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Research protocol for Sentinel Schools study: Monitoring and evaluation of SARS-CoV-2 epidemic in Catalan educational settings.

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Key words: COVID-19, severe acute respiratory syndrome coronavirus 2, School Settings, Sentinel Surveillance

ABSTRACT

Introduction

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became of concern in January 2020 many preventive measures have been adopted in educational settings to ensure the control of coronavirus disease 2019 (COVID-19) pandemic among children and staff in schools. This study aims to set up a school sentinel surveillance network with the purpose of monitoring SARS-CoV-2 infection, seroprevalence as well as to analyse the impact of preventive interventions of SARS-CoV-2 in school settings. Additionally, we will assess diverse screening strategies in a cohort of students and school staff to monitor the screening acceptance and its potential impact. Altogether, we hope this study will enable the design of more effective strategies for the prevention of COVID-19 spread.

Methods and analysis

The sentinel schools' study is a cross-sectional, school-based project including twenty-six participating sentinel schools in Catalonia (Spain). Children, adolescents and staff at the schools will be invited to participate. This project will be carried out from January, 2021 until June, 2022 as follows: i) Twice yearly serological testing and molecular SARS-CoV-2 detection and questionnaires covering SARS-CoV-2 symptoms, tests, health, knowledge, attitudes and behaviours; ii) An environmental evaluation carried out in different classrooms; iii) SARS-CoV-2 transmission dynamics and the impact of different variants among confirmed cases and classmates; iv) A participatory process by which the participants are invited to act as co-investigators to evaluate prevention strategies and provide recommendations to improve COVID-19 prevention in schools. Descriptive analysis will be performed for the main variables collected. The incidence and seroprevalence will be calculated and the association with socio-demographic factors and school characteristics will be determined using multivariate logistic regression.

Ethics and dissemination

Ethical approval was obtained from the IDIAPJGol and the Hospital Universitari Vall d'Hebron ethics committees. A report will be generated quarterly. Findings will be disseminated at national and international conferences and published in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- A multicentre study combining cross-sectional and longitudinal studies, collecting data from sentinel schools throughout Catalonia.

- Planned to consolidate the sentinel school surveillance network to monitor and evaluate the epidemiology of SARS-CoV-2 in school settings and assess the effectiveness of future preventive and control measures, new diagnostic tests or vaccination.
- Transdisciplinary and participatory research, carried out in collaboration with the education community to ensure that the prevention and control strategy for SARS-CoV-2 fits with the needs and expectations of schools.

Limitations

- The participating school-population might not be representative of the entire Catalan school population distributed across all the territory.
- Participation in periodic screenings could be low due to fear of testing the younger children or because of pandemic fatigue due to the large number of tests being performed.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), first reported from Wuhan city, China in December 2019[1], was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on 30 January 2020 and defined as a pandemic on 11 March 2020. Although children were recognized as contributing to only a small proportion of laboratory-confirmed COVID-19 cases and rarely developing severe or fatal disease[2, 3], their role in asymptomatic infection and transmission, which is well-described for other respiratory viral infections such as influenza, was uncertain at the point of these restrictions and is still under discussion.

On the declaration of the global COVID pandemic most countries closed their schools as part of their national lockdown measures[4, 5], with more than 1 billion children and young people affected so far[6]. The closure of schools reduced the number of contacts within the population and, therefore, the subsequent transmission[5]. However, this measure can also cause considerable damage to children and their families with significant social and economic impacts, mainly on physical and mental health. On the other hand, most evidence from countries that have reopened schools or never closed them, suggests that schools have not been associated with significant increases in community transmission[7-10]. Thus, the transmission of SARS-CoV-2 from paediatric patients both at home and in schools has been an intensely topic since the beginning of the COVID-19 pandemic, also regarding the emergency of new variant scenarios[11-14].

Since Catalan schools reopened in September 2020 after 6-months of closure, there have been 83,911 accumulated positive COVID-19 cases, of which 74,246 were students (5.16%) and 8,996 school staff (5.49%)[15]. Likewise, a recent study that analysed the incidence dynamics of SARS-CoV-2 infection in children in the first term of the school reopening shows that the infection rate among children remained lower compared with the general population for pre-school (3-6 years) and primary pupils (6-12 years) but was equal to it or higher in secondary students (12-18 years)[16]. Moreover, several studies have shown that in this pandemic very few cases infect many contacts (super-spreaders) while most cases either infect nobody or very few people and this includes paediatric index cases[17-21]. Defining host-related, viral and environmental patterns that determine these super-spreading situations is relevant to the tailoring of measures to minimize the transmission of SARS-CoV-2 in schools[22].

