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The NOSO-COR Project

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Protocol for a multicentre study of nosocomial SARS-CoV2 transmission

The NOSO-COR Project

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Abstract

Introduction: The newly identified SARS-CoV2 can cause serious acute respiratory infections such as pneumonia with a mortality rate of approximately 2% to 4%. In the current context of high incidence rates of SARS-CoV2 in the community, a significant increase in the rate of nosocomial transmission is expected. The risk of nosocomial transmission could even be higher in low-income countries that have fragile healthcare systems. This protocol is intended to study and document suspected or confirmed cases of nosocomial SARS-CoV2 infection, the clinical spectrum and the determinants (risk factors/protective) at participating hospitals.

Methods and analysis: This will be an international multicentre prospective, observational, hospital-based study in adults and children. It will include volunteer patients, care givers and healthcare professionals in France and hospitals affiliated with the GABRIEL network. Demographic and clinical data will be collected using case-report forms designed especially for the purpose of the project. A nasopharyngeal swab will be collected and tested for SARS-CoV2 by RT-PCR. Characteristics of the study participants, the proportion of confirmed nosocomial SARS-CoV2 infections relative to all patients with syndromes suggestive of 2019-nCoV infection will be analysed. Appropriate multivariate modelling will be used to identify the determinants associated with nosocomial onset.

Ethics and dissemination: This study was approved by the clinical research and committee of Ile de France V on March 8, 2020.

Registration details: The trial was registered in ClinicalTrials (NCT04290780).

Key words: SARS-CoV2; nosocomial transmission, Multicentre prospective, France, Gabriel Network

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Strengths and limitations of the study

- This prospective study will generate and evaluate original data on nosocomial SARS-CoV2 infection in France and in the low-income countries of the GABRIEL network using the same protocol and standardised CRF.
- The results will provide the opportunity to compare the management of nosocomial Covid-19 infection in different settings for mutual exchanges and optimisation.
- The results will make it possible to refine the definition of nosocomial SARS-CoV2 infection, strengthen preventive campaigns for in-hospital transmission of SARS-CoV2 and pave the way for new recommendations in terms of preventive measures.
- Selection bias owing to access to care in different populations and bias owing to the extent of access to personal protective equipment, in particular, in low-income countries may occur.
- The non-exhaustivity of the confounders to be collected should be considered for interpretation of the results.

INTRODUCTION

Coronaviruses are enveloped viruses that mainly infect the upper digestive and respiratory tracts of mammals and birds. In humans, the viruses can cause mild respiratory infections but can also lead to serious infections such as pneumonia. During the past decade, two human coronaviruses SARS-CoV and MERS-CoV were the source of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics in 2002 and 2012 respectively.[1]

The newly identified SARS-CoV2 is a single-stranded RNA virus belonging to the coronavirus crown virus family of the subfamily Orthocoronaviridae. SARS-CoV2 appears to be a recombinant virus between the bat coronavirus and a coronavirus of unknown origin.[2] The virus was first detected in December 2019 in Hubei province of China[3-5] and spread widely throughout China before crossing the borders into other countries.[6] SARS-CoV2 is mainly transmitted by respiratory droplets but can also be spread through aerial droplets and contact.[7]

Covid-19 is the emerging infectious disease due to SARS-CoV2. The clinical features of Covid-19 are lower respiratory infection[8] with a mortality rate of approximately 2% to 4%,[9] but asymptomatic cases have also been reported.[10] The estimated median incubation period of COVID-19 was 5.1 days (CI, 4.5 to 5.8 days) in a pooled analysis of 181 confirmed cases reported from around the world.[11]

On March 11, 2020, the World Health Organization (WHO) declared Covid-19 a pandemic, pointing to the over 118,000 cases of coronavirus in over 110 countries and territories around the world with the sustained risk of further global spread.

Analysis of the clinical presentation of the first case series (n=41) showed that 31% of the patients were admitted to intensive care units (ICU) and the crude mortality rate was 15%.[12]

COVID-19 related complications including severe pneumonia, respiratory distress, secondary bacterial infection, or decompensation for chronic heart or respiratory disease, mainly affected patients over 65. The cases described to date mostly occurred among patients with a history of chronic pathology,[4, 12] who were therefore more likely to be hospitalised.

In the absence of a preventive vaccine or curative treatment, current efforts to prevent and control the spread of SARS-CoV2 are based on early detection of cases along with infection control measures such as droplet-type and contact-type precautions. In addition, specific measures are being applied to patients who should be cared for in single rooms if possible, wear surgical masks and practice strict hand hygiene using hydroalcoholic solutions. Specific recommendations have also been issued from the WHO and Centers for Disease Control.[13, 14]

As for the SARS and MERS-CoV epidemics and other respiratory viruses such as influenza or respiratory syncytial virus (RSV), cases of intra-hospital transmission of SARS-CoV2 have been reported and are going to continue to occur. In Wuhan alone, 1,080 healthcare professionals (HCP) were infected.[15] In China, more than 3,300 HCP were infected as of early March and in Italy, 20% of the HCP participating in a survey reported Covid-19 infections.[16]

HCP have a key position in the transmission process because they are exposed to both community-acquired and nosocomial cases.[17, 18] This risk is amplified when the incidence of the infection in the community is high. In the current context of high incidence rates of SARS-CoV2 in the community, a significant increase in the rate of nosocomial transmission is therefore expected. The risk of nosocomial transmission would be even higher in low-income countries owing to several factors such as the delay in diagnosis of Covid-19 patients, and the lack of infrastructure, trained personnel, isolation units, and infection control programs.

Beyond the morbidity and mortality associated with nosocomial Covid-19 infection, the impact on the organisation of care and the additional costs caused by longer hospital stays are still unknown, but will certainly be of consequence.

The link between hospital (nosocomial) and community attack rates is a good indicator of the effect of hospitalisation on the transmission of respiratory viruses.[19]

Better understanding of the transmission chains of SARS-CoV2 and the impact of control measures in healthcare units is essential to achieving control of the pandemic. For example, the configuration of care units also appears to play a role in transmission. Indeed, hospitalisation in a double room increased the risk of contracting influenza in a hospital by 2.67-fold.[20]

Description and implementation of appropriate hygiene and preventive measures play a decisive role in the control of nosocomial risk and are a major determinant of our ability to understand nosocomial dissemination of this emerging virus. These preventive measures should be included in appropriate hospital guidelines to control nosocomial risk.

The present manuscript describes the protocol of an international multicentre prospective study whose aims are to document suspected or confirmed nosocomial cases of Covid-19, their clinical spectrum and the determinants at participating hospitals.

Objectives

The principal aim of this study is to estimate the prevalence and incidence of suspected or confirmed cases of SARS-CoV2 infection among HCP, patients, and caregivers (CG).

A caregiver is defined as a family member or authorized guardian who regularly looks after the patient during his or her hospital stay and lives in the same household. The concept of including CG is of particular interest especially in low-income countries where parents/family members are the main source of support for their sick relatives.

The secondary objectives are to 1) to describe and document cases of community-acquired SARS-CoV2 infection (prevalent cases on hospital admission) likely to be the source of nosocomial infection and the clinical spectrum; 2) describe and document hospital-acquired SARS-CoV2 infection (incident cases) that may be the source of nosocomial transmission and their clinical spectrum; 3) describe infection control practices implemented during the occurrence of hospital cases of SARS-CoV2 and relate these practices to the attack rates of nosocomial SARS-CoV2 infection; 4) estimate the incidence of infectious syndromes attributed to SARS-CoV2 and the proportion of severe cases, including deaths; 5) describe subpopulations with SARS-CoV2 infection depending on the hospital ward (for example: internal medicine vs. surgery vs. intensive care units [ICU]); 6) compare the adjusted attack rates of nosocomial and community-acquired SARS-CoV2 infection to identify contextual and/or environmental protective and risk factors in both the hospital and community setting; 7) calculate the crude mortality rate and adjusted rates according to specific clinical features.

METHODS

Study design and setting

This prospective, observational, hospital-based study will be carried out among volunteers, patients, CG and HCP in university-affiliated hospitals (Lyon, France) and hospitals affiliated with the GABRIEL network (https://www.gabriel-network.org/), a network of research institutions mainly located in low-income countries and focused on the etiological agents of pneumonia. Other French or European university hospitals will be welcome and able to join the project on a voluntary basis.

Recruitment

The study flow chart is shown in Figure 1. Eligible patients will be identified by a clinical research assistant who will regularly contact hospital wards (emergency, geriatric, infectious

diseases, etc.) and will review the results of the virology laboratory. The clinical research assistant will meet eligible individuals to explain the purpose of the study and obtain written informed consent. Nosocomial cases will be defined as infected patients hospitalised for more than 48 hours.

