Modulo richiesta assegno

TUTOR	**Paolo Boffetta**

TITOLO DEL PROGETTO Data management and analysis for WP5 of Orchestra project			
ASSEGNO FINANZIATO DA PROGETTO COMPETITIVO *(barrare la casella corrispondente)*	X SI	☐ NO	
SE IL FINANZIAMENTO È COMPETITIVO L'ENTE FINANZIATORE	Unione Europea		
PROGETTO/ATTIVITÀ A SCOPO COMMERCIALE *(es. sperimentazione profit)*	☐ SI	X NO	
CARATTERISTICHE DEL PROGETTO (*biomedico/osservazionale/clinico-interventistico/multidisciplinare*)	Studio osservazionale		
STATO DI APPROVAZIONE DEL PROGETTO DA PARTE DEL COMITATO ETICO (*se necessario per il tipo di studio barrare o evidenziare la casella corrispondente*)	☐ Ottenuto	X Da ottenere	

DESCRIZIONE DEL PROGETTO *(max 800 parole)*

Stato dell'Arte e Razionale

Healthcare workers (HCW) are a group at high risk of infection in general [Baker et al., 2020] and specifically SARS-CoV-2 infection [Zhou et al., 2020; Wu et al., 2020]. However, little data have been reported so far in the literature on prevalence of COVID-19, and on risk factors of the infection in this group of workers [Wander et al., 2020]. Given the lack of information on determinants of infection in this important occupational group, and the relevance of such data for other groups of the population, we propose a multicentre cohort of clinical, occupational and biological data collected HCW from four European and a non-European country. The builds on a preliminary analysis of data from 10,000 HCW conducted in seven academic centers from Italy [Boffetta et al., submitted for publication].

Obiettivi

The specific aims of WP5 of the ORCHESTRA project are:

1. To establish an ORCHESTRA cohort of HCW exposed to COVID-19 in Italy, Spain (high-risk European countries), Romania, Slovakia (intermediate-risk European countries) and India (high-risk extra-European country), including collection and harmonization of data on circumstances of occupational and non-occupational exposure to SARS-CoV-2, use of personal protection equipment (PPE), clinical history of the disease.
2. To investigate the prevalence of SARS-CoV-2 infection and of clinical course of COVID-19, and their occupational and non-occupational determinants.
3. To conduct a prospective follow-up of the cohort of HCW to study long-term effects of exposure to COVID-19, including duration of immunity induced by natural infection and risk of reinfection.
4. To assess the feasibility of HCWs population-based cohorts for phase-3 vaccine trials.
5. To collect biological samples from subsets of HCW to contribute to genomic and microbiomic analyses in WP6.

6. To develop recommendations on strategies to prevent infection in HCWs, based on the results of HCWs ORCHESTRA cohort study and the evidence available from other studies, with emphasis on less-developed countries.

Metodologia (*descrizione del campione, principali tecniche utilizzate, aspetti biostatistici, fattibilità…*)
The work planned in WP5 will build on a long-lasting collaboration between the partners, who have been involved in multiple joint studies during the last two decades [refs], including projects funded by the European Commission, and on the experience of the WP leader (P. Boffetta) in coordinating projects including multicenter occupational and non-occupational cohorts. In particular, Dr. Boffetta was the coordinator of the EC-funded project, CHANCES, that pooled data and biologic samples from 16 cohorts on healthy ageing from Europe and North America [Boffetta et al., 2014]. The work will be organized in five tasks, each corresponding to a specific aim (see above). Only tasks 1-3 are specified in detail, since the work to complete them will be conducted at University of Bologna.

