EU-COVID-19

- a multinational registry-based study with focus on risk *and* protective factors, clinical outcomes and mental health

RELEVANCE TO THE CALL

This proposal was prepared in accordance to the *"COVID-19 Emergency call for proposals: Collaborative and Knowledge-building Projects for the fight against Coronavirus disease (COVID-19)"* by the Norwegian Research Council.

The topics described in the call most relevant for this project are:

- Epidemiological observational studies, including risk factors
- Registry-based follow-up of critically ill patients

The project is relevant to the specific call, as it will enhance our understanding of risk/protective factors, spatio-temporal distribution, and clinical consequences of the Coronavirus disease (COVID-19). By doing so, the project will contribute to the global response to the current COVID-19 outbreak and analogous outbreaks in the future.

The project capitalizes on our access to high quality registry data in four countries**, Norway, Italy, Denmark** and **UK,** representing individual level patient data across countries with different incidences of COVID-19, and covering different types of health care systems. Among these, Lombardy in Italy was the second region, after Wuhan, to experience a large number of infected people and an ad-hoc database is collecting information on evaluated and tested persons for COVID-19. Beyond overcoming the risk of low statistical power, the data sources used in this project may partly overcome the bias due to low specificity, that is asymptomatic individuals that are in reality COVID-19 positive. By modelling the spatio-temporal distribution of the disease, the project will greatly help at identifying the factors explaining spatial variation in infection risk, and at forecasting its longitudinal evolution. The project is augmented by paediatric-specific nation-wide data Italy, via **PEDIANET**, which constitutes a unique opportunity to study COVID-19 epidemiology and consequences in children and clinical hospital data from one region in **Brazil**. The research team is highly interdisciplinary, with expertise spanning from the field of epidemiology to pharmacology, biostatistics (incl. machine learning techniques for risk prediction, time series modelling and forecasting), spatial statistics, paediatrics, infectious diseases, signal detection and regulatory pharmacovigilance.

Chapter 1. Excellence

1.1 STATE OF THE ART, KNOWLEDGE NEEDS AND PROJECT OBJECTIVES

The novel coronavirus (SARS-CoV-2) is a new strain of coronavirus that had not previously been identified in humans. On 30 January 2020, The World Health Organization (WHO) declared the outbreak a public health emergency of international concern. On 11 March 2020, WHO characterized COVID-19 as a pandemic[1-3]. As of March 30Th 2020, there are over 780 000 individuals infected and 37 000 individuals have died due to COVID-19 worldwide, and numbers are increasing every day[1]. In Norway, infection rates are currently about 8 per 10 000 whereas the situation is especially challenging in Italy with over 16 persons infected per 10 000 inhabitants and death rates among the highest in the world.

What do we know about risk factors?

Based on information from China[3], it seems that the groups with higher risk of serious illness from COVID-19-infections are i) individuals over 65 years, ii) those with underlying chronic diseases such as cardiovascular disease, diabetes, chronic lung diseases, cancer and hypertension, and iii) smokers. These early data also indicate that the risk of severe disease rises with increased age and more risk factors. The elderly and those with preexisting chronic health conditions have accounted for the majority of deaths from COVID-19[1-2].

However, we cannot automatically assume that risk factors in China are equal to those in Europe. For example, a patient in Norway, Denmark or Scotland with well-regulated diabetes without complications, may not have a particularly higher risk of a severe disease

course. Whether this is the case, is currently unknown. The presence of cases in young adults with a severe disease course has recently raised the question whether other health or background indicators beyond advanced age and morbidity, may contribute to higher susceptibility to COVID-19.

To summarize, to date we know little about the other risk factors. It is possible that people with chronic renal or liver disease, and people with impaired immunity (e.g. due to medical treatment) also have an increased risk of severe illness from COVID-19. Whether social disparities play a role on COVID-19 onset and more severe sequelae, is currently unknown.

What do we know about medications and COVID-19?

As the COVID-19 situation unfolds, the need for research and evidenced based information about medical treatments increases. There are currently no authorized treatments or vaccines in Norway nor in the EU to prevent or treat COVID-19 specifically or any other coronaviruses. Despite this, reports, especially on social media, claim that some medications may worsen the course of disease while others may be used to treat the viral infection.

- *Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and worsening of COVID-19*

There is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID 19[5,6]. On 18 March 2020 the European Medicines Agency (EMA) published a statement stating the lack of evidence of a causal link between use of ibuprofen and worsening of COVID-19[5]. At the same time, EMA called for further studies and highlighted the urgent need for epidemiological studies to provide evidence on any effect of NSAIDs on disease prognosis for COVID-19.