Identification of infected HCP will be based on data from the department of occupational medicine. A confidential interview with the symptomatic HCP will be organized to describe the purpose of the study and obtain written informed consent.

Identification of infected CG will be based on self-reporting. During their visits to the hospital, CG will be informed about the study and will be asked to report to the study team in case of symptoms suggestive of Covid-19.

Inclusion criteria: Any adult/child patient, CG or HCP from participating hospitals who presents an infectious syndrome based on the WHO definition of Covid-19.[21]

Exclusion criteria: Individuals who do not meet the above criteria.

Participant timeline: Enrolled participants will be followed up during their entire hospital stay and for a period of 30 days after discharge. Information on further complications occurred during the follow-up period and vital status will be collected from the patient's medical file.

Index case: An index case is defined as the first confirmed case of SARS-CoV2 infection in a given department during a given period.

Secondary case: A secondary case is defined as a patient i) who is in contact with an index case during the contagious period, currently defined as 5 days before and 15 days after the start of symptoms in the index case; ii) who develops clinical features compatible with the diagnostic criteria of SARS-CoV2 infection within 15 days of the onset of symptoms in the index case; and iii) if possible, a positive RT-PCR for the index case.

The period of detection of secondary cases will be calculated according to the period of contagiousness of the index case: [date of onset of symptoms] to [date of onset of symptoms + 15 days] and the incubation period of secondary cases (1 to 15 days). Secondary cases will therefore be clinically detected in the time interval between [start date of symptoms in the index case + 1 day] to [start date of symptoms in the index case +15 days].

Figure 1: Study flow chart

Data collection

Clinical data

Data will be collected using case-report forms (CRF) designed especially for the purpose of this project for patients, CG, and HCP. According to the operating modes of each participating hospital and their organization in terms of clinical or epidemiological research, the CRF will be completed during a face-to-face interview and the use of medical records.

All three CRF will include demographic characteristics, underlying comorbidities, medical history, clinical, biological and laboratory data on the SARS-CoV2 infectious episode. In case of HCP or CG hospitalisation, a patient's CRF including additional data regarding information on hospitalisation (ward specialty, type of room, etc.) and biological parameters (blood cell counts, etc.) will be completed.

The characteristics of the hospital and participating services (specialties, number of beds, number of nurses and doctors, presence of an infection control unit, etc.) and infection control policies regarding the risk of infection by SARS-CoV2 will also be collected.

Biological Sample collection and testing

These diagnostics will be enabled only at sites that have the capacity for testing or at sites where the capacity can be reached.

A nasopharyngeal swab will be collected and tested for the presence of SARS-CoV2 ribonucleic acid (RNA) by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) for each patient, CG, or HCP that meets inclusion criteria. Samples will be tested by the closest virology laboratory where state-of-the-art SARS-CoV2 assay is performed. The results will be reported on laboratory forms created specifically for this study.

If feasible, RT-PCR will be performed to detect a panel of other respiratory viruses (influenza A and B, RSV, rhinovirus, metapneumovirus, etc.) depending on the diagnostic practices available at each participating centre. Furthermore, SARS-CoV2 sequencing will be performed depending on the technical platforms available.

Biobanks are expected to be constituted and if possible, an aliquot of each sample will be stored in a Micronic tube at -20°C for at least 5 years after written informed consent is obtained.

Statistical methods

Sample size

Given the descriptive nature and surveillance objectives of this observational study, reaching a predefined number of subjects is not realistic.

Statistical analyses

Data will be analysed using statistical methods to describe the characteristics of the healthcare setting and study participants, the percentage of Covid-19 of those presenting influenza-like illnesses, the percentage of nosocomial Covid-19 patients among the confirmed cases, etc.

The primary criteria will be the proportion of patients, CG and HCP with confirmed nosocomial SARS-CoV2 infection relative to all patients, CG and HCP with syndromes suggestive of 2019-nCoV infection during the study period.

Secondary outcome criteria will be to i) describe the delay of onset of suspected or confirmed nosocomial Covid-19 infection for hospitalised patients; ii) estimate the attack rate of confirmed Covid-19 cases in hospitalised patients according to their length of stay; and iii) estimate the attack rate of confirmed Covid-19 cases among CG and HCP.

Appropriate multivariate modelling methods will be applied depending on the numbers of patients and the hypothesis tested (Poisson regression, Cox regression, logistic regression) to identify the determinants independently associated with outcomes. For example, the length of stay will be considered as the duration of exposure.

Data management and archiving

Case Report Form

All required information will be recorded on a paper-based CRF in a clear and legible manner and justification must be provided for all missing data. Erroneous data noted in the CRF will be clearly crossed out and the correct data will be written next to the crossed-out information, accompanied by the initials of the investigator or authorized person who made the correction, the date and, if possible, and a justification for the correction.

To reduce data-entry errors by predefining plausibility checks and facilitate the rapid transfer of data, the electronic CRF (e-CRF) version of the study CRF will also be available.

Transfer of the data to the coordinating centre in Lyon (France) will be performed via the e-CRF following approval by the French "**Commission nationale de l'informatique et des libertés (CNIL) - National Commission for Data Protection"**. An alternative possibility will be to ensure periodic reporting (every 10 inclusions) by e-mailing the scan of the completed CRF to the coordinating centre.

Data management

Collected data will be computerised in the coordinating centre in Lyon, France. Source documents and databases will be anonymous and locked with a password known only to the scientific staff. These data will be kept for a minimum of 10 years after the end of the study.

Archiving

According to French law, the sponsor will keep the study documents (protocol and annexes, possible amendments, information forms, CRF, statistical analysis plan and output and the final study report) for a minimum of 25 years. After this period, the sponsor will be consulted before any data is destroyed.

Study-related documents and reports may be subject to audit or inspection by the sponsor and/or other authorized bodies.

This study is part of the "Reference Methodology" (MR-003) in application of article 54, paragraph 5 of French law N°78-17 of January 6, 1978. This change was approved on January 5, 2006 and modified on July 21, 2016. The Hospices Civils de Lyon, the promoter of the study, has signed a commitment to comply with this "Reference Methodology".

Rights to access source documents

Source documents are defined as any original documents, data, records in which data collected for a clinical trial is first recorded. Source documents will be kept by the investigator for 10 years or, if hospital medical records, by the hospital for 10 years. Each centre will have access to its own data during the study.

To ensure quality control and auditing, the sponsor will be responsible for obtaining the agreement of all parties involved in the research to guarantee direct access to all places where the research is carried out and to source data, documents and reports.

In accordance with current laws and regulations (articles L.1121-3 and R.5121-13 of the French public health code), all documents and personal data required for monitoring, quality control or auditing will be available to the persons in charge of these activities.

Confidentiality

The principal and associate investigators are required to respect professional confidentiality (articles 226-13 and 226-14 of the French Penal Code). In accordance with French laws regarding the confidentiality of study participant personal data (article L.1121-3 of the French Public Health Code) and clinical/laboratory results obtained throughout the study (article R. 5121-13 of the French Public Health Code), individuals with direct access to the data will take all necessary precautions to ensure the confidentiality of the overall collected information.

All personal data concerning study participants will remain strictly confidential. To respect privacy, all participant details will be anonymous for the purpose of database preparation. Study subjects will be coded as follows: AAXXXXZZYY. The first two letters will be either PA for a patient, CG for caregiver and HP for HCP. The following four digits will depend on the order of inclusion of the case and the next two letters will correspond to the hospital code. Finally, the last two letters will correspond to the country in which the hospital is located.

Quality control and assurance

Quality assurance audits will be carried out by persons appointed by the promoter as well as the inspections carried out by the Competent Authorities. All data, documents and reports can be subject to regulatory audits and inspections without hindering medical confidentiality.

Ethics and dissemination

Ethical approval

The protocol, information notice, and CRF will be submitted to the ethics committee of each participating hospital for approval.

Informed consent

Patients, CG and HCP will be informed of the objectives and their rights to refuse to participate in the study or withdraw at any time using simple, understandable terms. This information will be provided by an information and consent form given to each participant. According to French law, voluntary, oral informed consent will be obtained by the investigator before inclusion for the epidemiological data while signed consent is needed for the collection of biological banks. Consenting will be performed following the country's ethical guidelines. Informed consent will be obtained from the parents of included children (<18 years old).

Regulatory compliance

The research will be conducted in accordance with applicable laws and regulations currently in place in France and internationally.

Withdrawal criteria

Subjects may request to withdraw from the study at any time and for any reason without having to justify. In the event of a premature withdrawal, the investigator must document the participant's reasons for withdrawal as completely as possible.

Stopping the research study

The sponsors reserve the right to interrupt the study at any time if the objectives are not being met. In the event of premature termination of the study for security reasons, the information will be transmitted by the sponsors to all concerned parties and to the local ethical committee within 15 days.

