PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a prospective, observational, hospital-based multicentre study of nosocomial SARS-CoV2 transmission: The NOSO-COR Project
AUTHORS	Saadatian-Elahi, Mitra; Picot, Valentina; Hénaff, Laetitia; Pradel, Florence; Escuret, Vanessa; Dananché, Cédric; Elias, Christelle; Endtz, Hubert; Vanhems, Philippe

VERSION 1 – REVIEW

REVIEWER	Dr John Ong The University of Cambridge, United Kingdom
REVIEW RETURNED	22-Apr-2020

GENERAL COMMENTS	The authors described a protocol to study the nosocomial transmission of SARS-CoV-2 in hospitals in France and those associated with the GABRIEL network. In general, more studies are urgently needed on the nosocomial transmission of SARS-COV-2 and the measures that can be taken to effectively reduce infection rates in healthcare workers. That said, this study protocol has several flaws (including two fatal ones), which needs to be addressed before it can be deemed suitable for publication. Abstract: - The death rates recorded by the European Centre for Disease Control (ECDC) show mortality rates are much higher than 2-4%. For example, in France alone it is about 10%. - Case report forms: have they been designed according to STROBE or CARE recommendations? - Line 37, RT-PCR has to be spelled in full in its first appearance in the text. - Line 40, what about patients who have pre-symptomatic or asymptomatic infection? - I'm not sure why ethics, dissemination and trial registration details are in the abstract. - What does this study hope to conclude from its results? Strength and limitations of the study - what is standardized CRF? It has not been previously abbreviated. - how will the results "refine the definition" of nosocomial SARS-CoV-2 infection? - The possibility of missing asymptomatic or pre-symptomatic infection should be mentioned if the authors are not screening everyone. Introduction

	- Page 4 Line 32, SARS-CoV2 spreads by respiratory droplets or fomites. - Page 4 Line 37, COVID-19 is the disease caused by SARS-COV-2 infection. - Page 4 Line 39 to 42 is inaccurate. COVID-19 can manifest in many ways and not just lower respiratory tract symptoms.E.g. gastrointestinal and eye disease as an example. As mentioned above, the mortality rates cited are inaccurate. - Page 5 Line 18, I believe the authors mean precautions against respiratory and direct-contact spread. - Page 5 Line 20, single room and negative pressure ventilation are recommended by a few bodies (e.g. US CDC). - Page 5 Line 23, the use of surgical masks for high-risk patients is debatable. If you look at South Korea or Singapore, they use FFP2/3 or PPAR. - Also, it is not just hydroalcoholic solutions. Some protocols recommend 70% ethanol solutions but others recommended chlorine-containing disinfectants e.g. China and UK. - Page 5 Line 38, the Italian National Institute of Health (ISS) just reported over 17,000 healthcare workers in Italy had been infected with COVID-19. - Page 6 Line 10, what are attack rates? The authors have not defined what they mean exactly and not stipulated an exposure period when using this term. - Page 6 Line 27 to 36 is problematic. The authors mix singular and plural terms together. Furthermore, the authors do not state if preventative measures within hospitals are the same throughout all hospitals involved in this study. Readers are left to assume they are not, correctly or incorrectly. - Page 6 Line 42, determinants of what exactly? Objectives - The primary aim of the text does not match the primary aim previously stated in the abstract. Previously, the authors stated the primary aim is to study nosocomial transmission of SARS-COV-2 but now it is "to estimate the prevalence and incidence of suspected or confirmed SARS-COV-2 infection among HCP, patients and caregivers (CG)." with no mention of the source of infection e.g. nosocomial or community-acquired. - Again, the use of "attack rates" which has not been well defined. Methods - Page 7, Line 43 Which university-affiliated hospitals specifically? - Case report forms should be included as supplemental data. - Inclusion and exclusion criteria should be mentioned earlier before the flow chart. - Reference 21 for WHO definition of COVID-19 is wrong. - Page 8, Line 8. Nosocomial infection usually implies that the infection has taken place within the hospital. How can nosocomial cases be defined as infected patients hospitalized for more than 48 hours? These patients may have acquired the infection in the community and presented later to the hospital with severe disease. The 99th percentile for symptom development in COVID-19 is 14 days. To prove nosocomial infection, one must show to a convincing degree that the infection was not present before admission, and patients acquired it in hospital. - Page 8, Line 28. WHO defines COVID-19 infection as a positive lab test regardless of symptoms. Are the authors including "probable" and "suspected" cases? It is not clear.

