, as most studies cover a restricted time span and are focused on specific investigations. In this context, the establishment of a prospective biobank and biorepository will permit storing biological samples from patients with specific conditions and link them with clinical and therapeutic data. This will allow research on a significant number of patients and guarantee access to stored samples that could be analysed in the future with the potential availability of new technologies, or after the emergence of new research hypotheses. This way, clinical data and biological samples will already be available, without the need for new specific prospective studies. For example, given the constant growing interest in the field of personalised medicine, biobanking and biorepositories would be extremely useful for studying samples of patients with specific infectious conditions, in order to identify biomarkers associated with disease evolution and treatment response, and potentially develop precision medicine approaches aimed at personalised treatment. In this regard, OMICs technologies have revolutionised the study of infectious diseases by allowing for a more comprehensive understanding of the molecular mechanisms underlying pathogen-host interactions. These technologies (encompassing genomics, transcriptomics, proteomics, metabolomics and microbiomics) enable detailed investigation of complex biological systems using high-throughput analysis.[20–23]

Moreover, in addition to the evaluation of the host response to infection and treatment, the storage of microbial isolates will be useful to investigate pathogen characteristics and susceptibility to treatment, including antimicrobials not yet available in clinical practice at the time of sample collection. Finally, prospective observational studies and biorepositories could be crucial in the study of emerging infectious diseases (EIDs), which have

become a significant public health concern globally due to their potential to cause epidemics and pandemics. The recent outbreaks of Ebola, Zika and COVID-19 are clear examples of the devastating impact that EIDs can have on human health, economies and societies.[24] Despite the efforts to control and prevent EIDs, these diseases continue to emerge, and there is a pressing need to better understand their epidemiology, clinical characteristics and pathogenesis.[25–27] Prospective observational studies with biorepositories are powerful tools to address these research questions by collecting and analysing clinical, demographic and biological data from patients with EIDs. Biorepositories provide a platform to store and analyse biological samples which can be used for molecular and immunological studies.[28 29] Nevertheless, a recent study showed that, despite the recent COVID-19 pandemic, infectious diseases remain underrepresented in biobank research.[30]

In conclusion, the creation of a framework for archiving uniform biological samples linked to clinical data for specific infectious diseases would constitute an invaluable resource for the study of infectious disease pathogenesis and response to treatment. This initiative would enhance the study of infectious diseases pathogenesis by enabling in-depth analyses at the molecular level on biological samples collected from a significant number of patients. It would also provide additional data to evaluate the response to various treatments, thus offering a real-world observation of data originally obtained from clinical trials on a restricted number of patients with very specific characteristics. Studies derived from a well-designed and well-performed registry can provide a real-world view of clinical practice, patient outcomes, safety, comparative effectiveness and can help support evidence and generate hypotheses. The integration of the data gained by the analysis of biological samples with the clinical data obtained by follow-up of patients with infectious diseases would also facilitate the identification of biomarkers for early diagnosis, disease severity and treatment outcomes, ultimately advancing personalised medicine and improving patient care. The registry-biobank workflow diagram is shown in figure 1.

METHODS AND ANALYSIS

Study design

INDI-REBIO is an observational, prospective, single-centre, open-ended registry with ad hoc procedures and a systematic collection of uniform clinical, laboratory, imaging and therapeutic data on patients with suspected or microbiologically documented bacterial, viral, fungal and parasitic infectious diseases (from now on referred to simply as infectious diseases). Biological samples from patients included in the registry are processed and stored by the institutional biobank Biological Resource Centre (CRB-OSR, Num ID CRB in BBMRI-ERIC: bbmri-eric:ID:IT_1383758011993577).