Protocol amendments

In the eventuality of changes in the existing protocol that significantly affect the scope or the scientific quality of the investigation, an amendment containing a verbatim description of the changes and reference (date and number) to the submission that contained the original protocol will be submitted to the ethical committee for their approval.

Dissemination

Communications and scientific reports that emerge from this study will be carried out under the responsibility of the principal investigator in agreement with the associated investigators. Publication rules will follow international recommendations.[22] The findings will also be shared with national health authorities.

Reporting will follow the guidelines in the Consolidated Standards of Reporting Trials (CONSORT) Statement.[23] Authorship will follow the guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/) which require substantive contributions to the design, conduct, interpretation, and reporting of a trial.

Discussion

Human-to-human transmission of SARS-CoV2, including nosocomial transmission, is now well documented. The risk of amplification of spread of the disease in healthcare facilities is strong in case of a lack of infection control measures. Early recognition of nosocomial Covid-19 infection in patients or HCP is therefore essential for the setting up of immediate investigation and implementation of appropriate hygiene measures. Describing the signs and symptoms associated with nosocomial Covid-19 will enable comparisons with existing data on other nosocomial viral respiratory infections (i.e. influenza, respiratory syncytial virus, SARS-CoV, MERS-CoV).

The prospective design and face-to-face interviews will make it possible to reduce recall bias and to collect accurate data. The expertise of French university affiliated hospitals is already strongly involved in the surveillance of nosocomial infections and the extensive experience of GABRIEL network countries in various research studies related to respiratory infections also strengthen this research project. Participation in this project will enable the subjects to benefit from the diagnostic results. Moreover, each centre will benefit from the overall data in order to explore a particular scientific theme.

The results of the NOSO-COR project will provide original results that could: 1) constitute additional evidence for a better understanding of the duration of the incubation and contagious period of SARS-CoV2; 2) make it possible to refine the definition of nosocomial SARS-CoV2 infection; 2) strengthen preventive campaigns for in-hospital transmission of SARS-CoV2; 3) pave the way for new recommendations in terms of preventive measures; 4) supplement existing recommendations by acquiring additional data concerning the transmission of the virus and thereby contribute to improving control guidelines for similar respiratory viral epidemics.

Communication of the results of this study could raise awareness among HCP and CG vis-à-vis their roles in preventing the spread of the virus in hospitals and in their immediate surroundings and could be used to support vaccination coverage should a vaccine become available in the future. The contribution of strain genotyping, when this data becomes available on a large scale, could complement epidemiological investigations targeting nosocomial transmission of Covid-19.[24]

Asymptomatic cases will not be included in this study although SARS-CoV2 transmission from asymptomatic cases has been documented.[25] Furthermore, there is a risk of missing even symptomatic cases owing to the intensity of the outbreak.

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Author contributions

PV designed the study. MSE, VPS, LH, FP, VE, CD, CE, HE and PV participated in the design of the CRF, drafting and revision of the protocol and manuscript and approved the final version.

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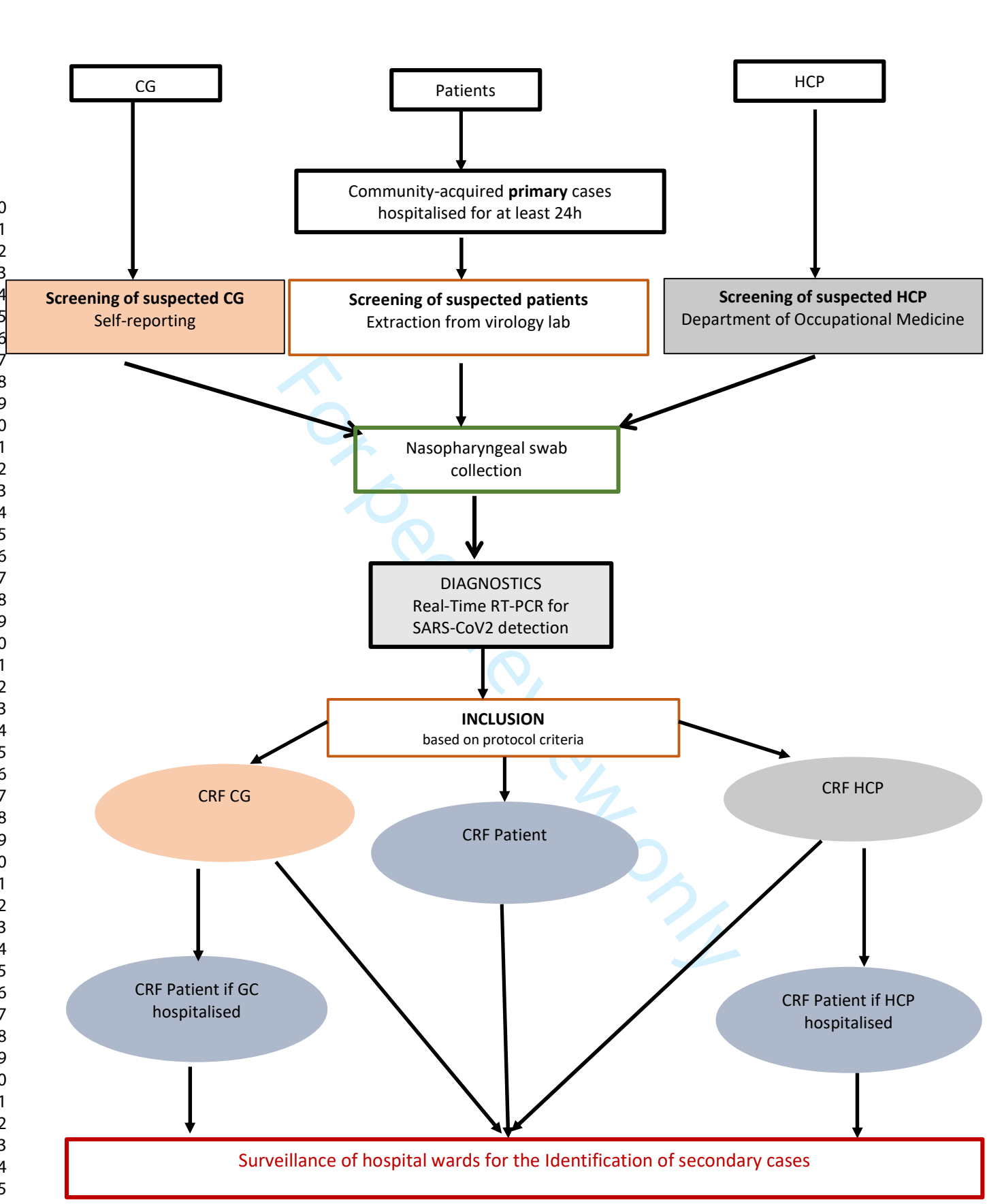

Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	All
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	22
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	22
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	NA

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N A
Objectives	#7	Specific objectives or hypotheses	7-8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	NA

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	NA

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15-16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix 2

BMJ Open

Protocol for a prospective, observational, hospital-based multicentre study of nosocomial SARS-CoV2 transmission: The NOSO-COR Project

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Protocol for a prospective, observational, hospital-based multicentre study of nosocomial SARS-CoV2 transmission

The NOSO-COR Project

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Abstract

Introduction: The newly identified SARS-CoV2 can cause serious acute respiratory infections such as pneumonia. In France mortality rate in the general population was approximately 10% and could reach higher levels at the hospital. In the current context of high incidence rates of SARS-CoV2 in the community, a significant increase in the rate of nosocomial transmission is expected. The risk of nosocomial transmission could even be higher in low-income countries that have fragile healthcare systems. This protocol is intended to estimate the prevalence and incidence of suspected or confirmed cases of nosocomial SARS-CoV2 infection, the clinical spectrum and the determinants (risk factors/protective) at participating hospitals.

Methods and analysis: This will be an international multicentre prospective, observational, hospital-based study in adults and children. It will include volunteer patients and healthcare professionals in France and hospitals affiliated with the GABRIEL network. Demographic and clinical data will be collected using case-report forms designed especially for the purpose of the project. A nasopharyngeal swab will be collected and tested for SARS-CoV2 by Reverse Transcriptase Polymerase Chain Reaction. Characteristics of the study participants, the proportion of confirmed nosocomial SARS-CoV2 infections relative to all patients with syndromes suggestive of SARS-CoV2 infection will be analysed. Appropriate multivariate modelling will be used to identify the determinants associated with nosocomial onset.

Ethics and dissemination: This study was approved by the clinical research and committee of all participating countries. The findings will be submitted to peer-reviewed journal for publication and shared with national health authorities.