Preventive interventions play an important role in working together to gain control of the COVID-19 pandemic, also in schools. In this sense, the social and behavioural sciences can provide valuable insights into managing the pandemic and its impacts[23]. Non-pharmacological preventive interventions in schools such as physical distancing, hygiene, use of masks, restricting interactions to clusters of students in bubble-groups, massive microbiological testing and other safety measures are essential to prevent transmission. These measures should be adapted to the setting and age group and prevent transmission while providing children with an optimal learning and social environment[4]. Furthermore, as it is known that SARS-CoV-2 transmission is via aerosols and virus-laden aerosols may easily accumulate in indoor environments, a proper ventilation of indoor spaces can be a great preventive measure. Additionally, the first set of COVID-19 vaccines provided a pharmacological intervention in the last quarter of 2020 when they received the authorization for emergency use by the European Medicines Agency (EMA) and the Food and Drug Agency in the United States[24]. So far, teaching and non-teaching staff and population over 16 years are being vaccinated as defined in the Spanish vaccination strategy raising hopes for a better control of the epidemic inside school settings. In this context, there is a need to understand the epidemiology of SARS-CoV-2 in children once the adult population has been vaccinated. The pandemic is moving very fast, and behaviours and attitudes may change in response to the COVID-19 pandemic. Understanding the drivers of vaccine acceptance will be crucial to the success of COVID-19 mass vaccination campaigns.

Therefore, the use of periodical cross-sectional surveys on the knowledge, attitude and practice (KAP) associated with COVID-19 will allow rapid and adaptive monitoring of demographics, preventive behaviours, knowledge, and perceptions over time, among others, and can be useful in order to identify misinformation as they emerge.

This article reports the design and protocol of a school-based study in several sentinel schools in Catalonia. The study is part of the COVID-19 monitoring and evaluation plan from the Ministry of Health of the Government of Catalonia, and it is conceived as a participatory and transdisciplinary research process where the students and school staff will be invited to participate. The monitoring and evaluation provide practical information for making timely decisions, addressing community needs, and identifying more effective strategies for the prevention of COVID-19 spread and future infectious threats. In addition, the protocol could be highly useful for adaption into other educational settings for the monitoring of the COVID-19 pandemic.

GENERAL OBJECTIVES

1. To describe over time the knowledge, attitudes and behaviours (KAB) of students and school staff (teaching and non-teaching staff) towards SARS-CoV-2 infection and its prevention, as well as its impact in school settings.
2. To assess over time the prevalence of SARS-CoV-2 infection and seroprevalence of antibodies against SARS-CoV-2 and to identify associated sociodemographic, biological, behavioural and environmental factors among both children and staff.
3. To identify and describe multi-level determinants, barriers and needs of SARS-CoV-2 prevention related measures in school settings over time.
4. To assess the secondary attack rate of SARS-CoV-2 children index cases and its multilevel determinants and factors, both in school and family settings.
5. To analyse the impact of preventive and control measures on the occurrence of SARS-CoV-2 in school settings.
6. To pilot alternative testing and screening technologies and strategies, to assess their acceptability, feasibility and performance and the occurrence of SARS-CoV-2 infection among students over 12 years old and school staff.
7. To analyse the impact of different SARS-CoV-2 variants' transmission in school settings.
8. To facilitate a participatory process where the education community will act as co-researchers elaborating recommendations to improve the prevention and control measures in the school environment.
9. To evaluate the impact on students' learning, attitudes and motivations of their participation in the research process and the teacher's perspectives on this impact.

METHODS AND ANALYSIS

Study design and Setting

The population of Catalonia was 7,619,494 in 2019. The Catalan school system includes 1,582,466 students, 117,398 teaching staff and 5,492 school centres[25].

This project is based on sentinel schools defined as a network of schools representing the diversity of schools and the scholar population in Catalonia, and chosen using the following criteria:

- Volunteering/commitment of both the school management team and the teaching staff as well as the children's parents to participate in the project

- Representation of schools located in the different Basic Health Areas (BHA) and territorial areas will be ensured taking into account tertiles of SARS-CoV-2 accumulated incidence and tertiles of socio-economic deprivation index[26]
- Representation of schools with different characteristics:
    - Sociodemographic indicators. At least two-to-five high complexity schools characterized by low socioeconomic level and specific educational needs
    - Some schools located in rural areas[27]
    - Schools with all levels of education, small school size and school centres with professional training courses
    - Public, charter and private schools

The sentinel surveillance is carried out by means of serial cross-sectional and longitudinal school-based studies, direct observation, index case study and participatory research approach in children, adolescent and school staff from the selected sentinel schools. In a subset of schools (n=5), a cohort of students from first grade of secondary school to high school (12->18 years) and school staff has been stablished in order to monitor the COVID-19 incidence and the feasibility and acceptability of different periodical screening practices for COVID-19 confirmation. All the study interventions will be carried out in two academic years starting from January 2021 to June 2022.

