ISARIC (International Severe Acute Respiratory and Emerging Infections Consortium)

A global federation of clinical research networks, providing a proficient, coordinated, and agile research response to outbreak-prone infectious disease

Analysis Plan for ISARIC International COVID-19 Patients

Please complete the following sections:

Title of proposed research
COVID-19 Among Healthcare Workers in a Worldwide Multi-center Study: Geographical Distribution, Characteristics and Outcomes

Version: (Date: Day/Month/Year)
13th of April 2021

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Final draft SAPs will be circulated to all ISARIC partners for their input with an invitation to participate. ISARIC can help to set up collaborator meetings; form a working group; support communications; and accessing data. Please note that the details of all approved applications will be made publicly available on the ISARIC website. Please complete all sections of this form fully and return to **ncov@isaric.org**

Introduction

COVID-19 outbreak creates a major risk for health care workers (HCWs) defined as people serving in health care facilities and exposed directly or indirectly to patients or infected materials in addition to community exposure.[1]

A report of the Centers for Disease Control and Prevention (CDC) published in April 2020 showed that 9,282 known coronavirus disease 2019 (COVID-19) cases were labeled as HCWs in the U.S, with numbers probably underestimated [2]. A meta-analysis that included 230,398 HCWs pooled from 97 studies published in the first semester of 2020 showed that the estimated prevalence of COVID-19 among HCWs was 11% with 5% developing severe clinical complications out of which 0.5% died.[1] The particularity of HCWs infection is the higher viral load which could be associated with worse clinical outcomes than non HCWs [3] but could be outweighed by overall better health status and access to medical care.[1]

No robust large scale data exists concerning the initial risk factors, characteristics, outcomes and the respective geographical variation of HCWs COVID-19 exposure compared to those of the general population. Such findings may aid in implementing national public health policies given the facts that mortality rates among HCWs could paralyze the response to COVID-19 with a possible long-term impact on healthcare services. [4]

Given the diversity and the multiplicity of countries, centers and health care organizations contributing to the ISARIC (International Severe Acute Respiratory and emerging Infections Consortium) database, we propose in this document an analysis plan to investigate and report prevalence, characteristics and outcomes of COVID-19 infection among HCWs. As of the 8th of April 2021, 340,312 individuals from 1609 sites across 54 countries. [5]

Participatory Approach

All contributors to the ISARIC database are invited to participate in this analysis through review and input on the statistical analysis plan and resulting publication. The outputs of this work will be disseminated as widely as possible to inform patient care and public health policy, this will include submission for publication in an international, peer-reviewed journal. ISARIC aims to include the names of all those who contribute data in the cited authorship of this publication, subject to the submission of contact details and confirmation of acceptance of the final manuscript within the required timelines, per ICMJE policies and the ISARIC publication policy.

Research Plan

Summary of Research Objectives
Report and describe the prevalence, characteristics and outcomes of COVID-19 among HCWs.

Proposed Target Population
We will include in this analysis patients from the ISARIC database whom data collection started before the 8th of April 2021 and with laboratory confirmed COVID-19 infection. Inclusion criteria: - Patient identification number - Laboratory confirmed COVID-19 infection - Known HCW status - Known admission date - Known clinical center/country

Clinical Questions/Descriptive Analyses

1. What is the prevalence of HCW among COVID-19 patients?
   a. What is the geographical distribution of this prevalence among countries participating in the ISARIC database?
2. What are the baseline characteristics of HCW in the study cohort? (Demographic, socioeconomic and clinical variables)?
   a. How do they differ from non-HCWs?
3. What is the distribution of outcomes of COVID-19 HCW patients in the study cohort according to the World Health Organization (WHO)[6]**?**
4. What is the case-fatality ratio (CFR) among HCWs?
   a. What is the geographical distribution of the HCWs specific CFR?
   b. Are they different from non HCWs?
5. What is the hospital length of stay (LOS) among HCWs?
   a. What is the geographical distribution of the HCWs specific LOS?
   b. Are they different from non HCWs?
6. Is the survival distribution of HCWs equal to non HCWs?
   a. What are the risk and prognostic factors of survival specifically for HCWs?

Planned Statistical Analyses, Methodology and Representation

Clinical question	Planned statistical analysis	Planned representation in manuscript
1. What is the incidence of HCW among COVID-19 patients? What is the geographical distribution of this prevalence among countries participating in the ISARIC database?	Percentage of HCW divided by all COVID-19 patients	Map representation of the prevalence of infected HCWs among all COVID-19 laboratory-confirmed patients