Registration details: The trial was registered in ClinicalTrials (NCT04290780).

Key words: SARS-CoV2; nosocomial transmission, Multicentre prospective, France, Gabriel Network

Word count: 3860

Strengths and limitations of the study

- This prospective study will generate original data on nosocomial SARS-CoV2 infection in France and in the low-income countries.
- The results will provide the opportunity to document nosocomial SARS-CoV2 infection and pave the way to set-up new preventive recommendations.
- Selection bias owing to access to care in different populations and bias owing to the extent of access to personal protective equipment, in particular, in low-income countries may occur.
- The non-exhaustivity of the confounders to be collected should be considered for interpretation of the results.

- Only symptomatic cases were included in the study. Pauci-symptomatic and asymptomatic carriers might have been missed.

INTRODUCTION

Coronaviruses are enveloped viruses that mainly infect the upper digestive and respiratory tracts of mammals and birds. In humans, the viruses can cause mild respiratory infections but can also lead to serious infections such as pneumonia. During the past decade, two human coronaviruses SARS-CoV and MERS-CoV were the source of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics in 2002 and 2012 respectively.[1]

The newly identified SARS-CoV2 is a single-stranded RNA virus belonging to the coronavirus crown virus family of the subfamily Orthocoronaviridae. SARS-CoV2 appears to be a recombinant virus between the bat coronavirus and a coronavirus of unknown origin.[2] The virus was first detected in December 2019 in Hubei province of China[3-5] and spread widely throughout China before crossing the borders into other countries.[6] SARS-CoV2 is mainly transmitted by respiratory droplets but can also be spread through aerial droplets or fomites by contact.[7]

COVID-19 is the emerging infectious disease caused by SARS-COV-2 infection. COVID-19 can manifest in many ways[8-10] even if asymptomatic cases have also been reported.[11] In France, mortality rate of 10% have been reported in the general population.[12] The estimated median incubation period of COVID-19 was 5.1 days (CI, 4.5 to 5.8 days) in a pooled analysis of 181 confirmed cases reported from around the world.[13]

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, pointing to the over 118,000 cases of coronavirus in over 110 countries and territories around the world with the sustained risk of further global spread.

Analysis of the clinical presentation of the first case series (n=41) showed that 31% of the patients were admitted to intensive care units (ICU) and the crude mortality rate was 15%.[14]

COVID-19 related complications including severe pneumonia, respiratory distress, secondary bacterial infection, or decompensation for chronic heart or respiratory disease, mainly affected patients over 65. The cases described to date mostly occurred among patients with a history of chronic pathology,[4, 14] who were therefore more likely to be hospitalised.

In the absence of a preventive vaccine or curative treatment, current efforts to prevent and control the spread of SARS-CoV2 are based on early detection of cases along with infection control measures such as precautions against respiratory and direct-contact spread. In addition, specific measures are being applied to patients who should be cared for in single rooms, negative pressure ventilation if possible, wear surgical masks and practice strict hand hygiene using hydroalcoholic solutions, 70% ethanol solutions or chlorine-containing disinfectants. Class 2 or 3 or N95 filtering facepiece respirators were recommended when performing aerosol-generating procedures. Specific recommendations have also been issued from the WHO and Center for Disease Control.[15, 16]

As for the SARS and MERS-CoV epidemics and other respiratory viruses such as influenza or respiratory syncytial virus (RSV), cases of intra-hospital transmission of SARS-CoV2 have been reported and are going to continue to occur. In Wuhan alone, 1,080 healthcare professionals (HCP) were infected.[17] In China, more than 3,300 HCP were infected as of early March and in Italy, 20% of the HCP participating in a survey reported Covid-19 infections.[18] According to the National French Public Health Agency, Santé Publique France, more than 30,000 HCP were infected since March 2020.[19]

HCP have a key position in the transmission process because they are exposed to both community-acquired and nosocomial cases.[20, 21] This risk is amplified when the incidence of the

infection in the community is high. In the current context of high incidence rates of SARS-CoV2 in the community, a significant increase in the rate of nosocomial transmission is therefore expected. The risk of nosocomial transmission would be even higher in low-income countries owing to several factors such as the delay in diagnosis of COVID-19 patients, and the lack of infrastructure, trained personnel, isolation units, and infection control programs.

Beyond the morbidity and mortality associated with nosocomial COVIDs-19 infection, the impact on the organisation of care and the additional costs caused by longer hospital stays are still unknown, but will certainly be of consequence.

The link between hospital (nosocomial) and community attack rates is a good indicator of the effect of hospitalisation on the transmission of respiratory viruses.[22] Attack rates is defined as the proportion of infected patients among the total number of patients at risk of being infected during the epidemic period. The denominator, i.e. total number of at-risk individuals in the community, is provided by the regional agency of public health for the calculation of attack rates in the community while the number of hospitalized patients or patient-days of hospitalization will be used as denominator for in-hospital calculation. Better understanding of the transmission chains of SARS-CoV2 and the impact of control measures in healthcare units is essential to achieving control of the pandemic. For example, the configuration of care units also appears to play a role in transmission. Indeed, hospitalisation in a double room increased the risk of contracting influenza in a hospital by 2.67-fold.[23]

Implementation of appropriate hygiene and preventive measures play a decisive role in the control of nosocomial risk. Countries have implemented various measures according to their national guidelines to curb the propagation of this emergent virus, thus, their comparison could

allow to identify possible areas for improvement in patient care. The present manuscript describes the protocol of an international multicentre prospective study whose aims are to document suspected or confirmed nosocomial cases of COVID-19, their clinical spectrum and the prognostic factors at participating hospitals.

Objectives

The principal aim of this study is to estimate the prevalence and incidence of suspected or confirmed cases of nosocomial SARS-CoV2 infection among HCP and patients.

The secondary objectives are to 1) to describe and document cases of community-acquired SARS-CoV2 infection (prevalent cases on hospital admission) likely to be the source of nosocomial infection and the clinical spectrum; 2) describe and document hospital-acquired SARS-CoV2 infection (incident cases) that may be the source of nosocomial transmission and their clinical spectrum; 3) describe observance of infection control practices in settings where nosocomial transmission could occur and compare the attack rates between the hospital and the community. ; 4) estimate the incidence of infectious syndromes attributed to SARS-CoV2 and the proportion of severe cases, including deaths; 5) describe subpopulations with SARS-CoV2 infection depending on the hospital ward (for example: internal medicine vs. surgery vs. intensive care units [ICU]); 6) compare the adjusted attack rates of nosocomial and community-acquired SARS-CoV2 infection to identify contextual and/or environmental protective and risk factors in both the hospital and community setting; 7) 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.

METHODS

Study design and setting

This prospective, observational, hospital-based study will be carried out among volunteers patients, and HCP in university-affiliated hospitals (Hospices Civils de Lyon, Lyon, France), eight volunteered hospitals across France (Dijon, Grenoble, Paris, Puy-en-Velay, Saint Etienne, Périgueux, Eaubonne, Suresnes) and hospitals affiliated with the GABRIEL network (https://www.gabriel-network.org/), a network of research institutions mainly located in low-income countries and focused on the etiological agents of pneumonia. Other French or European university hospitals will be welcome and able to join the project on a voluntary basis.

Patient and Public Involvement

No patient involved in our study.

Recruitment

Inclusion criteria: Any adult/child patient or HCP from participating hospitals who give oral or written informed consent and who presents an infectious syndrome based on the WHO definition of COVID-19.[24]:

Suspected case: A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath)

OR, a patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (household, professional activity, travel) in the last 14 days prior to symptom onset;

OR, a patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the

absence of an alternative diagnosis that fully explains the clinical presentation.

Confirmed case: A person with laboratory confirmation of COVID-19 infection.

Exclusion criteria: Individuals who do not meet the above criteria.

The study flow chart is shown in Figure 1. Eligible patients will be identified by a clinical research assistant who will regularly contact hospital wards (emergency, geriatric, infectious diseases, etc.) and will review the results of the virology laboratory. The clinical research assistant will meet eligible individuals to explain the purpose of the study and obtain written informed consent. Nosocomial cases will be defined according to the SARS-CoV-2 incubation period, estimated on average at 5 days and ranging from 1 to 14 days.[13] We assumed that a delay greater than 48 hours between hospital admission and the onset of symptoms could be used to define a nosocomial case in order to ensure high sensitivity.

Identification of infected HCP will be based on data from the department of occupational medicine. A confidential interview with the symptomatic HCP will be organized to describe the purpose of the study and obtain written informed consent.

Participant timeline: Enrolled participants will be followed up during their entire hospital stay. Information on further complications occurred during the follow-up period and vital status will be collected from the patient's medical file.