- *ACE inhibitors or ARBs and the worsening of COVID-19*

It is hypothesized that medicines such as ACE-inhibitors or ARBs that act on the renin angiotensin aldosterone system can affect virus activity in the body since SARS-Cov-2 uses the enzyme called ACE_2 to enter human cells. Currently, there is no evidence from clinical or epidemiological studies establishing a link between ACE inhibitors or ARBs and the worsening of COVID-19. The European Society for Cardiology stated that there is no reason to change treatment with antihypertensive medicines based on the coronavirus outbreak[7]. They also advise against stopping ongoing immunosuppressant treatment. The EMA is currently calling for epidemiological studies on potential adverse effects of ACE-inhibitors and ARBs in COVID-19 infected subjects.

- *Treatment of COVID-19*

Currently, there are no approved medications for treatment of patients with COVID-19. Several medications approved for other indications are currently being used off-label in clinical practice and studied in several hundred clinical trials across the globe. These include antiviral drugs like remdesivir, and lopinavir-ritonavir in combination as well as high dose (hydroxy)chloroquine and eparins. These medications have in-vitro activity against SARS-CoV, SARS-CoV-2, and other coronaviruses. In Norway, there has been reports of physicians stacking (hydroxy)chloroquine. The lack of evidence also applies to other medicines such as corticosteroids. The WHO currently recommends against routine use of corticosteroids in patients with SARS-CoV-2, as available data suggest corticosteroids are associated with no survival benefit and possible harm[2-3].

What do we know about health outcomes of patients with COVID-19?

According to the WHO, approximately 15% of patients develop severe disease requiring hospitalization and oxygen support and 5% require admission to an intensive care unit[2-3]. Health outcomes, including mortality, have not been well described taking into account the short observation time and risk factors, especially in a European population.

There is sparse data on the clinical presentation of COVID-19 in specific populations, such as children and pregnant women. In children with COVID-19 the symptoms are usually less severe than adults and present mainly with cough and fever. Yet, this has not been verified by methodologically rigorous research. Whether pregnancy per se is a risk factor for COVID-19, like it was for the 2009 influenza A(H_1N_1) pandemic[8], has not been elucidated.

What do we know about mental health outcomes of the general population following the COVID-19 threat?

In any epidemic, it is common for individuals to feel anxious. Fear of being infected and infecting others, and fear of deterioration of physical and mental health, loss of income and of isolation, are widespread in the population. The restrictive measures taken to confine the spread of COVID-19 in Italy and other European countries have posed important psychological challenges to individuals, especially to the most vulnerable for mental health problems.

There is currently no scientific evidence on the impact of the COVID-19 pandemic on the populations mental health as measured by contacts with the healthcare system for mental health issues, psychotropic medication use, nor the impact of the pandemic on patients with pre-existing mental health conditions.

PROJECT OBJECTIVES

Given the above, it is imperative to fill our urgent knowledge gaps on **epidemiological risk factors, course and consequences** of COVID-19 in the general and potentially vulnerable population, including children, and to determine health outcomes of patients with the infection.

Understanding whether available **pharmacotherapy** options may modify the course and severity of COVID-19 using **real-world pharmacoepidemiological data,** is an impelling clinical question. The proposed project aims to fill part of these gaps, and will generate timely, methodologically sound evidence stemming from **high-quality, detailed, and already available population-based data** covering a population of over 30 million inhabitants in Norway, Italy, Denmark and Scotland. The specific objectives are divided in three work packages (WP), as illustrated in Figure 1 below.

As part of the research output, we aim to develop an innovative electronic, risk algorithm that can be used to predict individual-specific risk for severe COVID-19 and prognosis, which is understandable to lay persons, and applicable in clinical setting, also in pediatrics.