	- Page 8, Line 33. Exclusion criteria are not clear since the inclusion criteria are poorly defined. - Page 8, Line 47 to 57. This is a weak definition. If the index case does not have a positive RT-PCR result for SARS-COV-2, then infection of the "secondary" case could be due to other causes e.g. H1N1, norovirus etc. Strong evidence is needed for the authors label their "index" and "secondary case". - The authors also do not mention how they intend to prove that infected healthcare workers, CGs etc acquired infection in hospitals and not in the community. Data collection - How were case report forms designed and to what standards? - Have they been tested for reliability and validity? - Has it only be designed in French and distributed to french speaking countries? - How is data collected? quantitatively or qualitatively? both? - How is data on infection control policies and protocols captured on a case report form? Is data such as type of PPE used recorded etc? There is a lot the authors have not answered. - Page 9 Line 58-60, I do not know what this statement means. Biological sample collection and testing should be made available to all in the study. Data should not be collected from cases where the authors cannot prove SARS-COV-2 infection has occurred. Statistical analyses - This will be limited by the clinical definition of nosocomial infection. - The secondary objectives will be difficult to achieve because of the current limitations of the study design. - Regression methods are only meaningful if the sample size is large enough. Dissemination - Why are CONSORT guidelines being referred to since this is not a clinical trial? This is an observational study. Discussion - The authors have not discussed the limitations of their study to a reasonble degree. - Asymptomatic infection is a major problem to health services worldwide, the authors have not provided any strong justifications as to why they chose to omit this group. This group is particularly important in the nosocomial transmission of SARS-COV-2..

REVIEWER	Melvin LK Chua National Cancer Centre Singapore, Singapore
REVIEW RETURNED	02-May-2020

GENERAL COMMENTS	Here, the authors from the GABRIEL network report their protocol of a cross-sectional study to capture the incidence of COVID-19 among hospitalised patients and healthcare workers. This will help to ascertain the risk of nosocomial spread of SARS-CoV-2 virus in the hospital setting. Overall the study plan is clear. I have the following comments and suggestions on the methods and study design. Major 1. In order to ascertain the crude risk, it is also important to be accurate in recording the number of cases exposed. The method

	to accurately record them, across the different hospitals is not outlined in the study protocol. 2. Next, there are also several confounders that are not addressed in the study protocol. I list them below: a) How do the authors attempt to address false -ve SAR-CoV-2 RT-PCR test results among the tested patients? Will they be subjecting all suspect cases to multiple testing when hospitalised? b) Additionally, have they established if all the different hospitals will have comparable testing capacity? Or is there a centralised testing facility among the different hospitals? This may introduce discrepancies in prevalence between hospitals. c) Here the authors are also proposing to study mortality from COVID-19, which can be variable across the different patient subpopulations e.g. cancer vs non-cancer patients, COPD patients and other susceptible subgroups etc. The intent to study this should be outlined from the outset, rather than an afterthought. Already there are good evidence to suggest a higher incidence of severe COVID-19 and deaths among cancer patients. d) On this note, the availability of COVID-19 e.g ventilators, steroid, anti-viral therapies is likely to be a confounder for outcomes relating to COVID-19. The authors ought to evaluate if the different hospitals have similar access to these treatments or at least attempt to stratify for this covariate in their statistical analyses. 3. Since this is a cross-section study, the authors would be cognisant that their study has to adhere to the STROBE guidelines at the time of reporting. Therefore, it would be highly beneficial to the readers if the authors could present their statistical analysis plan (SAP), either in point form or as a flow chart in the main paper. Explicitly, the methods to estimate risk of exposure (which is hospitalisation in this study); evaluating the risks in the different subpopulations etc. 4. In fact, there have been some reports on risk of COVID-19 among at-risk patient populations e.g. cancer and hospitalised patients (Liang et al. Lancet Oncology; Wang et al. JAMA; Yu et al. JAMA Oncology). Therefore, the authors could in fact include some theoretical assumptions on the probable risk in their cohort and perform some preliminary sample size estimates.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Abstract

1- The death rates recorded by the European Centre for Disease Control (ECDC) show mortality rates are much higher than 2-4%. For example, in France alone it is about 10%.