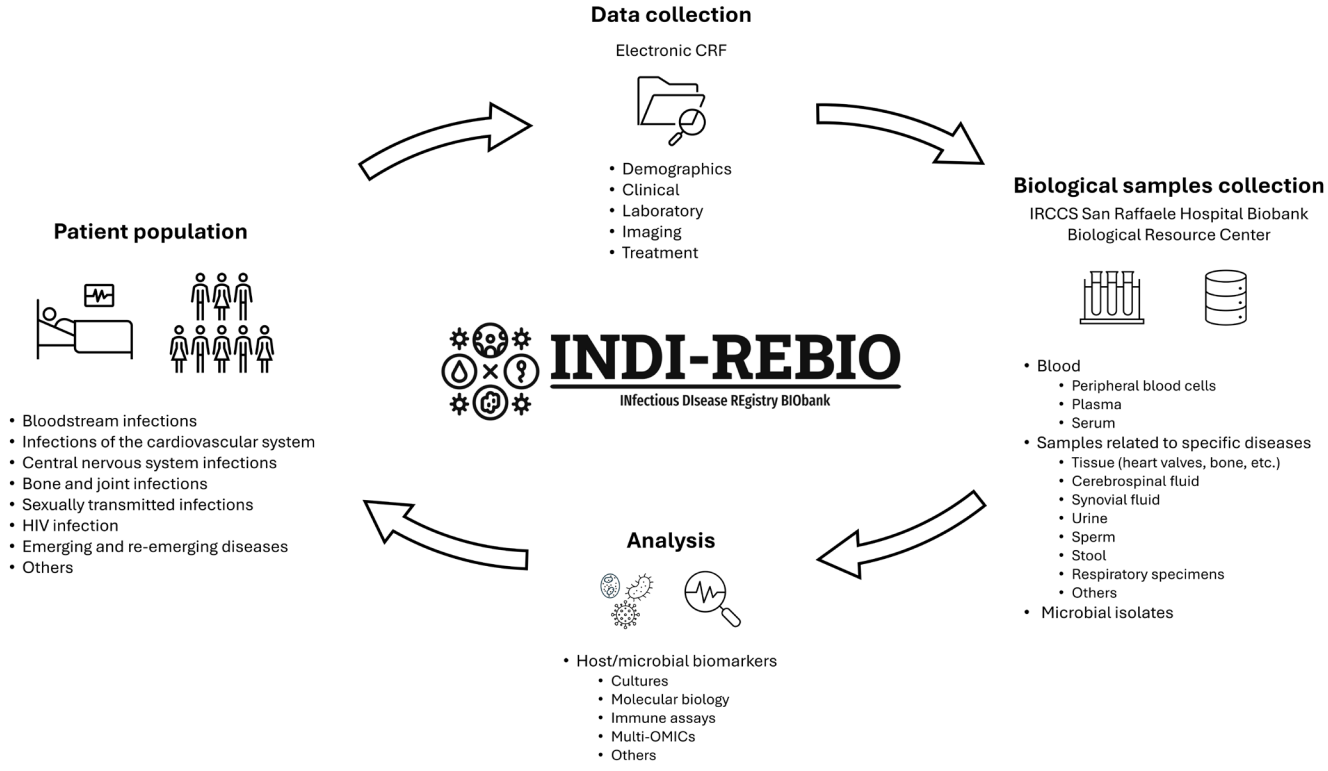

Figure 1 INfectious DIsease REgistry BIObank workflow diagram.

Study aims

The aim of the study is to provide a registry equipped with a comprehensive database and collection of samples from a vast population of patients with infectious diseases, allowing the analyses of clinical, laboratory, therapeutic and biological data related to infectious conditions.

Specific infectious diseases of major interest include, among others:

- Bloodstream infections (eg, infectious syndromes presenting with bacteraemia).
- Infections of the cardiovascular system (eg, infective endocarditis, cardiac implanted device infections, vascular graft infections, etc).
- Central nervous system infections (eg, meningitis, encephalitis, cerebral abscess, ventricular shunt infections, etc).
- Bone and joint infections (eg, osteomyelitis, spondylodiscitis, prosthetic joint infections, etc).
- Sexually transmitted infections (eg, gonococcal and non-gonococcal urethritis, proctitis, epididymo-orchitis, syphilis, etc).
- HIV infection.
- Emerging and re-emerging infectious diseases.

Objectives of the study for each specific infectious disease include:

- Description and longitudinal evaluation of clinical and laboratory characteristics of patients with specific infectious diseases.
- Description and evolution over time of microbial isolates, including antimicrobial susceptibility testing.
- Description and evolution over time of treatment employed in patients with specific infectious diseases.
- Identification of predictive factors for treatment success and mortality in patients with specific infectious diseases.
- Description, evaluation and prognostic impact of microbial, immunological and inflammatory biomarkers.

The general study objectives, along with more specific objectives related to a specific infectious disease, will be evaluated in ad hoc observational studies, nested within the Registry. These studies will use data and biological samples collected within the Registry and may include additional analyses on available samples. Data and specimens will not be shared externally; all research activities will be conducted under the governance of the Registry.