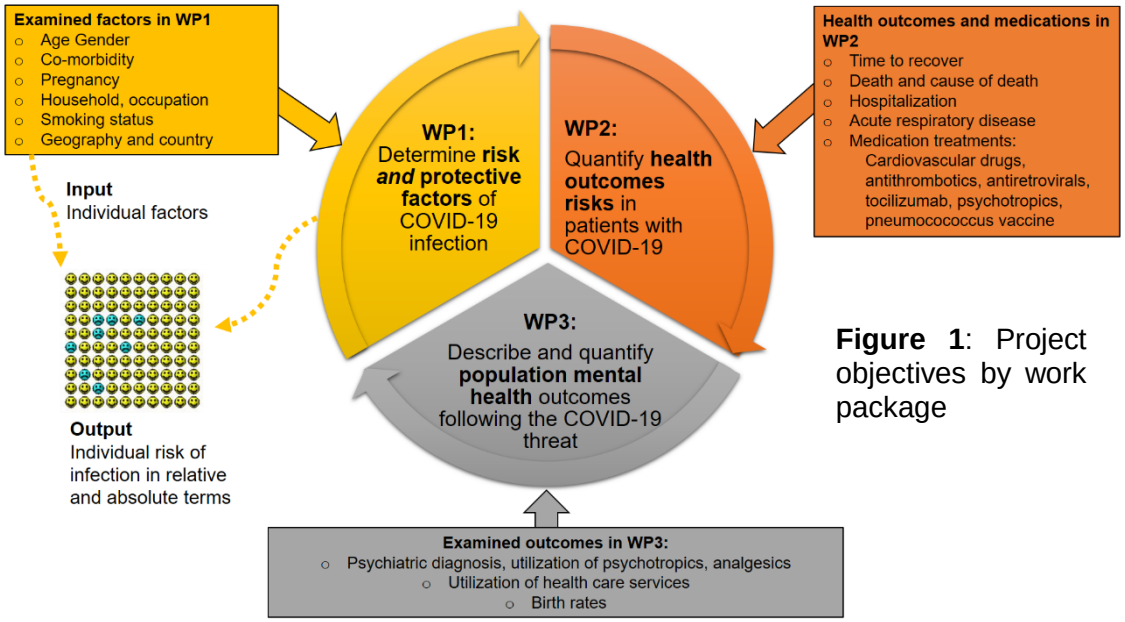

Figure 1: Project objectives by work package

1.2 RESEARCH QUESTIONS AND HYPOTHESES, THEORETICAL APPROACH AND METHODOLOGY

Using health care registries in **Norway, Italy, Denmark and Scotland** and **advanced epidemiological and statistical methods**, we specifically aim to answer the following research questions:

WP1. What are the most important risk factors *and* protective factors of COVID-19?

We will specifically focus on age, including children, gender, pregnancy, co-morbidities and co-prescribed medications. We will:

1. Provide pooled and country specific estimates for the impact of socio-demographic characteristics such as age, gender, and co-morbidities on risk for COVID-19.

2. Develop an online algorithm used to predict individual risk for severe COVID-19. The algorithm will generate a pooled risk score based on the most important risk factors for severe COVID-19.

3. Determine whether NSAIDs or antihypertensive medications influence the risk of a serious outcome among patients with COVID-19.

4. Determine the use and impact of antiviral medication and high dose chloroquine on health outcomes among patients with COVID-19.

WP2. What are the health outcomes of patients with COVID-19?

The study will particularly examine morbidity and mortality, and follow-up of critically ill patients. Critically ill is defined as COVID-19 requiring hospitalization. Markers of disease severity include utilization of health care services and prescribed medications. Patients with influenza will serve as an active comparison group.

We will:

5. Determine mortality rates of patients with COVID-19 according to severity of infection and risk factors, and underlying cause of death

6. Determine morbidity and mortality rates among patients with COVID-19 compared to patients with influenza.

WP3. What are the mental health outcomes of the general population following the COVID-19 threat?

To answer this question, the study will focus on anxiety and depressive disorders in the population, as relapse and new onset disease, using interrupted time series analyses. As proxy of severity, we will examine the frequency of psychotropic prescription dispensing. Special population groups such as children, patients with cardiovascular disease, the elderly and pregnant women will specifically be considered. In relation to the latter group, the study will explore patterns of birth rates in the year 2020, compared to 2018 and 2019.

7. Determine mental health outcomes of the general population following the COVID-19 threat

8. Determine mental health outcomes among individuals with pre-existing mental health disorders following the COVID-19 threat

9. Compare rates of live births before (2018-2019) and after (2020) the declaration of COVID-19 pandemic.

As additional aim bridging WP1 and WP2, we will map the longitudinal evolution of COVID-19 to help at identifying the factors explaining spatial variation in disease risk. This is achieved via use of spatio-temporal point processes, mapping the micro-geographic individual-level spatio-temporal patterns of infections, deaths, cases in intensive therapy and swabbed patients.

Our working hypotheses are that although health-related risk factors of COVID-19 may be the same in different European populations, their magnitude and impact on health outcomes will differ, partly because of different socio-demographic structure across countries. We hypothesize that currently available medications will only have a marginal effect on infection severity and health outcomes. We expect the pandemic to have a substantial negative impact on population mental health, and to reduce birth rates. We hypothesis that vulnerable groups may be discovered.