Authors: We modified and added the reference corresponding to mortality rate in France in the revised version.

2- Case report forms: have they been designed according to STROBE or CARE recommendations?

Authors: The case-report form for the study was adapted from the interim case reporting form for 2019 Novel Coronavirus (2019-nCoV) of WHO: https://www.who.int/docs/default-

source/coronaviruse/20200121-2019-ncov-reporting-form.pdf?sfvrsn=96eff954_4). We added more sections to collect biological data and some information that could allow to investigate the nosocomial transmission. The CRF is now provided in supplementary material.

3- Line 37, RT-PCR has to be spelled in full in its first appearance in the text.

Authors: We spelled it out as requested.

4- Line 40, what about patients who have pre-symptomatic or asymptomatic infection?

Authors: We did not include pre-symptomatic and asymptomatic patients. This represents a limit of our study but due to the intensity of the epidemic, systematic RT-PCR were not carried out and without systematic RT-PCR testing it was not possible to include these patients.

5- I'm not sure why ethics, dissemination and trial registration details are in the abstract.

Authors: Trial registration and ethics, dissemination are required by the journal instructions to authors.

6- What does this study hope to conclude from its results?

Authors: A conclusion was added to the abstract to answer the reviewer's question.

Strength and limitations of the study

7- what is standardized CRF? It has not been previously abbreviated.

Authors: By standardised, we meant that the case-report form was identical for all centres in both low income countries and France. To avoid confusion, we removed the word "standardized". The CRF was spelled out. As explained above, the CRF was adapted from the WHO validated CRF for COVID-19.

8- how will the results "refine the definition" of nosocomial SARS-CoV-2 infection?

Authors: The word refine" was wrongly used by the authors. The authors reworded the sentence given that no definition of nosocomial infection is currently existing. The objective is to try to define the nosocomial transmission by taking into account the incubation period of the virus. We modified the text and provided more information in the revised manuscript.

9- The possibility of missing asymptomatic or pre-symptomatic infection should be mentioned if the authors are not screening everyone.

Authors: We acknowledge this point even though our inclusion criteria were based on a symptomatic approach. We added a bullet point in the strengths and limitations section accordingly to address this limitation. Similar to flu and without systematic RT-PCR it was not possible to include these patients.

Introduction

10- Page 4 Line 32, SARS-CoV2 spreads by respiratory droplets or fomites.

Authors: We added the word fomites as suggested by the reviewer.

11- Page 4 Line 37, COVID-19 is the disease caused by SARS-COV-2 infection.

Authors: We modified the sentence according to the reviewer suggestion.

12- Page 4 Line 39 to 42 is inaccurate. COVID-19 can manifest in many ways and not just lower respiratory tract symptoms. E.g. gastrointestinal and eye disease as an example. As mentioned above, the mortality rates cited are inaccurate.

Authors: We modified the sentence and added 2 more references that provide evidence on other manifestation of the disease.

13- Page 5 Line 18, I believe the authors mean precautions against respiratory and direct-contact spread.

Authors: We confirm that we meant precautions against respiratory and direct-contact spread. We modified the text to avoid confusion.

14- Page 5 Line 20, single room and negative pressure ventilation are recommended by a few bodies (e.g. US CDC).

Authors: We added these specific recommendations in the revised manuscript.

15- Page 5 Line 23, the use of surgical masks for high-risk patients is debatable. If you look at South Korea or Singapore, they use FFP2/3 or PPAR.

Authors: We added FFP2/3 or N95 mask in the revised manuscript.