Task 1. Establishment of multicenter cohort of HCW, including data collection and harmonization.
National components of the cohort of HCW exposed to COVID-19 will be enrolled in Italy and other European and non-European countries. In each country, cohorts will comprise multiple groups of HCW, including physicians, nurses, assistant health workers, technicians, other workers with patients' contact, and workers without patients' contact. In all countries HCW have been or are being tested for SARS-CoV-2 infection. During March and early April 2020, testing was mainly conducted on high-risk HCW (those reporting a contact with a COVID-19 patient or developing symptoms) with PCR-based test; starting in April 2020, all HCW are being tested for antibodies against SARS-CoV-2, primarily using ELISA-based kits. HCW with positive serology results undergo one or multiple PCR-based tests. Multiple tests are performed – with different protocols between the centers – in a large proportion of HCW even in the presence of negative PCR or serology results.

Information on circumstances of exposure to SRS-CoV-2 (e.g., contact with infected patient or colleague) and use of PPE (surgical mask, FFP2/FFP3 mask, face shield, gloves, disposable gown, etc.) is being collected from HCW at the time of test. Clinical information (presence of symptoms, quarantine, hospitalization, etc.) either is collected at the time of test or is obtained from the medical records.

Given the heterogeneity of instruments used to collect the data, it will be necessary to develop a strategy for data harmonization, similar to that implemented in other multicenter projects such as CHANCES [Boffetta et al., 2014]. Data assessment procedures will include examination of availability and comparability of data from each cohort, questionnaires and measurement procedures used in the individual cohorts, and indicators of the quality of the existing data. Harmonization procedures include mainly definitions of new harmonized variables for the data analyses to be carried out in WP5. Availability and the characteristics of the data on each domain will be assessed for each cohort. Joint variables will be defined based on the results of the assessment and research priorities. A wiki site will be used for collecting relevant information from the centres and documenting the cohort descriptions, availability and assessment of the data, the common variable definitions and the rules for deriving the common (harmonized) variables from the local data sets. The wiki site, where all WP5 investigators from the difference centres will have writing access, is a powerful tool for drafting, commenting, and finalizing the various documents. If a subset of data is missing from a participating cohort, HCW will be re-contacted, either by telephone or at the workplace, to complete ad-hoc questionnaires on the missing data. In addition, all HCW will be re-contacted to gather information on COVID-19 related bumout and mood disorders (see Task 3).

Variables to be included in the pooled dataset will include demographic and job-related characteristics, circumstances of exposure to SARS-CoV-2, use of PPE, presence of symptoms, clinical course of

COVID-19, if relevant, results of PCR and serology tests. In addition, information on non-occupational exposure circumstances and on factors potentially interacting with COVID-19 (e.g., chronic conditions, obesity) will be collected. Multiple records will be available for HCW who undergo more than one test. Trajectories addressing the temporal course of exposure circumstances, symptoms, disease and testing will be derived for each HCW. The pooled dataset will be anonymized and personal identifiers will be retained in the participating centers.

Task 2. To investigate the prevalence of SARS-CoV-2 infection and of clinical course of COVID-19, and their occupational and non-occupational determinants.

In order to take into account the inherent differences across cohorts in measurement of exposures and outcomes due to different protocols used, statistical analyses for the different research hypotheses will be carried out by means of meta-analysis of harmonized variables. The approach will address individual-level data that will be shared after signing a data transfer agreement.

Multivariable logistic regression models and longitudinal (e.g., Cox regression) models will be fitted to the data to estimate prevalence odds ratios risks of SARS-CoV-2 infection and clinical course of COVID-19; additional regression models will explore the role of potential determinants identified in Task 1 and include potential confounders. Given the heterogeneity of data, center-specific risk estimates will be combined using a random-effects meta-analysis [DerSimonian & Laird, 1986], and sources of heterogeneity in the pooled results will be explored. A detailed plan for analysis will be developed when the full details of the available data will be known.

Task 3. To conduct a prospective follow-up of the cohort of HCW to study long-term effects of exposure to COVID-19, including duration of immunity induced by natural infection and risk of reinfection.