Index case: An index case is defined as the first RT-PCR confirmed case of SARS-CoV2 infection in a given department during a given period.

Secondary case: A secondary case is defined as a RT-PCR confirmed case i) who was in contact with an index case during the contagious period, currently defined as 5 days before and 15 days after the onset of symptoms in the index case; ii) who developed clinical features compatible

with the diagnostic criteria of SARS-CoV2 infection within 15 days of the onset of symptoms in the index case.

The period of detection of secondary cases will be calculated according to the period of contagiousness of the index case: [date of onset of symptoms] to [date of onset of symptoms + 15 days] and the incubation period of secondary cases (1 to 15 days). Secondary cases will therefore be clinically detected in the time interval between [start date of symptoms in the index case + 1 day] to [start date of symptoms in the index case +15 days].

Figure 1: Study flow chart

Data collection

Clinical data

Data will be collected using case-report forms (CRF) designed especially for the purpose of this project for patients, and HCP (Supplementary data). According to the operating modes of each participating hospital and their organization in terms of clinical or epidemiological research, the CRF will be completed during a face-to-face interview and the use of medical records. The CRF has been pre-tested on a small number of patients and HCP and adjusted accordingly.

CRF will include demographic characteristics, underlying comorbidities, medical history, clinical, biological and laboratory data on the SARS-CoV2 infectious episode. In case the HCP is hospitalized, a patient's CRF including additional data regarding information on hospitalisation (ward specialty, type of room, etc.) and biological parameters (blood cell counts, etc.) will be completed.

The characteristics of the hospital and participating wards (specialties, number of beds, number of nurses and doctors, presence of an infection control unit, etc.) and infection control policies regarding the risk of infection by SARS-CoV2 will also be collected (Supplementary data). In addition, all participating centres are requested to provide a copy of their guidelines regarding COVID-19 preventive measures and the adjustments of the guideline over the epidemic period.

Biological Sample collection and testing

A nasopharyngeal swab will be collected and tested for the presence of SARS-CoV2 ribonucleic acid (RNA) by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) for each patient or HCP that meets inclusion criteria. Samples will be tested by the closest virology laboratory where state-of-the-art SARS-CoV2 assay is performed. The results will be reported on laboratory forms created specifically for this study.

If feasible, RT-PCR will be performed to detect a panel of other respiratory viruses (influenza A and B, RSV, rhinovirus, metapneumovirus, etc.) depending on the diagnostic practices available at each participating centre. Furthermore, SARS-CoV2 sequencing will be performed depending on the technical platforms available.

Biobanks are expected to be constituted and if possible, an aliquot of each sample will be stored in a Micronic tube at -20°C for at least 5 years after written informed consent is obtained.

Statistical methods

Sample size

Given the descriptive nature and surveillance objectives of this observational study, reaching a predefined number of subjects is not realistic.

Statistical analyses

Data will be analysed using statistical methods to describe the characteristics of the healthcare setting and study participants, the percentage of COVID-19 of those presenting influenza-like illnesses, the percentage of nosocomial COVID-19 patients among the confirmed cases, etc.

The primary criteria will be the proportion of patients, and HCP with confirmed nosocomial SARS-CoV2 infection relative to all patients, and HCP with syndromes suggestive of SARS-CoV2 infection during the study period.

Secondary outcome criteria will be to i) describe the delay of onset of suspected or confirmed nosocomial COVID-19 infection for hospitalised patients; ii) estimate the attack rate of confirmed COVID-19 cases in hospitalised patients according to their length of stay; and iii) estimate the attack rate of confirmed COVID-19 cases among HCP.

Categorical variables will be described with frequencies (%) and compared using Chi-square or Fisher exact test as appropriate. Continuous variables will be described using mean and standard deviation or median and interquartile range according to normal distribution, and compared using Mann-Whitney or Kruskal-Wallis test as appropriate. Relative risk and 95% confidence interval will be used as a measure of association. Statistical tests were 2-tailed with a level of statistical significance of <0.05.

Appropriate multivariate modelling methods will be applied depending on the numbers of patients and the hypothesis tested (Poisson regression, Cox regression, logistic regression) to identify the determinants independently associated with outcomes. For example, the length of stay will be considered as the duration of exposure.

Data management and archiving

Case Report Form

All required information will be recorded on a paper-based CRF in a clear and legible manner and justification must be provided for all missing data. Erroneous data noted in the CRF will be clearly crossed out and the correct data will be written next to the crossed-out information, accompanied by the initials of the investigator or authorized person who made the correction, the date and, if possible, and a justification for the correction.

To reduce data-entry errors by predefining plausibility checks and facilitate the rapid transfer of data, the electronic CRF (e-CRF) version of the study CRF will also be available.

Transfer of the data to the coordinating centre in Lyon (France) will be performed via the e-CRF following approval by the French "**Commission nationale de l'informatique et des libertés (CNIL) - National Commission for Data Protection"**. An alternative possibility will be to ensure periodic reporting (every 10 inclusions) by e-mailing the scan of the completed CRF to the coordinating centre.

Data management

Collected data will be computerised in the coordinating centre in Lyon, France. Source documents and databases will be anonymous and locked with a password known only to the scientific staff. These data will be kept for a minimum of 10 years after the end of the study.

Archiving

According to French law, the sponsor will keep the study documents (protocol and annexes, possible amendments, information forms, CRF, statistical analysis plan and output and the final study report) for a minimum of 25 years. After this period, the sponsor will be consulted before any data is destroyed.

Study-related documents and reports may be subject to audit or inspection by the sponsor and/or other authorized bodies.

This study is part of the "Reference Methodology" (MR-003) in application of article 54, paragraph 5 of French law N°78-17 of January 6, 1978. This change was approved on January 5, 2006 and modified on July 21, 2016. The Hospices Civils de Lyon, the promoter of the study, has signed a commitment to comply with this "Reference Methodology".

Rights to access source documents

Source documents are defined as any original documents, data, records in which data collected for a clinical trial is first recorded. Source documents will be kept by the investigator for 10 years or, if hospital medical records, by the hospital for 10 years. Each centre will have access to its own data during the study.

To ensure quality control and auditing, the sponsor will be responsible for obtaining the agreement of all parties involved in the research to guarantee direct access to all places where the research is carried out and to source data, documents and reports.

In accordance with current laws and regulations (articles L.1121-3 and R.5121-13 of the French public health code), all documents and personal data required for monitoring, quality control or auditing will be available to the persons in charge of these activities.

Confidentiality

The principal and associate investigators are required to respect professional confidentiality (articles 226-13 and 226-14 of the French Penal Code). In accordance with French laws regarding the confidentiality of study participant personal data (article L.1121-3 of the French Public Health Code) and clinical/laboratory results obtained throughout the study (article R. 5121-13 of the

French Public Health Code), individuals with direct access to the data will take all necessary precautions to ensure the confidentiality of the overall collected information.

All personal data concerning study participants will remain strictly confidential. To respect privacy, all participant details will be anonymous for the purpose of database preparation. Study subjects will be coded as follows: AAXXXXZZYY. The first two letters will be either PA for a patient, and HP for HCP. The following four digits will depend on the order of inclusion of the case and the next two letters will correspond to the hospital code. Finally, the last two letters will correspond to the country in which the hospital is located.

Quality control and assurance

Quality assurance audits will be carried out by persons appointed by the promoter as well as the inspections carried out by the Competent Authorities. All data, documents and reports can be subject to regulatory audits and inspections without hindering medical confidentiality.

Ethics and dissemination

Ethical approval

Ethical approval has been obtained from all participating hospitals as follow: France (clinical research and committee of Ile de France V, March 8, 2020); Guinea (Comité National d'éthique pour la recherche en santé (CNRS), April 20, 2020); Mali (Comité d'Ethique des Facultés de Médecine et de Pharmacie, FMOS/FPHAP, April 16, 2020); Ivory coast (Comité National d'Ethique des Sciences et de la Santé- MI la Recherche en Sant é (CNESVS), April 10, 2020); Madagascar (Comité National d'Ethique de la Recherche Biomédicale, March 30, 2020); Bangladesh (ICCDR,B

ethical committee, April 10, 2020); Lebanon (USJ Hôtel Dieux comité d'éthique, March 5, 2020) and Brazil (COMITÊS DE ÉTICA EM PESQUISAS (CEPS), May 28, 2020).

Informed consent

Patients and HCP will be informed of the objectives and their rights to refuse to participate in the study or withdraw at any time using simple, understandable terms. This information will be provided by an information and consent form given to each participant. According to French law, voluntary, oral informed consent will be obtained by the investigator before inclusion for the epidemiological data while signed consent is needed for the collection of biological banks. Consenting will be performed following the country's ethical guidelines. Informed consent will be obtained from the parents of included children (<18 years old).