16- Also, it is not just hydroalcoholic solutions. Some protocols recommend 70% ethanol solutions but others recommended chlorine-containing disinfectants e.g. China and UK.

Authors: We added 70% ethanol solutions and chlorine-containing disinfectants in the revised manuscript.

17- Page 5 Line 38, the Italian National Institute of Health (ISS) just reported over 17,000 healthcare workers in Italy had been infected with COVID-19.

Authors: The references cited in the text are those that were available at the time of the submission of our paper (06/04/2020). To update the manuscript, we added a reference on the number of HCP infected in France.

18- Page 6 Line 10, what are attack rates? The authors have not defined what they mean exactly and not stipulated an exposure period when using this term.

Authors: We defined the attack rate as the proportion of infected patients among the total number of patients at risk of being infected during the study period. Please see the details provided in the revised version of the manuscript. We performed similar approaches for nosocomial influenza (Vanhems P, Voirin N, Bénet T, et al. Detection of hospital outbreaks of influenza-like illness based on excess of incidence rates compared to the community. *Am J Infect Control*. 2014;42(12):1325-1327. doi:10.1016/j.ajic.2014.08.011).

19- Page 6 Line 27 to 36 is problematic. The authors mix singular and plural terms together. Furthermore, the authors do not state if preventative measures within hospitals are the same throughout all hospitals involved in this study. Readers are left to assume they are not, correctly or incorrectly.

Authors: We agree with the reviewer. We removed these lines and we added some information about differences in the preventive measures in the participating hospitals. In addition, we will ask all participating centres to provide us a copy of their guidelines regarding COVID-19 preventive measures and the adjustments of the guideline over the epidemic period.

20- Page 6 Line 42, determinants of what exactly?

Authors: By determinant, we mean risk factors or protective factors of the prognosis. We clarified this point in the revised manuscript.

Objectives

21- The primary aim of the text does not match the primary aim previously stated in the abstract. Previously, the authors stated the primary aim is to study nosocomial transmission of SARS-COV-2 but now it is "to estimate the prevalence and incidence of suspected or confirmed SARS-COV-2 infection among HCP, patients and caregivers (CG)." with no mention of the source of infection e.g. nosocomial or community-acquired.

Authors: We harmonized the way the objectives are expressed in both abstract and the main text. We added the source of infection i.e. nosocomial. Please see the revised manuscript and the abstract.

22- Again, the use of "attack rates" which has not been well defined.

Authors: Please see the explanation provided to the comment 18.

Methods

23- Page 7, Line 43 Which university-affiliated hospitals specifically?

Authors: We added the city of all French participating centres in the revised manuscript.

24- Case report forms should be included as supplemental data.

Authors: We added the CRF in the supplementary data.

25- Inclusion and exclusion criteria should be mentioned earlier before the flow chart.

Authors: We moved inclusion and exclusion criteria before the flow chart.

26- Reference 21 for WHO definition of COVID-19 is wrong.

Authors: Indeed, the correct reference was reference 20 (now 24). We corrected the mistake.

27- Page 8, Line 8. Nosocomial infection usually implies that the infection has taken place within the hospital. How can nosocomial cases be defined as infected patients hospitalized for more than 48 hours? These patients may have acquired the infection in the community and presented later to the hospital with severe disease. The 99th percentile for symptom development in COVID-19 is 14 days. To prove nosocomial infection, one must show to a convincing degree that the infection was not present before admission, and patients acquired it in hospital.

Authors: We fully agree with the reviewer. The present protocol was written at the very early phase of the pandemic and we used the definition of 48 hours usually used for the definition of nosocomial infections of other respiratory viruses such as influenza. We modified the text accordingly.

28- Page 8, Line 28. WHO defines COVID-19 infection as a positive lab test regardless of symptoms. Are the authors including "probable" and "suspected" cases? It is not clear.

Authors: We included suspected and confirmed cases. Detailed on inclusion criteria are in the revised manuscript.

29- Page 8, Line 33. Exclusion criteria are not clear since the inclusion criteria are poorly defined.