We will conduct a prospective follow-up of HCW included in the multicenter cohort, to assess long-term effects of exposure to COVID-19. As part of the follow-up, HCW included in the cohort will be conducted at 6 months and 12 months to collect information on additional exposure circumstances, psychological conditions, and novel symptoms. In parallel, results on additional tests performed on the HCW, and on clinical evidence of COVID-19, if any, will be collected. The follow-up will last a total of 12 months after enrolment.

The primary endpoint of the analysis of psychological consequences of COVID-19 exposure will be burnout, with mood disturbance and mindfulness as secondary outcomes. For their assessment both at baseline and during follow-up, we will use validated national versions of self- administered questionnaires. Burnout will be measured with the Maslach Burnout Inventory (MBI) [Maslach er al., 1996] of 22 items, which comprises three subscales (emotional exhaustion, depersonalization, and personal accomplishment). Mood disturbance, will be measured with a short version of the POMS Questionnaire [McNair et al., 1971], comprising 15 items distributed in five domains: tension-anxiety, depression-dejection, anger- hostility, vigor-activity, and fatigue-inertia. Mindfulness will be measured using the Five Facets Mindfulness Questionnaire (FFMQ) [Baer et al., 2006], which comprises 39 items addressing five aspects of mindfulness in daily life: observing, describing, acting with awareness, non-judging, and non-reactivity.

The statistical analysis of the follow-up data will be based on time-to-event models, including survival analysis and proportionate hazards. The primary analysis will address determinants of changes in prevalence of infection or disease. The analysis of psychologic consequences will address the difference

of the score (final minus baseline, expressed as standardized effect size [SES]) at different follow-up times. SES is calculated as the mean difference between the intervention and the control groups, divided by the standard deviation of the control group, and allows comparison between groups, between measures in the same study and between different studies [Kazis et al., 1989].

Risultati attesi
See above.

DESCRIZIONE DELLE ATTIVITÀ DELL'ASSEGNISTA

*(per i **nuovi** assegni: max 400 parole; competenze richieste, scansione temporale della formazione, scansione temporale dell'attività, obiettivi primari e secondari)*

*(per i **rinnovi**: max 600 parole – da integrare con la relazione dell'assegnista; formazione raggiunta, attività effettuata, obiettivi raggiunti/competenze acquisite, formazione ancora da acquisire (se pertinente), scansione temporale dell'attività durante il rinnovo)*

Fellow will work in the management of data to be acquired from Italian and international centers and in the analysis of the pooled cohort. They will also collaborate with WP partners to prepare the resources for the follow-up. Specific tasks will include: - obtaining data on HCW included in the national cohorts from collaborating centers, including contacts with collaborators to check potential errors - harmonizing data across national cohorts of HCW - conducting descriptive and analytical statistical analyses on determinants of COVID-19 infection among HCW using standard epidemiology methods (e.g., multivariable logistic and Cox regression) under SAS, STATA or R - developing database for follow-up of HCW cohorts - obtaining follow-up data from collaborating centers, including contacts with collaborators to check potential errors - harmonizing data across national cohorts of HCW - conducting preliminary analyses of follow-up data

SE RINNOVO, SI RICORDA DI ALLEGARE ANCHE LA RELAZIONE DELL'ASSEGNISTA CON LA SUA PRODUZIONE SCIENTIFICA.

Scheda attività assistenziale (se prevista)

ATTIVITÀ ASSISTENZIALI DELL'ASSEGNISTA/ N. ORE SETTIMANA
Nessuna
AZIENDA SANITARIA PRESSO CUI SI SVOLGERÀ L'ATTIVITÀ
N/A

Si ricorda che, come previsto dagli Accordi sull'impiego nell'attività assistenziale dei Titolari di assegni di ricerca, sottoscritti tra l'Università di Bologna e le Aziende Ospedaliere di riferimento, una volta stipulato il contratto con il vincitore della selezione, il tutor deve consegnare alla Direzione Medica Ospedaliera la relativa modulistica, nella quale andranno riportate le attività qui segnalate.