Study proposals with specific objectives and requests for access to biological samples stored in the biobank will be reviewed by the INDI-REBIO Steering Committee, which includes the Principal Investigator (PI), co-Principal Investigators with domain expertise and a statistician. Each proposal must clearly outline the primary and secondary objectives, methodology, required data and samples and feasibility. The committee will assess the scientific merit, originality and availability of requested materials and will resolve any overlapping or competing requests. Only on receiving approval from the Steering Committee can the proposal be submitted to the appropriate Ethics Committee. This governance framework ensures transparency, scientific integrity and ethical oversight. The study proposal process is illustrated in figure 2.

Subjects are asked to participate with biological samples (blood, cerebrospinal fluid, urine, other relevant biological samples related to the specific infectious disease, collected according to good clinical practice and available guidelines) as the registry will promote/perform studies aimed at identifying modifiers of disease progression and to establishing and validating biological markers to track the progressive course of the disease, along with drug efficacy and toxicity.

Population and sample size

The INDI-REBIO includes patients with specific infectious diseases followed at the IRCCS San Raffaele Hospital (either as inpatients or outpatients) managed according to good clinical practice and available guidelines. Participants include those who fulfil inclusion and exclusion

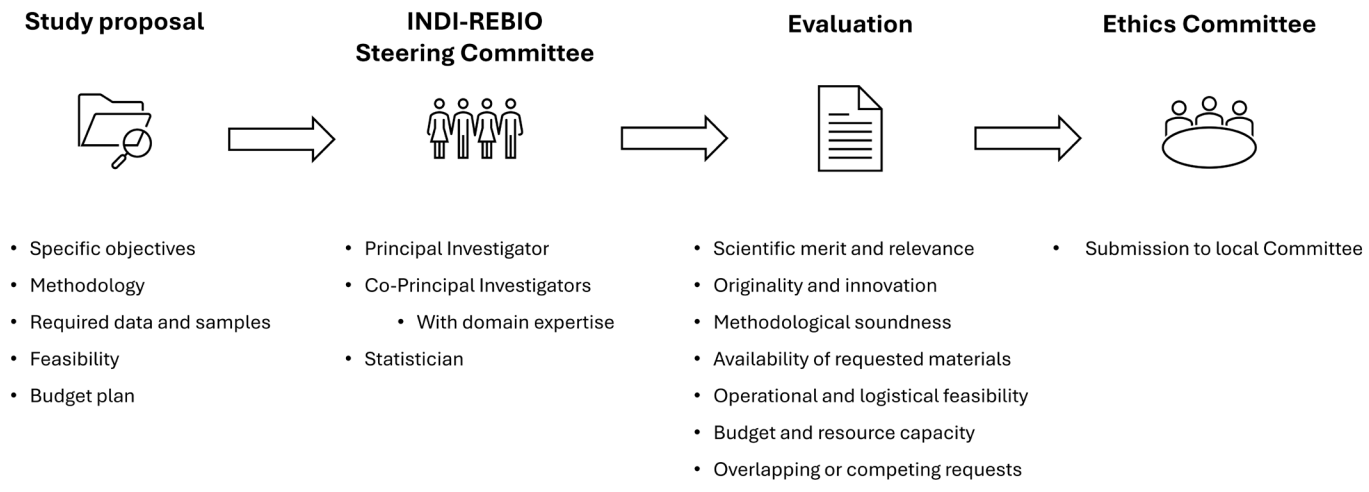

Figure 2 Study proposal process.

criteria and are willing to participate in the registry. "Enrolment" into the registry is defined as providing informed consent for inclusion and participation in data and sample collection.

The following individuals may be eligible to participate:

- Patients with clinically suspected or microbiologically documented infectious diseases (bacterial, viral, fungal or parasitic).
- Age>18 years.
- Patients who are able to provide informed consent.
- Participants who are unable to understand the study protocol or are unable to give informed consent but have a legal representative.

Participants who are unable to understand the study protocol or are unable to give informed consent and have no legal representative will not be considered eligible.

The Registry is implemented with the aim of providing large clinical data sets and significant number of samples to answer research questions by conducting well-powered studies. The number of participants needed to answer scientific questions will depend on specific outcomes and objectives under consideration.