Authors: We provided details on inclusion criteria in the revised manuscript.

30- Page 8, Line 47 to 57. This is a weak definition. If the index case does not have a positive RT-PCR result for SARS-COV-2, then infection of the "secondary" case could be due to other causes e.g.

H1N1, norovirus etc. Strong evidence is needed for the authors label their "index" and "secondary case".

Authors: We agree with the reviewers. The index case is defined as a patient with a positive RT-PCR result. Please see the revised manuscript.

31- The authors also do not mention how they intend to prove that infected healthcare workers, CGs etc acquired infection in hospitals and not in the community.

Authors: The CRF administered to HCP or patients collect information on the time and location of exposure to identify if the contact has occurred at hospital or elsewhere. The CRF has been added in the Supplementary data to address this point.

Data collection

32- How were case report forms designed and to what standards?

Authors: We adapted our CRF from the interim case reporting form for 2019 Novel Coronavirus (2019-nCoV) of WHO (World Health Organization)

https://www.who.int/docs/default-source/coronaviruse/20200121-2019-ncov-reporting-form.pdf?sfvrsn=96eff954_4.

33- Have they been tested for reliability and validity?

Authors: Yes, the CRF was tested at the Lyon university of hospitals among 10 patients before the start of the recruitment. We adjusted the manuscript accordingly.

34- Has it only be designed in French and distributed to french speaking countries?

Authors: We have two versions of the CRF in French and English as some participating countries such as Brazil and Bangladesh are not French speaking.

35- How is data collected? quantitatively or qualitatively? both?

Authors: Data were collected quantitatively. We adapted the statistical methods section accordingly.

36- How is data on infection control policies and protocols captured on a case report form? Is data such as type of PPE used recorded etc? There is a lot the authors have not answered.

Authors: We designed a CRF to capture information on hospital characteristics including infection control protocols and guidance in place. Data on the observance of infection prevention and control measures were gathered during the patient hospital stay. This CRF is now available in supplementary data. In addition, each centre is requested to provide a copy of their guidelines regarding Covod-19 preventive measures and the adjustments of the guideline over the epidemic period.

37- Page 9 Line 58-60, I do not know what this statement means. Biological sample collection and testing should be made available to all in the study. Data should not be collected from cases where the authors cannot prove SARS-COV-2 infection has occurred.

Authors: At the time of the preparation of the protocol, some of low-income participating countries did not have the diagnostic test, so the decision was to include only suspect cases. However, as soon as the identification of first cases, the RT-PCR diagnostic test became available in all participating countries. We remove this sentence from the manuscript as it is not anymore valid.

Statistical analyses

38- This will be limited by the clinical definition of nosocomial infection.

Authors: Nosocomial SARS-CoV2 infection has been defined previously. Please see answer to comment 27.

39- The secondary objectives will be difficult to achieve because of the current limitations of the study design.

Authors: We agree with this point and have better developed the limitations of the study according to this point.

40- Regression methods are only meaningful if the sample size is large enough.

Authors: We fully agree however at the time the protocol was submitted, we were not able to predict the magnitude of the epidemic and how many people will be infected.

Dissemination

41- Why are CONSORT guidelines being referred to since this is not a clinical trial? This is an observational study.

Authors: We thanks the reviewer for this point. We removed this sentence from the manuscript.

Discussion

42- The authors have not discussed the limitations of their study to a reasonable degree.

Authors: Limitations of our study are discussed in more detailed in the revised manuscript.

43- Asymptomatic infection is a major problem to health services worldwide, the authors have not provided any strong justifications as to why they chose to omit this group. This group is particularly important in the nosocomial transmission of SARS-COV-2.

Authors: We recognize this limitation but the identification of asymptomatic individuals needs RT-PCR screening of all patients/HCP. Given the high pressure and workload in hospital words caused by the pandemic, screening of all staff/patients was not the priority of the hospitals. Our study being an observational study, we did not have any influence on the identification/ management of asymptomatic patients.