THEORETICAL APPROACH AND METHODOLOGY

Study population: Individuals infected with COVID-19 as recorded in national surveillance systems in 2020 and 2021 in Norway, Italy, Scotland and Denmark. In Norway, infected

individuals are identified through The Norwegian Surveillance System for Communicable Diseases (MSIS). Infected individuals are identified in the other countries through the regional surveillance system for COVID-19 (Italy, Denmark) and/or hospital contact (Italy, Denmark, Scotland). In Brazil all suspected and confirmed cases are under mandatory notification through a special on-line form centralized by the Ministry of Health.

Table 1. Number of individuals with COVID-19 as per 31.03.2020 (www.worldometers.info/coronavirus)

	Norway	**Italy**	**UK**	**Denmark**	**Brazil**
Infected	4 462	101 739	22 141	2 577	4 461
Dead	32	11 591	1 408	77	165

Study design: Register-linkage cohort study with cross-sectional and longitudinal analysis to examine time trends (2018 – 2020).

Data sources: Data sources are national and regional registries presented in Table 2 that will be linked at a person level. Registries cover a total population of over **30 million inhabitants**.

Table 2. Summary of country-specific data sources

	Norway	Italy	UK	Denmark
Region:	Nationwide	Regions of Tuscany, Lombardy All regions for the pediatric cohort	Scotland	Nationwide
Population:	5.4 MIO	18.7 MIO	0.8 MIO	5.8 MIO
Data source: - Coronavirus disease (COVID-19)	-Norwegian Surveillance System for Communicable Diseases (MSIS)	- Surveillance system for covid-19 - HCU, covering all population	- Surveillance system for covid-19 - Hospital admissions	- Surveillance system for covid-19 - Lab-tests
Data sources: - Risk/protective factors - Follow-up of infected and critically ill patients - Population-level outcomes (Mental health, birth rates)	**KUHR, NPR, NorPD, SSB includes:** - Dispensed Rx - Death registry - Hospitalization - Demographics **MBRN:** birth rates, abortions > 12 week	**HUC includes:** - Dispensed Rx - Death registry - Hospitalization - Demographics - CEDAP: birth rates **Pedianet:** pediatric primary care database	**ISD includes:** - Dispensed Rx - Death registry - Hospitalization - Demographics **SBR**: birth rates, neonatal care	**NHDA includes:** - Dispensed Rx - Death registry - Hospitalizations - Births and abortions - Primary care contacts - Demographics - Lab data

Norway: Norwegian Registry for Primary Health Care (KUHR), Norwegian Patient Registry (NPR), Norwegian Prescription Database (NorPD), SSB (Statistics Norway), MBRN: Medical Birth Registry of Norway. Italy: HealthCare Utilization Databases (HCU), Certificate of Delivery Assistance (CEDAP). Scotland: ISD: Information Services Division Scotland. SBR: Scottish Birth Record. Denmark: National Health Data Authority (NHDA).

In Norway[9], the whole population is covered by the mandatory Norwegian Surveillance System for Communicable Diseases (MSIS), which can be linked to national health registries, i.e. the Medical Birth Registry (compulsory medical records on all live births, stillbirths and induced abortions), the National Patient Register (admission records to hospitals and specialist health care), and the National Prescription Registry (records on all prescriptions dispensed in Norway since 2004).

In Italy[10], the National Health Service covers the entire population, which is associated with an automated system of regional databases named Health Care Utilization (HCU). The HCU system collects demographic and administrative data, their health care use, hospitalization records and filled prescriptions. In the region of Lombardy, an ad-hoc database is building to collect information on evaluated and tested persons for COVID-19. The linking of records across HCU databases and this ad-hoc database via the unique patient-identifier, allows us to reconstruct relevant socio-demographics and care pathways of people affected by COVID-19.

Moreover, the pediatric primary care database Pedianet (www.pedianet.it) collects data from an established Italian network of around 40% of the whole Italian pediatric population (almost 100% coverage in the most affected Italian regions in the North). The data are generated during routine patient care, and cover information on demographics, clinical data including diagnosis, symptoms, ambulatory diagnostic exams, pharmaceutical prescriptions, specialist visits and diagnostic procedures, emergency room visits and hospitalization.

In Denmark[9]**,** the Danish Civil Registration System (all births and residents in Denmark) is linked to all national health registries, including the Medical Birth Registry (compulsory medical records on all live births, stillbirths and induced abortions), the National Patient Register (admission records to hospitals and specialist health care), and the National Prescription Registry (records on all prescriptions dispensed in Denmark since 1995).

In Scotland, the Prescribing Information System (PIS) records all medicines dispensed from pharmacies in Scotland since 2009 and these can be record-linked using the person-unique Community Health Index (CHI) number to demographic data, Scottish Morbidity Records and National Records of Scotland (NRS) death registrations for the entire population.