Regulatory compliance

The research will be conducted in accordance with applicable laws and regulations currently in place in France and internationally.

Withdrawal criteria

Subjects may request to withdraw from the study at any time and for any reason without having to justify. In the event of a premature withdrawal, the investigator must document the participant's reasons for withdrawal as completely as possible.

Stopping the research study

The sponsors reserve the right to interrupt the study at any time if the objectives are not being met. In the event of premature termination of the study for security reasons, the information will be transmitted by the sponsors to all concerned parties and to the local ethical committee within 15 days.

Protocol amendments

In the eventuality of changes in the existing protocol that significantly affect the scope or the scientific quality of the investigation, an amendment containing a verbatim description of the changes and reference (date and number) to the submission that contained the original protocol will be submitted to the ethical committee for their approval.

Dissemination

Communications and scientific reports that emerge from this study will be carried out under the responsibility of the principal investigator in agreement with the associated investigators. Publication rules will follow international recommendations.[25]The findings will also be shared with national health authorities.

Authorship will follow the guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/) which require substantive contributions to the design, conduct, interpretation, and reporting of a trial.

Discussion

Human-to-human transmission of SARS-CoV2, including nosocomial transmission, is now well documented. The risk of amplification of spread of the disease in healthcare facilities is strong in case of a lack of infection control measures. Early recognition of nosocomial COVID-19 infection in patients or HCP is therefore essential for the setting up of immediate investigation and implementation of appropriate hygiene measures. Describing the signs and symptoms associated with nosocomial COVID-19 will enable comparisons with existing data on other nosocomial viral respiratory infections (i.e. influenza, respiratory syncytial virus, SARS-CoV, MERS-CoV).

The prospective design and face-to-face interviews will make it possible to reduce recall bias and to collect accurate data. The expertise of the Lyon university-affiliated hospitals already strongly involved in the surveillance of nosocomial infections and the extensive experience of GABRIEL network countries in various research studies related to respiratory infections also strengthen this research project. Participation in this project will enable the subjects to benefit from the diagnostic results. Moreover, each centre will benefit from the overall data in order to explore a particular scientific theme. The multicentric approach will allow high power for this study and enable comparison of clinical characteristics of COVID-19 in worldwide settings.

The results of the NOSO-COR project will provide original results that could: 1) constitute additional evidence for a better understanding of the duration of the incubation and contagious period of SARS-CoV2; 2) make it possible to tailor the definition of nosocomial SARS-CoV2 infection; 2) strengthen preventive campaigns for in-hospital transmission of SARS-CoV2; 3) pave the way for new recommendations in terms of preventive measures; 4) supplement existing recommendations by acquiring additional data concerning the transmission of the virus and thereby contribute to improving control guidelines for similar respiratory viral epidemics. 5) identify subpopulations that are at risk of acquiring COVID-19 at both community and hospital level.

Communication of the results of this study could raise awareness among HCP vis-à-vis their roles in preventing the spread of the virus in hospitals and in their immediate surroundings and could be used to support vaccination coverage if a vaccine becomes available in the future. The contribution of strain genotyping, when this data becomes available on a large scale, could complement epidemiological investigations targeting nosocomial transmission of Covid-19.[26]

Asymptomatic and pauci-symptomatic cases will not be included in this study although SARS-CoV2 transmission from asymptomatic cases has been documented.[27] This represents a major weakness of our study because asymptomatic individuals may not be recognized by healthcare workers, although they can become the source of nosocomial transmission in the hospital. Furthermore, there is a risk of missing even symptomatic cases owing to the intensity of the outbreak. This protocol has been drafted at the early stage of the epidemic. Data might change over time. As many hospitals in France and overseas will be included, reporting bias may be existing according to the availability of the data across the participating facilities. A measurement bias on the laboratory parameters may occur as the laboratory tests are not performed by a centralised testing facility.

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Author contributions

PV designed the study. MSE, VPS, LH, FP, VE, CD, CE, HE and PV participated in the design of the CRF, drafting and revision of the protocol and manuscript and approved the final version.

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Competing interests

The authors declare that there are no competing interests.

Sponsor contact information

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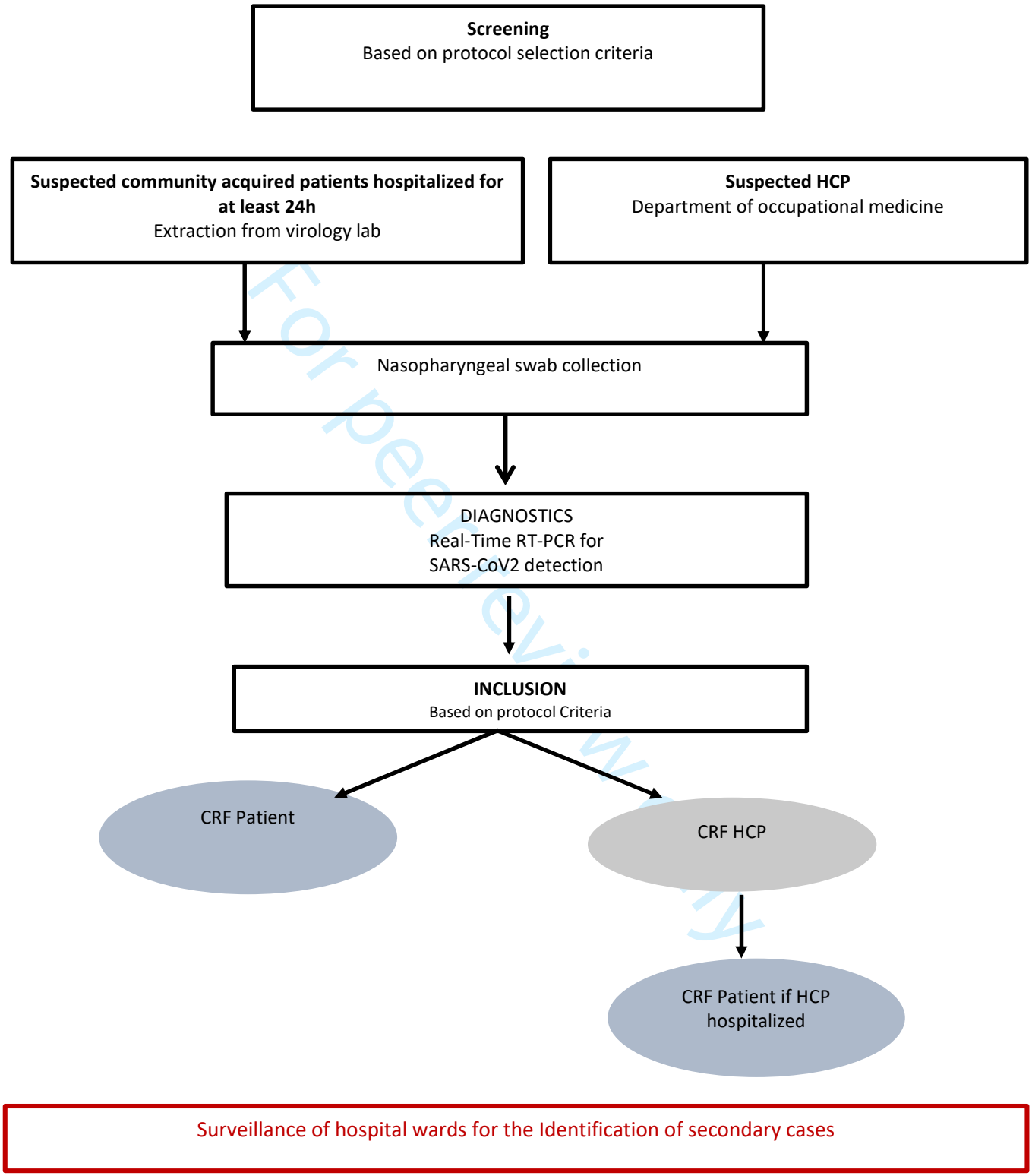
Figure 1: Study flow chart



HCP: Health care professional

Supplementary material

Patient - Case Report Form
NOSO-COR project
Version 3

Date of reporting to national health authority: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]
Reporting institution: _____
Reporting country:_____
Case classification: ▫ Confirmed ▫ Suspected
Detected at admission ▫ No ▫ Yes ▫ Unknown If yes, date [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Section 1: Patient information

Unique Case Identifier (used in country): : [_ _][_ _] [_ _][_ _] [_ _][_ _][_ _][_ _][_][_ _]