Reviewer: 2

Please leave your comments for the authors below Here, the authors from the GABRIEL network report their protocol of a cross-sectional study to capture the incidence of COVID-19 among hospitalised patients and healthcare workers. This will help to ascertain the risk of nosocomial spread of SARS-CoV-2 virus in the hospital setting. Overall the study plan is clear. I have the following comments and suggestions on the methods and study design.

Major

1. In order to ascertain the crude risk, it is also important to be accurate in recording the number of cases exposed. The method to accurately record them, across the different hospitals is not outlined in the study protocol.

Authors: In the CRF patient, now available in the supplementary material, we collect the number of contacts, the number of beds in the unit where the patient is hospitalized

2. Next, there are also several confounders that are not addressed in the study protocol. I list them below:

a) How do the authors attempt to address false -ve SAR-CoV-2 RT-PCR test results among the tested patients? Will they be subjecting all suspect cases to multiple testing when hospitalised?

Authors: This is an observational study, so we cannot request multiple testing. The majority of patients have also a thoracic scan that can be used to address false negativeSARS-COV-2 RT-PCR test results.

b) Additionally, have they established if all the different hospitals will have comparable testing capacity? Or is there a centralised testing facility among the different hospitals? This may introduce discrepancies in prevalence between hospitals.

Authors: There is not a centralized testing facility among participating hospitals. The testing capacity is not different in French participating centres but could probably differ in centres out of France. This point has been addressed as an additional limitation of the study.

c) Here the authors are also proposing to study mortality from COVID-19, which can be variable across the different patient subpopulations e.g. cancer vs non-cancer patients, COPD patients and other susceptible subgroups etc. The intent to study this should be outlined from the outset, rather than an afterthought. Already there are good evidence to suggest a higher incidence of severe COVID-19 and deaths among cancer patients.

Authors: We specified the mentioned groups in the revised version of the manuscript.

d) On this note, the availability of COVID-19 e.g ventilators, steroid, anti-viral therapies is likely to be a confounder for outcomes relating to COVID-19. The authors ought to evaluate if the different hospitals have similar access to these treatments or at least attempt to stratify for this covariate in their statistical analyses.

Authors: Data on treatment or medical devices were not collected. We aimed to gather data only at admission (for community-acquired cases) and at suspicion (for hospital-acquired cases).

3. Since this is a cross-section study, the authors would be cognisant that their study has to adhere to the STROBE guidelines at the time of reporting. Therefore, it would be highly beneficial to the readers if the authors could present their statistical analysis plan (SAP), either in point form or as a flow chart in the main paper. Explicitly, the methods to estimate risk of exposure (which is hospitalisation in this study); evaluating the risks in the different subpopulations etc.

Authors: A better description of the statistical analysis has been integrated in the methods section.

Concerning the statistical analysis plan:

- description of the baseline characteristics of the patients and HCP included

- identification of determinants of admission at the hospital among COVID-19 patients

- comparison between community-acquired and hospital-acquired COVID-19 patients and identification of determinants of nosocomial transmission

- identification of the determinants associated with the delay between the onset of symptoms and admission at the hospital

- identification of subpopulations that are at risk stratified by age, type of ward, comorbidities (cardiovascular, cancer, diabetes).

4. In fact, there have been some reports on risk of COVID-19 among at-risk patient populations e.g. cancer and hospitalised patients (Liang et al. Lancet Oncology; Wang et al. JAMA; Yu et al. JAMA Oncology). Therefore, the authors could in fact include some theoretical assumptions on the probable risk in their cohort and perform some preliminary sample size estimates.

Authors: As mentioned earlier, the protocol was drafted at the very initial phase of the epidemic. Therefore, we did not have the necessary information to include theoretical assumptions. We plan to calculate the crude mortality rate and adjusted rates according to clinical features stratified by age, comorbidities, type of ward, and community versus hospital-acquired infection.

VERSION 2 – REVIEW

REVIEWER	Melvin L.K. Chua Divisions of Radiation Oncology and Medical Sciences, National Cancer Centre Singapore, Singapore
REVIEW RETURNED	05-Sep-2020

GENERAL COMMENTS	The authors have adequately addressed my concerns.