The expected number of patients with specific conditions to be annually included in the registry will approximately be as follows:

- Bloodstream infections: 1000 patients per year.
- Infections of the cardiovascular system: 200 patients per year.
- Central nervous system infections: 200 patients per year.
- Bone and joint infections: 100 patients per year.
- Sexually transmitted infections: 1000 patients per year.
- HIV infection: 50 patients per year.
- Intestinal colonisation due to MDROs: 100 patients per year.

The estimated numbers for each specific condition are based on local hospital epidemiology, case mix and feasibility considerations and may therefore vary over the course of the study.

Among the patients enrolled in the registry, the collection of biological samples is proposed to specific relevant subgroups (identified on the basis of clinical significance, potential impact on research evaluations, adequate collection timing and feasibility, in subjects who do not present conditions of frailty that preclude the collection of additional material), with a sample size for specific conditions expected to be approximately as follows:

- Bloodstream infections: 100 patients per year.
- Infections of the cardiovascular system: 50 patients per year.
- Central nervous system infections: 50 patients per year.
- Bone and joint infections: 50 patients per year.
- Sexually transmitted infections: 100 patients per year.
- HIV infection: 30 patients per year.
- Intestinal colonisation due to MDROs: 80 patients per year.

Study procedures

The Registry consists of 2 components: (a) the collection of demographics, clinical, laboratory and treatment data (b) the collection of biological specimens (this component of the study is optional, and will be proposed to a subgroup of patients identified on the basis of clinical significance, potential impact on research evaluations, adequate collection timing and feasibility, in subjects who do not present conditions of frailty that preclude the collection of additional material).

The overall structure, content and timing of data and specimen collection are coordinated by the PI, in collaboration with the INDI-REBIO Steering Committee, who are responsible for defining both the core dataset to be collected across all participants and any additional disease-specific modules.

All the study procedures are done according to good clinical practice and available local, national and international guidelines. Specific biological samples are additionally collected from patients who do not present conditions of frailty that preclude the collection of additional material and who agree to participate in component "b" (collection of biological specimens) of the study, after providing informed consent. Patients may choose to participate in the registry without consenting to provide biological samples. Separate consent forms are in place for registry and biospecimen collection.

Both data and samples are collected starting from the baseline of the infectious disease after obtaining informed consent. Follow-up data and samples are collected at the end of treatment (EOT) and at 6 months after the EOT for the specific condition or, in case of no therapeutic intervention, at 6 months after diagnosis. In patients with HIV, infection follow-up data and samples are collected annually after baseline. Additional data and samples might be collected at other time-points according to the usual temporal evolution of specific diseases, and in case of relevant clinical events or therapeutic modification.

Potential participants are screened for eligibility. Eligible participants are informed about the study and required to provide written informed consent before enrolling in the study.

At baseline, the following procedures are conducted:

- Data Collection: demographic, clinical, microbiological, imaging and treatment data.
- Blood sample collection.
- Collection of other biological samples: relevant biological specimens will be collected according to specific infectious disease syndromes.

Participants are asked at the time of enrolment for inclusion in the registry (= at baseline visit) to attend as many planned follow-up visits as possible.

At follow-up visits, the following procedures are conducted:

- Evaluation of patients' status: alive/dead, clinical cure, microbiological cure.
- Data collection: demographic, clinical, microbiological, imaging and treatment data.

Table 1 Study procedures

Procedures	Day	Baseline 0	Follow-Up visits Variable (according to clinical evolution and temporal evolution of specific infectious diseases)	End of treatment (EOT) EOT (±7)	Final study visit* EOT+180 (±15)
Informed consent		X			
Demographics		X			
Medical history		X			
Eligibility assessment		X			
Physical examination (including height and weight)		X	X	X	X
Vital signs		X	X	X	X
Treatment data		X	X	X	X
Laboratory tests		X†	X†	X†	X†
Microbiological assessment		X			
Radiologic/Imaging assessment		X†	X†	X†	X†
Peripheral blood collection		X†	X†	X†	X†
Other biological samples collection		X†	X†	X†	X†

*Not applicable for HIV infection.
†According to good clinical practice and available guidelines.

- Blood sample collection.
- Collection of other biological samples: relevant biological specimens will be collected according to specific infectious disease syndromes.

A study flow-chart is shown in table 1.