2. What are the baseline characteristics of HCW in the study cohort? (demographic, socioeconomic and clinical variables)	Comparison between HCW and non-HCW depending on nature of the variable: Chi-2 or exact Fisher for categorical, and student t-test for continuous variables.	Summary tables
3. What is the distribution of outcomes of COVID-19 HCW patients in the study cohort according to the WHO ordinal scale? (ambulatory, hospitalized with mild disease, hospitalized with severe disease, dead)	Comparison of the WHO ordinal scale outcomes among HCWs and non HCWs With a Mann-Whitney U test.	Bar diagrams and/or pie-charts
4. What is the case-fatality ratio (CFR) among HCWs? What is the geographical distribution of the HCWs specific CFR? Are they different from non HCWs?	Case-fatality ratio is calculated using the modified Kaplan-Meier method as proposed by Ghani et al. [7] and comparison between HCW and non-HCW.	Table representation along the WHO income group and Hospital bed number per 100,000 people. [8]
5. What is the hospital length of stay (LOS) among HCWs? What is the geographical distribution of the HCWs specific LOS? Are they different from non HCWs?	Length of stay is calculated as the difference between the date of discharge or the date of death and the admission date.	Results will be integrated in the table described in question 4.
6. Is the survival distribution of HCWs equal to non HCWs? What are the risk and prognostic factors of survival specifically for HCWs? (see below)	Survival analysis (see note below)	Kaplan-Meier curves comparing HCWs and non HCWs survival functions using the Log-Rank test

NOTES:
- In question 5, the WHO ordinal scale [6] is used in order to compare outcomes of COVID19 infection adapted to the corresponding data the categories are as follows:

CATEGORY	SCORE
o Ambulatory	1
o Hospitalized, mild disease	

▪ No oxygen therapy	2
▪ Oxygen by mask or nasal prongs	3
o Hospitalized, severe disease	
▪ Non-invasive ventilation or high-flow oxygen	4
▪ Intubation and mechanical ventilation	5
▪ Ventilation + additional organ support (pressors, RRT, ECMO)	6
o Death	7

- About the survival analysis in question 6:

characteristics	Description
Outcome variable	Time to death as reported in the CRF
Construction	Time between the date of onset of symptoms and death with censoring till the 13th of April 2021 for patients who were alive. Patients that are still hospitalized for less than 14 days as of the 13th of April 2021 will be excluded from the analysis.
Survival function	Hazard ratios will be exposed and survival curves of HCWs and non HCWs will be represented by Kaplan-Meier curves
Model construction and Variables	A Cox proportional hazard model will be used to assess the effect of the covariates on survival. Will be included demographic (ethnicity, age, recent travel, sex), socioeconomic (WHO income category) and clinical variables (symptoms at presentation, physical signs at presentation, biological parameters) in the model. Centers and countries will be included as random effects. The adequate model will be chosen in a stepwise pattern.

Handling of Missing Data

Preliminary analysis would be performed to ascertain a detailed overview of the extent of missingness in the data. This should enable the identification of variables which lack sufficient data to allow for any useful analysis to be performed on them. Type of missingness shall be considered including whether data are not missing at random and follow-up with sites will be conducted if appropriate. Variables with greater than 30% missingness will be excluded from analysis. Where appropriate, imputation will be performed using Multiple Imputation by Chained Equations (MICE).

Other Information

Research findings will be analyzed and a manuscript will be composed quickly, within a time frame of 4 -6 weeks, and submitted to a peer-reviewed journal.

Working Group Members

In the event of a need for consultation on this statistical analysis plan, please list your name and email address below if you would like to be added to a working group.

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References

[1]   S. A. Gómez-Ochoa *et al.*, "COVID-19 in Health-Care Workers: A Living Systematic Review and Meta-Analysis of Prevalence, Risk Factors, Clinical Characteristics, and Outcomes," *American Journal of Epidemiology*, vol. 190, no. 1. Oxford University Press, pp. 161–175, Jan. 01, 2021, doi: 10.1093/aje/kwaa191.

[2]   S. L. Burrer *et al.*, "Characteristics of Health Care Personnel with COVID-19 — United States, February 12–April 9, 2020," *MMWR. Morb. Mortal. Wkly. Rep.*, vol. 69, no. 15, Apr. 2020, doi: 10.15585/mmwr.mm6915e6.

[3]   Y. Liu *et al.*, "Viral dynamics in mild and severe cases of COVID-19," *The Lancet Infectious Diseases*, vol. 20, no. 6. Lancet Publishing Group, pp. 656–657, Jun. 01, 2020, doi: 10.1016/S1473-3099(20)30232-2.

[4]   S. Bandyopadhyay *et al.*, "Infection and mortality of healthcare workers worldwide from COVID-19: a systematic review," *BMJ Glob. Heal.*, vol. 5, p. 3097, 2020, doi: 10.1136/bmjgh-2020-003097.

[5]   M. Escher *et al.*, "ISARIC Clinical Data Report 10 February 2021 International Severe Acute Respiratory and emerging Infections Consortium," 2021, doi: 10.1101/2020.07.17.20155218.

[6]   "WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis," 2020.

[7]   A. C. Ghani *et al.*, "Methods for Estimating the Case Fatality Ratio for a Novel, Emerging

Infectious Disease," *Am. J. Epidemiol.*, vol. 162, no. 5, pp. 479–486, Sep. 2005, doi: 10.1093/aje/kwi230.

[8]   "Community health workers (per 1,000 people) | Data." https://data.worldbank.org/indicator/SH.MED.CMHW.P3?most_recent_year_desc=false&vie w=map (accessed Apr. 22, 2021).