Date of Birth: [_M_][_M_]/[_Y_][_Y_][_Y_][_Y_] or estimated age: [__][__][__] in years

if < **1** year old, [__][__] in months or if < **1** month, [__][__] in days
Sex at birth: ▫ Male ▫ Female
Weight (Kg) [__][__][__] Height (cm) [__][__][__][__]
Place where the case was diagnosed: Country: _____
Admin Level **1** (province): _____ Admin Level 2 (district): _____
Patient usual place of residency: Country: _____
Admin Level **1** (province): _____ Admin Level 2 (district): _____

Section 2: Clinical information

Patient clinical course

Date of onset of symptoms: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_] ▫ Unknown
Admission to hospital: ▫ No ▫ Yes ▫ Unknown
First date of admission to hospital: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]
Name of hospital: _____

Hospitalization in ICU at admission ▫ No ▫ Yes ▫ Unknown
If Yes, date of ICU hospitalization [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]
Date of discharge from ICU [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Hospitalization in ICU during hospital stay ▫ No ▫ Yes ▫ Unknown
If Yes, date of ICU hospitalization during stay [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]
Date of discharge from ICU [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Was the patient ventilated: ▫ No ▫ Yes ▫ Unknown
If Yes, date of start of ventilation [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]
Date of end of ventilation [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Date of discharge from Hospital [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Date of isolation: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Health status (circle) at time of reporting: recovered / not recovered / death / unknown

End date of symptoms: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_] ▫ Unknown

Complications after the event: ▫ Cardiac ▫ Respiratory ▫ Death ▫ No complication
▫ Unknown ▫ Pulmonary bacterial superinfection
▫ Other bacterial superinfection
▫ Cardiopulmonary Resuscitation
▫ Other: _____

Death ▫ No ▫ Yes ▫ Unknown
Date of death, if applicable: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Patient symptoms at admission (for community acquired cases) / at suspicion (for nosocomial cases)
(check all reported symptoms):

- ▫ History of fever / chills
- ▫ General weakness
- ▫ Cough
- ▫ Sore throat
- ▫ Runny nose
- ▫ Anosmia
- ▫ Other, specify _____
- ▫ Shortness of breath
- ▫ Diarrhoea
- ▫ Nausea/vomiting
- ▫ Headache
- ▫ Irritability/Confusion
- ▫ Ageusia
- ▫ Pain (check all that apply)
  - *( ) Muscular*
  - *( ) Chest*
  - *( ) Abdominal*
  - *( ) Joint*

Patient signs:
Temperature at admission/at suspicion: [__][__][__] ▫°C / ▫ F Unknown ▫
Check all observed signs seen at least once during hospitalization:

- ▫ Pharyngeal exudate
- ▫ Conjunctival injection
- ▫ Seizure
- ▫ Other, specify: _____
- ▫ Coma
- ▫ Dyspnoea / tachypnoea
- ▫ Abnormal lung auscultation

Lung X-ray: ▫ Yes ▫ No
If Yes: ▫ Abnormal lung X-ray finding

Underlying conditions and comorbidity at admission (check all that apply):

- ▫ Pregnancy (trimester: _____)
- ▫ Cardiovascular disease,
- ▫ Hypertension
- ▫ Diabetes
- ▫ Liver disease
- ▫ Chronic neurological or neuromuscular disease
- ▫ Hypothyroidism
- ▫ Malignancy
- ▫ Rheumatic disease
- ▫ Other, specify: _____
- ▫ Post-partum (< 6 weeks)
- ▫ Immunodeficiency, including HIV
- ▫ Heart failure
- ▫ Renal disease
- ▫ Chronic lung disease
  - ▫ Asthma
  - ▫ COPD
  - ▫ Emphysema
  - ▫ Chronic bronchitis

Smoking status
▫ Current smoker ▫ Ex-smoker, If Yes, Quit date [_Y_][_Y_][_Y_][_Y_] ▫ Never ▫ Data not available
Alcohol consumption: ▫ Daily ▫ Weekly ▫ Occasionally ▫ Never ▫ Data not available

Section 3: Exposure in the 14 days prior to symptom onset (prior to reporting if asymptomatic)

Occupation: (tick any that apply)
▫ Student ▫ Health care worker ▫ Other, specify: _____
▫ Working with animals ▫ Health laboratory worker

Has the patient **visited any health care facility(ies)** in the 14 days prior to symptom onset? ▫ No ▫ Yes ▫ Unknown

Has the patient had **close contact**[1] with a person with acute respiratory infection in the 14 days prior to symptom onset?
▫ No ▫ Yes ▫ Unknown
If yes, contact setting (check all that apply):
▫ Health care setting ▫ Family setting ▫ Work place ▫ Unknown ▫ Other, specify: _____

Has the patient **had contact with a probable or confirmed case** in the 14 days prior to symptom onset? :
▫ No ▫ Yes ▫ Unknown
If yes, please list unique case identifiers of all probable or confirmed cases:
Case 1 identifier. _____ Case 2 identifier. _____ Case 3 identifier. _____
If yes, contact setting (check all that apply):
▫ Health care setting ▫ Family setting ▫ Work place ▫ Unknown ▫ Other, specify: _____
If yes, location/city/country for exposure: _____

Has the patient visited any **live animal markets** in the 14 days prior to symptom onset? ▫ No ▫ Yes ▫ Unknown
If yes, location/city/country for exposure: _____

[1] **Close contact**' is defined as:

- Health care associated exposure, including providing direct care to SARS-CoV-2 patients, working with health care workers infected with novel coronavirus, visiting patients or staying in the same close environment of a SARS-CoV-2 patient.
- Working together in close proximity or sharing the same classroom environment with a with a SARS-CoV-2 patient.
- Traveling together with SARS-CoV-2 patient in any kind of conveyance.
- Living in the same household as a SARS-CoV-2 patient

Section 4: Laboratory information

Nasopharyngeal sample taken: Yes ☐ No ☐ If yes, date: _ _/ _ _/ _ _ _ Time (1 to 12): _____ ▫ AM (before noon) ▫ PM (after noon)

Name of confirming laboratory: _____

Date of laboratory confirmation: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_] Time (1 to 12): _____ ▫ AM (before noon) ▫ PM (after noon)

Please specify which assay was used: _____

Result: SARS-CoV-2 positive ☐ SARS-CoV-2 negative ☐ Other respiratory virus tested: Yes ☐ No ☐

If Yes, Influenza A (no sub-type) ☐ Influenza A(H1N1) pdm09 ☐ Influenza A(H3N2) ☐ Influenza B (no sub-type) ☐

Influenza B/Yamagata ☐ Influenza B/Victoria ☐ RSV ☐ Other virus (_____) ☐ No virus ☐

Sequencing done will be?: Yes ☐ No ☐ Unknown ☐

Several nasopharyngeal sample taken during hospitalization: Yes ☐ No ☐

If yes, date of first negative test: _ _/ _ _/ _ _ _

Section 5: Information regarding hospitalization* (NOSO-COR Project)

Specificity of the ward at inclusion: ▫ ICU ▫ Surgery ▫ Medicine ▫ Obstetrics ▫ Other: _____

Number of rooms in the ward; _____ Number of beds in the ward: _____

ID (or name) of the ward: _____ Room N°: _____

▫ Single room

▫ Double room If yes, roommate ▫ Present ▫ Absent

▫ More than 2 beds in the room, If yes, number of beds: _____ number of present roommate: _____

Did the patient move to other type of room during hospitalization? ▫ Yes ▫ No

▫ Single room

▫ Double room If yes, roommate ▫ Present ▫ Absent

▫ More than 2 beds in the room, If yes, number of beds: _____ number of present roommate: _____

Hygiene prevention measures at entrance of the room: ▫ Yes ▫ No

Modification of preventive measures during hospitalization ▫ Yes ▫ No

If Yes, please specify _____

Does the patient wear a-mask when outside of the room for clinical examination or any other reasons?