In Brazil, the public health care system has universal coverage for the Brazilian population (SUS, or Sistema Único de Saúde in Portuguese). The private system is another option most often used by companies and populations with higher incomes. Partnership with Brazil was confirmed on 27/3/2020. The nature of data provided by Hospital de Clinicas de Porto Alegre will be negotiated if the project is funded. This hospital is the COVID-19 referral hospital in the region of Porto Alegre, Brazil.

Data management:

Structural (same format) and semantic (same meaning) harmonization will be conducted across data sources and will be fully transparent using a common data model. Data will remain local, and only highly aggregated results or model estimates will be submitted for pooling (Figure 2).

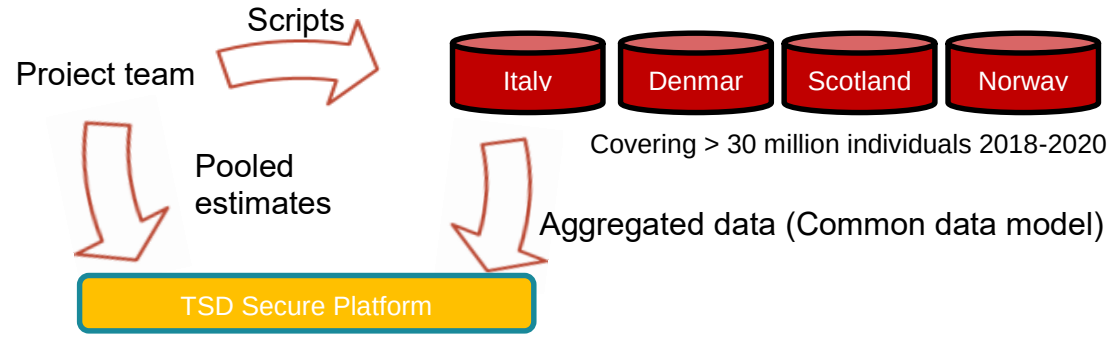

Figure 2. Data management

Measures:

COVID-19: This includes measures of notifiable disease (suspected/confirmed), month- and year of diagnosis, age groups, county of residence and place of infection.

We will also use the emergency ICD-10 code for COVID-19:

- U07.1: COVID-19 diagnosis confirmed by laboratory testing.
- U07.2: COVID-19 clinical or epidemiological diagnosis of where laboratory confirmation is inconclusive or not available.

In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.2.

Severity of COVID-19 will be categorized as recommended by WHO[1]:

- Mild disease: No requirement for hospitalization
- Moderate disease: Hospitalization, diagnosis of pneumonia
- Severe disease: Hospitalization; admission to intensive care unit (ICU), requiring a ventilator to breathe.

Influenza (ICD-10 codes J09-J11) will serve as an active comparator.

Risk/protective factors: These include age (child, adolescence, adult, elderly), gender, co-morbidity (e.g. cardiovascular, respiratory, diabetes, rheumatic diseases, cancer), pregnancy, household (number), occupation (e.g. student, healthcare personnel), geography (city/town), country (Norway, Denmark, Italy, UK, Brazil).

Longitudinal evolutions of COVID-19: All available official series (number of deaths, numbers of infected people, number of hospitalizations for COVID-19 symptoms, number of ICU patients), in order to forecast over time the longitudinal evolutions of COVID-19.

Medications: Cardiovascular drugs (e.g. ACE-inhibitors, statins, heparins), antiretroviral medications (e.g. chloroquines, lopinavir/ritonavir), tocilizumab, psychotropics (e.g. antidepressants, anxiolytics), analgesics. Medications are classified according to the ATC classification system.

Clinical outcomes: Time to recovery (days), death (yes/no), hospitalization (yes/no), acute respiratory disease (yes/no), medication use (type and extent, including pneumococcus vaccination). Diagnosis: ICD-10 codes (secondary care) and ICPC codes (primary care).

Mental health status: Diagnosis in secondary care: ICD-10 codes. Diagnosis in primary care: ICPC. Utilization of psychotropic (e.g. antidepressants, anxiolytics), analgesics, utilization of health care services.

Analytical approaches and statistics

Multiple analytical approaches will be employed depending on the specific aim. The **matched case-control** design will be used to study chronic risk/protective factors.[11] The target population will consist of all beneficiaries residing in the units collaborating in the project. From this population, we will select COVID-19 cases (positive, hospitalized, or fatal) between specific months of 2020, and the date of the evaluation for COVID-19 will be defined as the index date. Up to five controls will be randomly selected and matched to each case by key characteristics. Controls will be selected by incidence density sampling.