A standardised set of core variables and biospecimen types is implemented in the electronic case report forms (eCRFs) using REDCap, which ensures standardised data collection and facilitates future integration with hospital records. These variables are defined in accordance with clinical research guidelines and infectious disease standards. For particular infectious disease syndromes, the Steering Committee may introduce targeted extensions to the dataset and/or specific specimen types, depending on scientific priorities and clinical relevance.

All the biological samples are stored in the IRCCS San Raffaele Hospital Biobank "Biological Resource Centre (CRB)" (Num ID CRB in BBMRI-ERIC: bbmri-eric:ID:IT_1383758011993577). The CRB is responsible for sample check-in and assigns a unique identifier to the patient and to the sample. Only the CRB staff and clinicians authorised by the Principal Investigator of the study have access to the list of subjects enrolled to the study. In order to ensure the confidentiality of enrolled subjects, the CRB will distribute pseudonymised samples to researchers.

Sample collection and processing are performed according to hospital and biobank standard operating procedures. Additional details regarding sample processing are described in the online supplemental material. The analyses of the biological samples collected will be carried out primarily at the Research Laboratories of the Infectious Diseases Division. Patient records, source data and biological specimens will be retained for a minimum of 7 years following study completion. The study is currently planned to run for 20 years, with the possibility of extension subject to Ethics Committee approval.

Formal data and sample collection began in February 2024.

Samples analysis

The selection of specific analyses, including biomarker assays, multi-OMICs approaches and microbiological testing, is primarily project-driven. Research proposals submitted to the INDI-REBIO Steering Committee specify the analyses required based on their scientific objectives and the availability of biological specimens, as detailed above.

In addition to project-specific analyses, baseline or core assessments aligned with the primary objectives of the registry and biobank may be conducted systematically on collected samples. These foundational analyses aim to establish comprehensive datasets to support both current and future research initiatives.

Biomarkers

These will include soluble, cellular and functional markers. Soluble immunological markers will be tested by traditional ELISA arrays or through more recently introduced technologies. The cellular markers will be investigated by flow cytometry and the T-cell and B-cell functions by flow cytometry (eg, by intracellular staining) or ELISpot assays.

Multi-OMICs

In a subset of patients, high-throughput methodologies such as metagenomics, proteomics, transcriptomics and

metabolomics will also be applied. Moreover, genetic data from whole genome and exome sequencing will be generated. The specific methodology adopted for these analyses will vary depending on the specific condition and the available data in the literature.

Microbiology

Samples will be processed according to available guidelines and good clinical practice. Further analysis of susceptibility of the bacterial isolates to specific antimicrobials will be performed by reference broth microdilution methodology or by disc diffusion method. Detection of specific resistance genes will be tested on genomic DNA extracted from the bacterial strains by PCR using specific primers. Moreover, for selected isolates, total DNA (chromosomal and plasmid) extracted from the bacterial strain by Next Generation Sequencing will be analysed.

Data analysis plan

Data analysis is performed on approved proposals. Statistical methods have to be defined as part of the proposals and are ultimately the responsibility of the proposers. However, guidance from biostatisticians associated with the Registry will be provided and facilitated through central coordination of the Registry. Although the registry allows for open-ended data and sample collection, individual sub-studies will utilise defined datasets with pre-specified objectives and corresponding statistical analysis plans.

The variables of the study will be described using means or medians and SD or quartiles for continuous variables, and proportions with their 95% confidence intervals for categorical variables.

Comparisons between groups will be made using the chi-square test or Fisher's exact test (categorical variables) or using the Student's t-test or the non-parametric Mann-Whitney test (continuous variables).

Significant variations in continuous variables over time may be assessed using t-tests for paired data or the Wilcoxon signed-ranks test (only two timepoints) or analysis of variance for repeated measures or mixed linear models (all timepoints available during follow-up). Significant changes in categorical variables between timepoints may be assessed using the McNemar test or the Bowker test.

The presence of linear relationships between continuous variables can be tested by the Pearson correlation coefficient (parametric) or Spearman correlation coefficient (non-parametric).

Logistic regression models will be applied to determine the predictors of outcomes; risks (ORs) and the corresponding 95% confidence intervals will be reported.

Cox regression models will be applied to determine predictors of time-to-event data; risks (hazard ratios) and corresponding 95% confidence intervals will be reported.