Study population (Inclusion criteria)

- Students attending sentinel schools will be eligible for the study, from preschool (3-years-old) to high school (approximately 18-years-old)
- School staff of the sentinel schools, including teachers, administrators, canteen and cleaning staff, and other adults working in the educational settings such as extracurricular education instructors

Informed consent

Informed consent will be obtained from school staff, parents of children under 16 and pupils of 16 years-old or older. Participants will be free to decline/withdraw consent at any time without providing a reason and without being subject to any resulting detriment.

Study procedures

Summary information of questionnaires, biological samples and other information to be collected is provided in Table 1.

<u>Knowledge, attitudes and behaviours regarding COVID-19 (KAB) questionnaires and impact of preventive and control measures</u>

Each headteacher will send the study information pack (a study leaflet and the information sheet) and the link to the online informed consent and the baseline questionnaires by e-mail to the parents/guardians, school staff and older students (when necessary, on paper). We will send follow-up questionnaires twice a year. Three different questionnaire models will be designed: for teachers and other school staff (Questionnaire A); for students under 16, which will be answered by parents/guardian (Questionnaire B), and for students over 16 (Questionnaire C). The variables included in the KAB survey will be mainly based on the WHO recommendations, as described in WHO/Europe (2020)[28].

<u>Prevalence of SARS-CoV-2 active infection and seroprevalence of antibodies against SARS-CoV-2</u>

Cross-sectional study: A field team (FT) made up of three nurses and a field coordinator will visit each school equipped with personal protective equipment to collect the samples for testing.

They will schedule the number of intervention days with each participating school depending on school size. The following samples in the baseline and the following cross sectionals (twice yearly) will be collected from all participants: i) Nasal swabs to perform a transcription-mediated amplification assay (TMA) for detection of SARS-CoV-2; ii) Finger prick blood sample to assess with a quick anti SARS-CoV-2 IgM/IgG antibody test.

Longitudinal study: Follow-up interventions will be scheduled twice yearly during the school year as an alternative testing strategy. In each intervention, the FT will collect saliva and nasal specimens for the detection of SARS-CoV-2 by molecular or antigenic tests, respectively. The cohort participants will fill in an additional online epidemiological survey with information related to SARS-CoV-2 infection, their symptomatology, exposure and vaccine status.

Secondary attack rate and SARS-CoV-2 variants

This part of the study will be carried by the Paediatric Infectious Diseases and Immunodeficiencies Unit at Hospital Universitari Vall d'Hebron (HUVH). Data on COVID-19 index cases will be collected with appropriate social and geographical distribution. These cases will be detected by the routine data provided by the Catalan Public Health Department or detected during the study interventions and analysed in depth from then on. Data on demographic, social and clinical features, vaccination status, comorbidities and clinical outcome will be collected. School and household contacts will also be studied in depth to detect secondary cases. Samples from the index case and all COVID-19 confirmed contacts will be sequenced using whole genome sequencing (WGS) following the ARTIC Network protocol[29] for the characterization of SARS-CoV-2 (lineage and mutations), molecular tracing of sequences, and measurement of the viral load in these respiratory samples to assess its role in the transmission dynamics.

Environmental determinants and barriers

The environmental evaluation will be carried out by the ISGlobal team to obtain information on the structural characteristics of each participating sentinel school, ventilation practices and other environmental prevention measures using the KKmoon carbon dioxide detector device. This intervention will include: i) A structural evaluation by a field technician in at least one classroom for each grade; ii) Online twice yearly surveys addressed to teachers and headteachers regarding ventilation and other prevention practices; iii) Twice yearly 15-day assessment of CO_2, temperature and humidity – seven days assessed by the field technician and the remainder as an experimenting tool for students – in 5 to 8 previously chosen classrooms.