The **case-crossover design** will be applied for the analysis of more acute and transient factors.[12,13] This design studies the effects of short-term exposures on the risk of acute events. The study population consists of individuals with a COVID-19 comparing exposures in a time window before the event to that in a preceding time window. Each subject serves and his/her own control, minimizing the risk of confounding. A **case-time-control analysis** will compensate for time trends in exposure, included those that may be caused by the epidemic itself.

The prognosis of severe COVID-19 will be studied in a **cohort design**[11] and sequelae investigated by comparing healthcare system contact and medication use before and after the infection.

Statistics: Multivariable linear regression including models taking into account autocorrelation for interrupted time-series analyses, logistic regression, Cox proportional hazards regression (survival analysis), Poisson regression and G-methods will be used as appropriate. Advanced confounder adjustment methods, including propensity score methods, will be used to mitigate measured confounding.[11,14] **Effect-modification by medication use** will also be investigated. Appropriate measures will be used to handle missing data. Unmeasured confounding will be addressed by sensitivity analyses and probabilistic bias analysis (PBA). PBA will be used to quantify risk of bias due to low specificity of infectious status (i.e., asymptomatic but Covid-19 positive patients) under a range of scenarios.[15]

We suggest using **machine-learning techniques** to identify risk/protective factors (conditional inference trees). Identified risk factors will subsequently be validated in conventional epidemiological analyses. Predictive models for poor health outcomes of COVID-19 will be explored (Lasso-for inference, Machine learning techniques).[16-18]

To model actual evolutions and monitor future progressions of COVID-19, we propose to employ a **rigorous time series methodology**, using all available official series (number of dead patients, infected people, hospitalizations for COVID-19 symptoms, ICU patients. Based on preliminary data in Lombardy region during a time window 24-Feb/29-Mar, only the last two

series are eligible to be used (series not affected by self-selection mechanisms). To model the **spatio-temporal distribution of COVID-19**, micro-geographic individual-level spatio-temporal patterns of infections, deaths, ICU cases and swabbed patients will be identified via use of spatio-temporal point processes.[19] Moreover, in order to study the lethality risk of the disease, dynamic survival models with spatial frailty[20] will be estimated.

Pooling of country-specific effects, meta-analysis: Effect estimates will be pooled using a random-effects generic inverse variance method of analysis[21] and reported incidence used to calculate absolute risk.

Power analysis: For the most conservative scenario including the least common outcome (death: 4%) among COVID-19 positive individuals (82 000, see table 1), we have 80% power to detect moderate effects (risk ratio: 1.28, odds ratio: 1.30) for exposures and factors with prevalence as low as 1%, setting the Type I error rate to 5%. For more common outcomes and exposures, even smaller effect sizes can be detected.[22]

STAKEHOLDER ENGAGEMENT AND INVOLVEMENT

Stakeholders are patients with COVID-19 and their families, healthcare personnel, heath care authorities and policy makers, and the general public, as all are affected by the pandemic. Stakeholder representatives will be involved in all parts the project from planning to reporting of results to optimize the clinical benefits and public health impact. Stakeholder will also be actively involved in the dissemination of results (se pt 2.2). Stakeholders will be involved in the user-testing of the online risk prediction tool for severe COVID-19 to optimize user-friendliness.

ETHICAL AND LEGAL REQUIREMENTS

The project will follow the EU General Data Protection Regulation as well as all ethical and institutional regulations relevant for each data source in the project. Each data access provider will ensure that rules and regulations are followed and that required approvals are obtained. Databases may require approval indicating that informed consent is waived and the rational for this decision will be maintained. The protocol and waiver of informed consent will be reviewed and approved by the appropriate authority (e.g. Research Ethics Board/ Institutional Review Board/Data Protection Officer (REB, IRB/ DPO)) before study start). A Data Protection Impact Assessment (DPIA) will be performed by the appropriate Data Protection Officer (DPO).

GENDER ASPECTS

In line with the Research Council's goals of gender equality in research, the project includes data from both men and women. The project manager is a woman, and we ensure a mix of genders in the project organization. Our international collaborators are both male and female scientists.

1.3 NOVELTY AND AMBITION

The project capitalizes on our access to high quality registry data in four countries**, Norway, Italy, Denmark** and **UK,** representing individual level patient data across countries with different incidences of COVID-19, and covering different types of health care systems. Of these, one is a nation-wide, pediatric-specific primary care database.

The project has ambitious goals for the given time frame and the desired impact on public health and prevention. Yet, the multidisciplinary expertise of the research team, the extended experience of the collaborators with their own data source, and timely data access will make our ambitious goals within reach. The establishment of such a wide European collaboration to address impelling research questions, is *per se* an important advantage of this proposal.