Two-tailed probability levels <0.05 will be used (unless otherwise specified) to detect statistical significance in the analyses.

Analyses will be conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Any additional statistical analysis methodologies (including sub-studies on the collected samples) will be disclosed in the annual report of the study.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, the ICH guidelines for Good Clinical Practice, and in compliance with all international laws and regulations, as well as national laws and regulations, and any applicable guidelines.

The protocol as well as the Informed Consent have been submitted and approved by the Ethics Committee (Comitato Etico CET Lombardia 1, CET 138–2023); the registry was also registered on clinicaltrials.gov (NCT06418048), where key information and study results will be publicly available.

The investigators or a person designated by the investigators, and under the investigators' responsibility, will fully inform the patient or the patient's legal guardian of all pertinent aspects of the registry. Prior to the patient's participation in the registry, he/she or the patient's legal tutor will need to sign the written Informed Consent Form. It will also be made clear to the patient or the patient's legal tutor that he/she can withdraw from the study at any time without giving reasons and that he/she will not be in any way disadvantaged by this.

Side effects or unexpected events will depend on the procedures performed during the study (eg, blood collection, lumbar puncture, etc.) in accordance with good clinical practice and international guidelines. The collection of biological samples in patients undergoing procedures in accordance with good clinical practice carries minimal potential risks related to the procedure itself, such as bleeding, haematoma formation or damage to surrounding tissues or organs. In addition, sampling may cause discomfort or pain for the patient, especially if multiple sites or larger volumes are involved. Such complications are not expected to be serious or related to significant sequelae and will be managed according to good clinical practice.

Any side effects or unexpected events that may occur during the collection, however, will be kept under close surveillance by the doctor in charge of the study and their collaborators, in accordance with the rules of good clinical practice, until resolved, or until they are no longer considered clinically significant. Any adverse event will be managed according to clinical practice.

The study results will be submitted to the main Italian and international conferences. Manuscripts will be considered for submission to relevant research journals (to be defined depending on the considered diseases and results obtained).

Author affiliations
[1]Unit of Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy
[2]Vita-Salute San Raffaele University, Milan, Italy
[3]Laboratory of Microbiology and Virology, IRCCS San Raffaele Scientific Institute, Milan, Italy
[4]Pathology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
[5]Biological Resource Center, IRCCS San Raffaele Scientific Institute, Milan, Italy

Collaborators INDI-REBIO study group: Simona Bossolasco, Elena Bruzzesi, Diana Canetti, Massimo Cernuschi, Anna Danise, Raffaele Dell'Acqua, Giovanni Gaiera, Nicola Gianotti, Hamid Hasson, Emanuela Messina, Giulia Morsica, Camilla Muccini, Martina Ranzenigo, Paolo Scarpellini, Caterina Uberti-Foppa, Katia Ruggieri, Viviana Castagna, Gaetana Annicchiarico, Alessandro Baglivi, Liviana Della Torre, Sabrina Bagaglio, Elisabetta Carini, Michele Bellomo, Sara Diotallevi, Francesca Alberton, Flavia Badalucco Ciotta, Chiara Ballabio, Costanza Bertoni, Caterina Candela, Gaia Catalano, Tommaso Clemente, Carmen Garcia, Maria Francesca Lucente, Chiara Maci, Ilaria Mainardi, Roberta Monardo, Nicolò Moschetta, Marcella Negri, Rebecka Papaioannu Borjesson, Flavia Passini, Giacomo Ponta, Angelo Roberto Raccagni, Alessia Siribelli, Martina Strano, Golnaz Torkjazi, Benedetta Trentacapilli, Annapia Di Napoli, Floriana Gona, Marco Tonelli, Annunziata Macrì, Enzo Scifo.

Contributors MR developed the idea of the study. MR, LG, PC, SN, VS, GP, AC were involved in the study design and protocol. MR, PC, SN, VS, CTD, MG were involved in patient recruitment. LG developed the statistical and methodological part. SC, ML, FS, MP, EC, CT were involved in the development of the methodological part and the collection and processing of the biological samples. RL was involved in the management and maintenance of the electronic database. MR drafted the manuscript, which was critically reviewed and approved by all authors. MR is the guarantor of the work.

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ORCID iDs
Marco Ripa http://orcid.org/0000-0002-6380-0377
Silvia Nozza http://orcid.org/0000-0002-2673-2731

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