Participatory research

The project is conceived as a collaborative and transdisciplinary research project where the education community and families participate in different phases of the research process. They will act as co-researchers evaluating the prevention and control measure implementation of SARS-CoV-2 infection in the school environment with a systemic perspective, as well as elaborating their recommendations to improve the prevention and control strategy. This approach will be implemented in collaboration with the EC funded project CONNECT, which aims to improve science learning and increase students' motivation towards science careers by engaging schools, scientists and families to solve local challenges.

Participation will entail discussion groups: i) Online focus groups with teachers. Preliminary results of the bio-behavioural surveys will be shared and, based on these, they will be invited to analyse problems, opportunities and needs, and to develop proposals for improvement of prevention measures following a protocol; ii) Teachers conducting focus groups with their class-group students and then families, reproducing a similar protocol; iii) The edited list of recommendations will be presented by students to scientists and policy makers in an online conference; iv) Elaboration of the final list of recommendations; v) Capital science survey: a pre-

and post-intervention survey addressed to pupils regarding the science learning and students' attitudes and motivation, and a pre- and post-intervention survey addressed to teachers regarding the education process.

Sample management, microbiological analysis and test result communication

As described above, diverse biological samples will be collected during the study.

The finger prick blood collected at the baseline and the follow-up will be processed at the time of collection to perform a quick SARS-CoV-2 serological test (COVID-19 IgG/IgM Rapid Test Kit, Lambra, Spain) with sensitivities of 97,2% (IgG) and 87,9% (IgM), and specificities of 100% for both immunoglobulins as the manufacturers describe. This approach will be used to assess the exposure to SARS-CoV-2 infection or vaccination by the presence of antibodies. In addition, the nasal swab sample collected in the longitudinal study will be processed at the time of collection for detection of SARS-CoV-2 antigen using the Panbio COVID-19 Ag Rapid Test (Abbot, USA) with a sensitivity of 93.3% (95% CI: 83.8-98.2%) and specificity of 99.4% (95% CI: 97.0-100%) as the manufacturers describe. The nursing team will upload the rapid test results on an online research database using electronic tablets. These results will be introduced afterwards to the electronic health record of all participants, who will be able to consult them in the online patient health portal (La Meva Salut app). In case of Ag positive with IgG negative, the COVID-school manager, a new sanitary staff role acting as a liaison between the primary care team and the school centres, will activate the public health protocol established by the Catalan Ministry of Health[30].

Nasal swabs and saliva samples will be maintained at 4ºC during sampling procedures and transport to laboratory facilities. A molecular assay based on the transcription mediated amplification assay (Procleix SARS-CoV-2, Grifols) will be conducted in HUVH for detection of SARS-CoV-2 in nasal swabs, and RT-PCR assay (Allplex SARS-CoV-2/FluA/FluB/RSV, Werfen) will be conducted at the Hospital Universitari Germans Trias i Pujol (HUGTiP) laboratories to determine SARS-CoV-2 infection in saliva specimens. If the TMA assay (HUVH) or RT-PCR assay (HUGTiP) is positive, an active infection will be confirmed. Once the nasal samples have been tested, all positive specimens will be stored in sample collection C.0001145 on the *Instituto de Salud Carlos III* register. On the other hand, saliva samples with positive SARS-CoV-2 results will be frozen and stored at the IGTP-HUGTiP Biobank and conserved for two years. TMA/PCR results will be uploaded by the microbiology laboratories to the electronic health record, and the participants and their general practitioners or paediatricians will be able to check them.

Regarding the transmissibility study, nasopharyngeal or nasal swab samples from index cases and positive secondary cases will be sent to the HUVH laboratory for genetic SARS-CoV-2 characterisation, to measure the viral load and to detect other respiratory viruses. The genetic characterisation of SARS-CoV-2 will be performed through WGS according to the ARTIC Network protocol[29] by using MiSeq and NextSeq 2000 platforms (Illumina, CA, USA). Other respiratory viruses will be detected by a real-time multiplex RT-PCR assay (Allplex Respiratory Panel Assay, Seegene); total nucleic acids will be extracted using NucliSENS EasyMAG (bioMérieux, Marcy l'Etoile, France) or Microlab STARlet System (Hamilton, CA, USA) according to the manufacturer's instructions. Additionally, to measure the SARS-CoV-2 viral load, an in-house quantitative RT-PCR assay using the primer/probe set targeting the nucleocapsid protein (N1) and the human RNase P (housekeeping gene) from the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel will be carried out. The Ct values of the viral target will be normalized to a housekeeping gene based on the ΔCt method (Ctsample − Cthousekeeping gene) in order to minimize the variations due to the non-standardized collection of a heterogenous specimens.