Our ambition is to translate the gained knowledge into a predictive risk algorithm for both infection and prognosis which is individual specific, understandable to lay persons, and useful in the clinical settings within patient-doctor encounters. By using forecasting and spatial statistics methods, we will explain and predict the epidemiological behaviour of COVID-19. By endorsing active patient and public engagement in the project, at European level, and by using advanced data visualization techniques**,** we will be able to reach out and disseminate new epidemiological knowledge on COVID-19 to a broad target audience that urgently needs conclusive answers: scientific community, patients, health authorities, health care personnel and the public at large.

Chapter 2. Impact

2.1 POTENTIAL IMPACT OF THE PROPOSED RESEARCH

We anticipate generating new epidemiological knowledge on COVID-19, with special focus on vulnerable patient groups including children, pharmacotherapy options, and population mental health at large. The research output will also help at Identifying factors explaining spatial variation in disease risk. By doing so, the project will contribute to the global response to the current COVID-19 outbreak and analogous outbreaks in the future, which has important impact on public health and preventive measures. By quantifying the magnitude of effect of different pharmacotherapies on health outcomes, according to patient-specific baseline factors and infection indicators, the study can provide substantial impact on treatment guidelines and practices for current and future COVID-19 epidemics, in Norway and worldwide. Likewise, identification of major risk factors for COVID-19, longitudinal course and prognosis, is crucial for prevention and prioritization in healthcare. Recognizing patients that are highly at risk of death and severe health outcomes at the time of first symptom presentation, is imperative for prevention. To amplify the impact of our research at population level, we will incorporate our results into an innovative online risk prediction tool that can predict individual-specific risk for severe COVID-19, which is applicable in clinical setting, including pediatrics. Lastly, our multivariate time series models may serve as timely tool for short-run forecasting of the number of beds needed in ICUs, allowing health authorities to face the eventual shortage of hospital beds, ICU beds, doctors, nurses and ventilators.

The expected results are:

- Identification of risk *and* protective factors for severe COVID-19, incl. **impact of medications** and longitudinal evolution of the infection
- Estimate of time to recovery according to risk factors, disease severity and medications use
- Estimates of sequelae for critically and non-critically ill patients overall and by country
- Ecological associations between COVID-19 threat and population mental health and birth rates
- Individual-specific online risk prediction tool based on the most important risk factors for severe COVID-19, which is applicable in clinical setting and at population level.

This ambitious goal is in line with the United Nations sustainable development goal 3 “Ensure healthy lives and promote well-being for all at all ages”. Our scope aligns specifically with the UN goal to address the growing threat of infection diseases (i.e., COVID-19 and future epidemics) and increasing burden of non-communicable diseases (i.e., mental health).

2.2 MEASURES FOR COMMUNICATION AND EXPLOITATION

Our target audience is far-reaching and beyond the national context. We will disseminate our results to the scientific community through at least three scientific papers in international referee-based, highly ranked journals that offer open access publication and scientific video abstracts. Preparation of such manuscripts will be prepared independently by the investigators and in accordance with the current guidelines of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and the ENCePPP code of conduct.

We will disseminate results in a balanced and timely manner, for example by presenting absolute risks and measures of population impact (e.g., population attributable fraction) in addition to the relative risk estimates. Our target audience also comprises European national authorities and medicine agencies, which will receive ad hoc summary reports of our research. The purpose of this is to facilitate policymaking and increase preparedness for future epidemics. Dissemination to the public at large is central to this project, and the project’s international nature allows us to apply public dissemination strategies in parallel within each participating country, and in different languages. We will write plain-language summaries of our research findings in various languages, which we will communicate through appropriate social media channels (Twitter, Facebook). We will use the communication departments at our institutions to send out press releases and, furthermore, post these in social media.

In collaborations with various patient and stakeholder organizations involved in the project, in Norway and other countries, we will organize online open seminars and lectures to disseminate our findings to a broader segment of the public. Patient and public engagement will aid our public dissemination of results in a language that is understandable to lay people, and via channels that increase visibility and impact of these findings on population health and preventative medicine. The overall scope of this active dissemination strategy is to increase awareness about infectious diseases and preventive measures at population level, and thereby facilitate preparedness for future epidemics.

Chapter 3. Implementation

3.1 PROJECT MANAGER AND PROJECT GROUP

EU-COVID-19 is a multinational project led by the Dpt. of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo (UiO). **The project manager**, Prof. Hedvig Nordeng, is head of the Pharmacoepidemiology and Drug Safety Research group at UiO. She is also a scientific expert appointed by the European Commission to PRAC, **European Medicines Agency (EMA)** and holds a position (20%) at **the Norwegian Institute of Public health**.