▫ Never ▫ Sometimes ▫ Always

Date admitted to the ward: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Date discharged from the ward: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Section 6: Biological parameters

Parameter	Value	Parameter	Value
White blood cell count, G/L		Neutrophil count, G/L	
Lymphocyte count, G/L		Monocyte count, G/L	
Platelet count, G/L		Red blood cells count T/L	
Haemoglobin, g/L		Prothrombin %	
Creatinine, µmol/L		Urea mmol/L	
AST U/L		ALT U/L	
LDH U/L		CRP mg/L	
Sodium (Na+) mmol/L		Potassium (K+) mmol/L	

Sections 1-4 are adapted 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

***Sections 5 is added to the WHO CRF to explore more in details the nosocomial risk**

Patient – Case Report Form- NOSO-COR project – Version 3_2020.03.19

Health Care Professional (HCP) Case Report Form

NOSO-COR project

If the HCP is hospitalized, please complete also a patient CRF for this HCP

Section 1: Hospital administrative information

Date of inclusion: __ / __ / ___ HCP Identification code: [_ _][_ _] [_ _][_ _] [_ _][_ _][_ _][_ _][_][_ _]

Hospital name: Country :

Region: Zip code:

Section 2: Socio-demographic characteristics of HCP

Case classification: Confirmed ☐ Probable ☐

Date of positive sampling: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Date of birth: [_M_][_M_]/[_Y_][_Y_][_Y_][_Y_] Gender: Male ☐ Female ☐

Weight (Kg) [__][__] Height (cm) [__][__][__][__]

Occupation: ☐ Nurse ☐ Nurse-assistant ☐ Medical doctor ☐ Biologist ☐ Laboratory technician

☐ Others: _____

Specificity of the working ward ☐ ICU ☐ Surgery ☐ Medicine ☐ Obstetrics ☐ Other: _____

Do you work in several wards: Yes ☐ No ☐

If Yes, please specify _____

Section 3 : Clinical information

Date of first symptoms: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_] Do not know ☐

Date of end symptoms: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_] Do not know ☐

Health status at inclusion: Not recovered ☐ Recovered ☐

If the HCP is hospitalized, please complete also a patient CRF for this HCP

Symptoms at suspicion: (Please tick all reported symptoms)

☐ Fever/chills ☐ Sore throat ☐ Diarrhoeas ☐ Irritability/confusion

☐ General weakness ☐ Runny nose ☐ Nauseas/vomiting ☐ Pain *(tick all that apply)*

☐ Cough ☐ Shortness of breath ☐ Headache ( ) Muscular ( ) Chest

☐ Anosmia ☐ Ageusia ( ) Abdominal ( ) Joints

☐ Others: _____

Clinical signs:

Temperature at suspicion: [__][__][__] ▫ °C / ▫ F Unknown ▫

Check all observed signs:

▫ Pharyngeal exudate ▫ Coma Lung X-ray: ▫ Yes ▫ No

▫ Conjunctival injection ▫ Dyspnoea / tachypnoea If Yes: ▫ Abnormal lung X-ray finding

▫ Seizure ▫ Abnormal lung auscultation

▫ Other, specify: _____

Underlying conditions and comorbidity at admission: (Please tick all reported)

- ▫ Pregnancy (trimester: _____)
- ▫ Cardiovascular disease
- ▫ Hypertension
- ▫ Diabetes
- ▫ Liver disease
- ▫ Post-partum (< 6 weeks)
- ▫ Immunodeficiency, including HIV
- ▫ Heart failure
- ▫ Renal disease
- ▫ Chronic lung disease
  - ▫ Asthma
  - ▫ COPD
  - ▫ Emphysema
  - ▫ Chronic bronchitis
- ▫ Chronic neurological or neuromuscular disease
- ▫ Malignancy
- ▫ Hypothyroidism
- ▫ Rheumatic disease
- ▫ Other, specify: _____

Smoking status
- ▫ Current smoker
- ▫ Ex-smoker, If Yes, quit date [_Y_][_Y_][_Y_][_Y_]
- ▫ Never

Alcohol consumption: ▫ Daily ▫ Weekly ▫ Occasionally ▫ Never

Section 4: Sources of exposure for suspected or confirmed SARS-Cov-2 infected HCP

Information on the unit where nosocomial transmission might have been occurred:

Number of patients in the unit: _____

Number of beds in the unit: _____

Number of probable or confirmed 2019-nCoV patients in contact with the HCP: _____

Number of beds per room of the infected patient ☐ 1 ☐ 2 ☐ Others : ___

Information on the hospitalization room of SARS-Cov-2 infected patients:

Closed room: Yes ☐ No ☐

Room identified with a warning sticker: Yes ☐ No ☐

If yes (Multiple choice):

☐ Caution « droplets » ☐ « Caution« contact » ☐ « Caution « air » ☐ « Contact complementary caution »

Air conditioner: Yes ☐ No ☐

Other aeration: Yes ☐ No ☐

If Yes, please detail: _____

Room with airlock: Yes ☐ No ☐

Bio-cleaning: Yes ☐ No ☐

☐ Detergent-disinfectant only ☐Bleach alone 0,5% ☐ Detergent-disinfectant + bleach 0,5% ☐Others_____

If Yes, frequency: ☐ Once a day ☐Every 2 days ☐ Once a week ☐Others_____

Availability of personal protective equipment *in the ward:*

Mask fit-tested NIOSH-certified disposable N95: Yes ☐ No ☐ NA ☐

Surgical mask: Yes ☐ No ☐ NA ☐

Single use Long sleeve over-blouse: Yes ☐ No ☐ NA ☐

Protective apron: Yes ☐ No ☐ NA ☐

Vinyl gloves (single utilisation) Yes ☐ No ☐ NA ☐

Single use nitrile gloves: Yes ☐ No ☐ NA ☐

Protective glasses: Yes ☐ No ☐ NA ☐

Availability of hand rub hydroalcoholic solution *in the unit:*

Available in the unit: Yes ☐ No ☐

If available: ☐ Individual format ☐ in unit's room ☐ in common parts of the unit

Section 5: Laboratory information

Nasopharyngeal sample taken: Yes ☐ No ☐ If yes, date: __ / __ / ___ Time (1 to 12):
▫ AM (before noon)
▫ PM (after noon)

Name of confirming laboratory: _____

Date of laboratory confirmation: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_] Time (1 to 12):
▫ AM (before noon)
▫ PM (after noon)

Please specify which assay was used: _____

Result: SARS-CoV-2 positive ☐ SARS-CoV-2 negative ☐ Other respiratory virus tested: Yes ☐ No ☐

If Yes, Influenza A (no sub-type) ☐ Influenza A(H1N1) $_{pdm09}$ ☐ Influenza A(H3N2) ☐ Influenza B (no sub-type) ☐ Influenza B/Yamagata ☐ Influenza B/Victoria ☐ RSV ☐ Other virus (_____) ☐ No virus ☐

Sequencing will be done? Yes ☐ No ☐ Unknown ☐

Hospital characteristics and infection control policies - NOSO-COR project

Section 1: Administrative data

Name of the hospital: _____ Country : _____

Name of the city: _____ University-affiliated hospital: Yes ☐ No ☐

Number of admissions per year (2018): _____ Number of hospitalizations per year (2018):

Section 2: Hospital capacities at the time of the survey

Number (Nb) of adult beds		Nb of pediatric beds:	
Nb in medicine units:		Nb in medicine units:	
Nb in surgery:		Nb in surgery:	
Nb in obstetrics:		Nb in neonatology:	
Nb in intensive care units		Nb in intensive care units	
Other units:		Other units:	

Section 3: Health Care Professionals (HCP)

Nb of nurses: _____

Nb of assistant-nurses: _____

Nb of permanent medical doctors: _____

Nb of lab staff: _____

Nb of administrative staff: _____

Others (pharmacists, physio, etc.) _____

Section 3: SARS-Cov-2 local alert

Presence of at least one infection control unit in the hospital: Yes ☐ No ☐

Presence of a validated protocol exist regarding infection control in the hospital: Yes ☐ No ☐

Date of the protocol validation: [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]

Local guidelines regarding SARS-Cov-2: Airborne precautions ☐ Contact precautions ☐ Droplets precautions ☐

For the infected patient:

- Surgical mask if moving: Yes ☐ No ☐ Not applicable ☐
- Isolation Yes ☐ No ☐ Not applicable ☐
- Mandatory room door closed: Yes ☐ No ☐ Not applicable ☐
- Air conditioning room stopped: Yes ☐ No ☐ Not applicable ☐
- Hand disinfection before moving outside the room: Yes ☐ No ☐ Not applicable ☐
- Cohorting (HCP dedicated for the patient): Yes ☐ No ☐ Not applicable ☐

Visits restriction: Yes ☐ No ☐ Not applicable ☐

For non-infected patients from the same unit as the case:

- Identification of contact patients: Yes ☐ No ☐ Not applicable ☐
- Cohorting (HCP dedicated for the contacts): Yes ☐ No ☐ Not applicable ☐
- **Other preventive measures:** _____

For HCP providing care for the infected patient before entrance in the room

- Mask :fit-tested NIOSH-certified disposable N95 filtering facepiece respirator before entrance in the patient room: Yes ☐ No ☐ Not applicable ☐
- Hand disinfection : Yes ☐ No ☐ Not applicable ☐
- Use non sterile gloves Yes ☐ No ☐ Not applicable ☐
- Wearing gowns : Yes ☐ No ☐ Not applicable ☐
- Eye protection : Yes ☐ No ☐ Not applicable ☐
- Dedicated medical equipment: Yes ☐ No ☐ Not applicable ☐
- Adapted environmental cleaning and disinfection procedures Yes ☐ No ☐ Not applicable ☐
- Others specific measures : _____

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