Data management, data protection and patient confidentiality

Informed consents and the different surveys will be designed and published by means of the EUSurvey management system, an official online survey management tool of the European Commission. For those participants for whom online access is not possible, printed surveys will be distributed by the field team and afterwards digitalized. The periodical surveys from the cohort study will be published by means of the OpenTIC software.

After giving their consent to participate (or allow their child to participate), each participant will be allocated a unique participant ID number on enrolment to the study. This unique identifier will serve as a link to all the data needed for the study (questioners, biological samples). The file that relates the identifier or pseudonym to the personally identifiable data will be encrypted and the access to this file will be restricted to a very small number of authorized persons (EM, YD, JA, LA). The process will comply with the General Data Protection Regulation (GDPR) requirements.

Study definitions:

Given that all the participants attending the school should be asymptomatic, a confirmed COVID-19 case will be defined as any individual testing SARS-CoV-2 positive by molecular assays (PCR or TMA-based) or COVID-19 Ag Rapid Test (RAT) in a respiratory or saliva specimen[31].

A paediatric index case will be established when the child is the first confirmed COVID-19 case in the classroom noticed by health authorities or the research team[21]. A secondary case will be defined as a classmate or household contact subsequently testing positive for SARS-CoV-2 by molecular assay or RAT. Close contacts will be defined as all people who have shared space with a positive COVID-19 less than 2 metres away, for more than 15 minutes, without protection and from the 48 hours prior to the onset of symptoms. If the positive person has not had symptoms, onset will be defined as the date of performing the diagnostic test.

Variables collected

i) Individual data

- Sociodemographic and socioeconomic indicators: age, gender, ethnic origin, household and career, economic status, job situation of their parents in the case of pupils
- Clinical data and infection by SARS-CoV-2: symptoms, hospitalization, exposure, contact with positive cases
- Attitude, behaviour and knowledge regarding COVID-19 and preventive measures
- Pandemic impact indicators such as changes on mental and physic health and the purchasing power of parents and school staff
- Vaccination data: manufacturer, number of doses, date of doses, refusal to vaccinate (date and reason)
- Attitude and usability of focus groups regarding scientific contribution

ii) Collective data

Number of classrooms, number of tables/classroom, number of pupils/m^2, school surface, schoolyard surface, concentration of CO_2, temperature and humidity in the classrooms.

iii) Ecological data

These data will be collected and provided by the Primary Care Services Information System (SISAP) and the Data analytics program for health research and innovation (PADRIS) and will include data from different data sources in order to obtain the information mentioned below:

- Number of new COVID-19 confirmed cases or tested positive for SARS-CoV-2 by TMA/PCR or RAT /total of residents.
- Number of new COVID-19 confirmed cases or tested positive for SARS-CoV-2 by TMA/PCR or RAT/total of tested people.
- Number of new COVID-19 confirmed cases or tested positive for SARS-CoV-2 by TMA/PCR or RAT/total of suspected cases.
- Number of confined classrooms/total number of classrooms.

Data analysis plan and sample size

We estimate a 70% participation among the total of 11,000 individuals who are on the census at the 26 sentinel schools. A descriptive analysis will be performed for all the main aforementioned variables collected: participant's sociodemographic characteristics, SARS-CoV-2 infection characterization, its associated factors, behaviour information and other outcomes of interest. For quantitative variables, we will use measures of central tendency and dispersion (mean, standard deviation, median, interquartile range, 95% confidence interval). For qualitative variables, we will calculate absolute frequencies and percentages. To estimate the statistical significance of time trends in SARS-CoV-2 laboratory confirmed cases we will use multivariate logistic regression analysis with robust standard errors clustered at the individual-level and school-level, adjusting for sociodemographic, environmental and school structural variables.

In order to address the fourth objective related to the transmissibility study, a descriptive analysis will be performed for all cases and contacts identified in school clusters. Analyses will include chi-square and independent sample t-test procedures to assess differences between super-spreaders and non-spreaders for index cases and secondary cases using socio-demographics, number of classmates and household contacts, clinical and environmental variables. Finally, we will use univariate and multivariate logistic regression models to assess the association between transmission risk factors and SARS-CoV-2 infection among index cases and close contacts. All models will be adjusted for gender, age, vaccination status, number of classmates, and household contacts and whether or not the index cases are symptomatic.