Project group: Partners have specifically been selected based on their scientific expertise and experience. It includes experts in epidemiology, pharmacology, biostatistics, paediatrics, infectious diseases, signal detection and regulatory pharmacovigilance. All project members have extensive experience in conducting multi-database studies using advanced methods in biostatistics and epidemiology.

Table 3. Overview of key team members

Team members	Institution	Expertise
Prof. Hedvig Nordeng (HN), Dr. Angela Lupattelli (AL), Dr. Helle Wallach Kildemoes (HWK)	Dpt. Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Norway	Pharmacoepidemiology causal inference, pharmacology, registry-linkage studies (HN, AL, HWD). **HN is scientific expert appointed by the PRAC at the EMA**, and **PI for the project**
Dr Rosa Gini	Tuscany Regional Health Agency, Italy	Common Data models, pharmacoepidemiology
Prof Giovanni Corrao (GC), Dr Anna Cantarutti (AC), Dr Federico Rea (FR), DR Matteo Franchi (MF), Prof Piergiorgio Lovaglio (PB), Dr Paolo Berta (PB), Prof Giuseppe Espa (GE)*, Dr Maria Michela Dickson (MMD), Dr Diego Giuliani (DG), Prof Giorgio Vittadini (GV)	Dpt. of Statistics and Quantitative Methods University of Milano-Bicocca, Lombardy, Italy *Dpt of Economics and Management, University of Trento, Italy	Statistical learning, time series modeling and forecasting (PL, PB); spatial statistics, small area estimation and sampling theory (GE, DG, MMD); biostatistics, pharmacoepidemiology (AC, GC, FR, MF). **GC is a member of the network for the pharmacological and therapeutically assessment on patients affected by COVID-19**.
Prof Carlo Giaquinto (CG) Prof Daniele Donà (DD) Prof Luigi Cantarutti (LC)	Dpt. of Woman's and Child's Health, University of Padua, Italy	Pediatrics, clinical expertise, infectious epidemiology, pediatric infectious disease (CG, DD, LC). **CG and LC are Pedianet Coordinators.**
Dr. Daniel Morales (DM)	University of Dundee, Scotland, UK	Primary care, pharmacoepidemiology, regulatory sciences. **Scientific expert appointed by the PRAC at the EMA.**
Prof. Morten Andersen	University of Copenhagen, Denmark	Common Data models, pharmacoepidemiology, **machine learning** techniques for risk prediction
Dr. Birgitta Grundmark	Uppsala Monitoring Centre, Sweden	Signal detection, pharmacovigilance. **Scientific expert appointed by the PRAC at the EMA.**
Prof. Antoine Pariente	Université de Bordeaux, France	Pharmacoepidemiology. **Scientific expert appointed by the PRAC at the EMA.**
Prof. Lavinia Schuler-Faccini	Federal University of Rio Grande do Sul, Porto Alegre, Brazil	Viral toxicology (incl. Zika-infection), clinical management of COVID-19 in Brazil.

PRAC= The Pharmacovigilance Risk Assessment Committee. EMA=European Medicines Agency. Dpt=Department.

We will collaborate closely with UiOs University Center for Information Technology (USIT) for the development of the novel on-line risk prediction tool. We have previously developed digitals tools (MySafeStart app) in collaboration with this center. USIT is also a national centre of competency in IT for the higher education sector.

3.2 PROJECT ORGANISATION AND MANAGEMENT

Planned project period: The project is a two-year project starting 1. July 2020 and ending 30. June 2022. Due to the urgency of providing results, and taking the lag time for data delivery into account, we will include data from 01.01.2018 to 31.12.2020, with a possibility to provide updates in further research projects. The main milestones are presented in Table 4.

Table 4. Time schedule – main milestone (see online form for details)

Activity	Spring - 2020	Fall-2020	Spring - 2021	Fall-2021	Spring - 2022
Protocol preparation and approvals					
Statistical analyses plan/Common Data Model					
DAP: Data access and analysis					
Report and manuscripts (Open access)					
Dissemination to stakeholders					

Allocation of tasks: Upon the project start, UiO and partners will assign a study team consisting of a statistician, a study coordinator, and a clinical consultant. Each country's investigators will be responsible for obtaining the necessary permissions from ethical authorities and registry holders. Data management and analysis will be done in each of the four countries using the same scripts. Partners in Italy, Scotland and Denmark will deliver the aggregated output to UiO (See Fig. 1). Regular project meetings with the international collaborators will be held over video conferences, but in-person meetings may be held in Europe and at specific international conferences.

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