Global data on the COVID-19 epidemic in Catalonia and the school basic health area (BHA) will be collected to contextualize the current epidemic situation. Data will be provided globally and stratified by age groups and collectives. This data will be provided by the Catalan Agency for Quality and Health Assessment (AQuAS) and SISAP. Analysis of the interrupted time series of SARS-CoV-2 seroprevalence and COVID-19 confirmed cases will be performed to assess the public health implemented measures including vaccination programmes. The confirmed cases will be modelled as ARIMA processes to estimate the expected numbers to be compared to those observed and estimate the impact of the different analysed measures, to do this we will calculate absolute and relative changes between expected-observed confirmed cases in each time point of the implemented measures. Analysis will be conducted in R (R Core Team, 2014).

ETHICS AND DISSEMINATION

The ethical aspects of the present study include:

- Recruitment of participants with informed consent
- Collection and storage of biological samples
- Questionnaires with non-anonymized data
- Collection and storage of personal data

The confidentiality of data and other ethical considerations will be managed in accordance with the recommendations of the Spanish Law 14/2007 of 3 July, on Biomedical Research and the

Spanish Royal Decree RD 1716/2011 of 18 November, which lays down the basic requirements for the authorisation and operation of biobanks for purposes of Biomedical Research and the treatment of biological samples of human origin. Informed consent is required for this project as is established in article 59 of the law.

The necessary measures will be taken to ensure the protection of personal data and their confidentiality, in accordance with EU Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (RGPD), and in the Spanish Organic Law 3/2018 of 5 December, for the protection of personal data and Guarantee of digital rights (LOPD-GDD).

The data protection office of the Ministry of Health of the Government of Catalonia has reached an agreement signed by all the organizations in the research team to align with all the ethical considerations mentioned above and recommended by the same office.

The data and results provided by this project will be valuable in the current context of the public health emergency of international concern declared by the WHO for the COVID-19 pandemic and taking into account the urgent need for information coming from COVID-19 studies.

The CEEISCAT research team will generate a quarterly report with qualitative and quantitative data to give feedback to the stakeholders. Findings from this study will be disseminated at national and international conferences, reported on the public webpage of the project and published in peer-reviewed journals.

Study registration

Ethical approval was obtained from the Foundation University Institute for Research in Primary Health Care Jordi Gol i Gurina (IDIAPJGol) ethics committee with code 20/192-PCV on 17 December 2020 and the Hospital Universitari Vall d'Hebron ethics committee with code PR(AMI)668/2020.

AUTHORS' CONTRIBUTIONS

All authors have read, reviewed and agreed to the finalized submitted version of the manuscript. Conceptualisation: JC. Design study: JC, CF, AS, AB, JR, JS, PS, AS and MG. Operational procedures: JC, JR, AB, CF, AC, JS, MG, AA, TP, IB, JF, RM, PS, AS, and JB. Resources: RF, JM, JMA, CC and JB. Writing and draft preparation: AB, CF, AC. Writing, review and edition; all authors.

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COMPETING INTEREST STATMENT

All of the authors declare that they have no conflicts of interest.

PATIENT AND PUBLIC INVOLVEMENT

No patient involved

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Table 1. Summary information of study procedures.

Type of intervention	Determination	Type of Test	Coordination	Frequency
Bio-behavioural questionnaires			CEEISCAT	
- Questionnaire A (teaching and non-teaching staff) - Questionnaire B (parents or foster parents of students under 16 years old) - Questionnaire C (16-years-old or older students)				Once during 2020-2021 school year and twice during 2021-2022 school year
Biological sampling			CEEISCAT	
Baseline - Blood from finger prick - Nasal swab sample Longitudinal study (> 1st grade of middle school and school staff) - Saliva sample - Nasal swab sample	Ab anti-SARS-CoV-2 Viral RNA (SARS-CoV-2) Viral RNA (SARS-CoV-2) SARS-CoV-2 Ag rapid test	LFA TMA RT-PCR LFA		Once during 2020-2021 school year and twice during 2021-2022 school year Bi-monthly
Environmental and structural evaluation in each sentinel school			ISGlobal	
- Environmental questionnaires (Directors and teachers) - Structural and environmental evaluation by a field technician - CO_2, humidity and temperature measurements	Prevention measures (e.g. ventilation practices)			Once during 2020-2021 school year and twice during 2021-2022 school year
Transmissibility study			HUVH	
- COVID-19 index cases - Household and classmate contacts evaluation - Secondary attack rate	Viral coinfections Viral RNA (SARS-CoV-2) SARS-CoV-2 characterisations Viral load measurement	RT-PCR TMA/PCR Whole genome sequencing Quantitative PCR assay		
Participatory research			Living lab (IRSICaixa)	
- Scientific capital surveys - Focus groups - List of recommendations - Annual school conference				Once during 2020-2021 school year and twice during 2021-2022school year

Ab: antibodies; Ag: antigens; LFA: Lateral flow assay; TMA: Transcription mediated amplification assay

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Study protocol for monitoring SARS-CoV-2 infection and its determinants in Catalonia (Spain): an observational and participatory research approach in a Sentinel Network of Schools.

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Study protocol for monitoring SARS-CoV-2 infection and its determinants in Catalonia (Spain): an observational and participatory research approach in a Sentinel Network of Schools.

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Key words: COVID-19, severe acute respiratory syndrome coronavirus 2, School Settings, Sentinel Surveillance

ABSTRACT

Introduction

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became of concern in January 2020 many preventive measures have been adopted in educational settings to ensure the control of coronavirus disease 2019 (COVID-19) pandemic among children and staff in schools. This study aims to set up a school sentinel surveillance network with the purpose of monitoring SARS-CoV-2 infection, seroprevalence as well as to analyse the impact of preventive interventions of SARS-CoV-2 in school settings. Additionally, we will assess diverse screening strategies in a cohort of students and school staff to monitor the screening acceptance and its potential impact. Altogether, we hope this study will enable the design of more effective strategies for the prevention of COVID-19 spread.

Methods and analysis

The sentinel schools' study is a cross-sectional, school-based project including twenty-six participating sentinel schools in Catalonia (Spain). Children, adolescents and staff at the schools will be invited to participate. This project will be carried out from January, 2021 until June, 2022 as follows: i) Twice yearly serological testing and molecular SARS-CoV-2 detection and questionnaires covering SARS-CoV-2 symptoms, tests, health, knowledge, attitudes and behaviours; ii) An environmental evaluation carried out in different classrooms; iii) SARS-CoV-2 transmission dynamics and the impact of different variants among confirmed cases and classmates; iv) A participatory process by which the participants are invited to act as co-investigators to evaluate prevention strategies and provide recommendations to improve COVID-19 prevention in schools. Descriptive analysis will be performed for the main variables collected. The incidence and seroprevalence will be calculated and the association with socio-demographic factors and school characteristics will be determined using multivariate logistic regression.

Ethics and dissemination

Ethical approval was obtained from the IDIAPJGol and the Hospital Universitari Vall d'Hebron ethics committees. A report will be generated quarterly. Findings will be disseminated at national and international conferences and published in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- A multicentre study combining cross-sectional and longitudinal studies, collecting data from sentinel schools throughout Catalonia.
- Planned to consolidate the sentinel school surveillance network to monitor and evaluate the epidemiology of SARS-CoV-2 in school settings and assess the effectiveness of future preventive and control measures, new diagnostic tests or vaccination.
- Transdisciplinary and participatory research, carried out in collaboration with the education community to ensure that the prevention and control strategy for SARS-CoV-2 fits with the needs and expectations of schools.

Limitations

- The participating school-population might not be representative of the entire Catalan school population distributed across all the territory.
- Participation in periodic screenings could be low due to fear of testing the younger children or because of pandemic fatigue due to the large number of tests being performed.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), first reported from Wuhan city, China in December 2019[1], was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on 30 January 2020 and defined as a pandemic on 11 March 2020. Although children were recognized as contributing to only a small proportion of laboratory-confirmed COVID-19 cases and rarely developing severe or fatal disease[2, 3], their role in asymptomatic infection and transmission, which is well-described for other respiratory viral infections such as influenza, was uncertain at the point of these restrictions and is still under discussion.

On the declaration of the global COVID-19 pandemic most countries closed their schools as part of their national lockdown measures[4, 5], with more than 1 billion children and young people affected so far[6]. The closure of schools reduced the number of contacts within the population and, therefore, the subsequent transmission[5]. However, this measure can also cause considerable damage to children and their families with significant social and economic impacts, mainly on physical and mental health[7-11]. On the other hand, most evidence from countries that have reopened schools or never closed them, suggests that schools have not been associated with significant increases in community transmission[12-15]. Thus, the transmission of SARS-CoV-2 from paediatric patients both at home and in schools has been an intensely topic since the beginning of the COVID-19 pandemic, also regarding the emergency of new variant scenarios[16-19].

Since Catalan schools reopened in September 2020 after 6-months of closure, there have been 83,911 accumulated positive COVID-19 cases, of which 74,246 were students (5.16%) and 8,996 school staff (5.49%)[20]. Likewise, a recent study that analysed the incidence dynamics of SARS-CoV-2 infection in children in the first term of the school reopening shows that the infection rate among children remained lower compared with the general population for pre-school (3-6 years) and primary pupils (6-12 years) but was equal to it or higher in secondary students (12-18 years)[21]. Moreover, several studies have shown that in this pandemic very few cases infect many contacts (super-spreaders) while most cases either infect nobody or very few people and this includes paediatric index cases[22-26]. Defining host-related, viral and environmental patterns that determine these super-spreading situations is relevant to the tailoring of measures to minimize the transmission of SARS-CoV-2 in schools[27].

Preventive interventions play an important role in working together to gain control of the COVID-19 pandemic, also in schools. In this sense, the social and behavioural sciences can provide valuable insights into managing the pandemic and its impacts[28]. Non-pharmacological preventive interventions in schools such as physical distancing, hygiene, use of masks, restricting interactions to clusters of students in bubble-groups, massive microbiological testing and other safety measures are essential to prevent transmission[29]. These measures should be adapted to the setting and age group and prevent transmission while providing children with an optimal learning and social environment[4]. Furthermore, as it is known that SARS-CoV-2 transmission is via aerosols and virus-laden aerosols may easily accumulate in indoor environments, a proper ventilation of indoor spaces can be a great preventive measure[29]. Additionally, the first set of COVID-19 vaccines provided a pharmacological intervention in the last quarter of 2020 when they received the authorization for emergency use by the European Medicines Agency (EMA) and the Food and Drug Agency in the United States[30]. So far, teaching and non-teaching staff and population over 12 years are being vaccinated as defined in the Spanish vaccination strategy raising hopes for a better control of the epidemic inside school settings. In this context, there is a need to understand the epidemiology of SARS-CoV-2 in children once the adult population has been vaccinated. The pandemic is moving very fast, and behaviours and attitudes may change in response to the COVID-19 pandemic. Understanding the drivers of vaccine acceptance will be crucial to the success of COVID-19 mass vaccination campaigns.

Therefore, the use of periodical cross-sectional surveys on the knowledge, attitude and practice (KAP) associated with COVID-19 will allow rapid and adaptive monitoring of demographics, preventive behaviours, knowledge, and perceptions over time, among others, and can be useful in order to identify misinformation as they emerge.

This article reports the design and protocol of a school-based study in several sentinel schools in Catalonia. The study is part of the COVID-19 monitoring and evaluation plan from the Ministry of Health of the Government of Catalonia, and it is conceived as a participatory and transdisciplinary research process where the students and school staff will be invited to participate. The monitoring and evaluation provide practical information for making timely decisions, addressing community needs, and identifying more effective strategies for the prevention of COVID-19 spread and future infectious threats. In addition, the protocol could be highly useful for adaption into other educational settings for the monitoring of the COVID-19 pandemic.

GENERAL OBJECTIVES

1. To describe over time the knowledge, attitudes and behaviours (KAB) of students and school staff (teaching and non-teaching staff) towards SARS-CoV-2 infection and its prevention, as well as its impact in school settings.
2. To assess over time the prevalence of SARS-CoV-2 infection and seroprevalence of antibodies against SARS-CoV-2 and to identify associated sociodemographic, biological, behavioural and environmental factors among both children and staff.
3. To identify and describe multi-level determinants, barriers and needs of SARS-CoV-2 prevention related measures in school settings over time.
4. To assess the secondary attack rate of SARS-CoV-2 children index cases and its multilevel determinants and factors, both in school and family settings.
5. To analyse the impact of preventive and control measures on the occurrence of SARS-CoV-2 in school settings.
6. To pilot alternative testing and screening technologies and strategies, to assess their acceptability, feasibility and performance and the occurrence of SARS-CoV-2 infection among students and school staff.
7. To analyse the impact of different SARS-CoV-2 variants' transmission in school settings.
8. To facilitate a participatory process where the education community will act as co-researchers elaborating recommendations to improve the prevention and control measures in the school environment.
9. To evaluate the impact on students' learning, attitudes and motivations of their participation in the research process and the teacher's perspectives on this impact.

METHODS AND ANALYSIS

Study design and Setting

The population of Catalonia was 7,619,494 in 2019. The Catalan school system includes 1,582,466 students, 117,398 teaching staff and 5,492 school centres[31].

This project is based on sentinel schools defined as a network of schools representing the diversity of schools and the scholar population in Catalonia, and chosen using the following criteria:

- Volunteering/commitment of both the school management team and the teaching staff as well as the children's parents to participate in the project

- Representation of schools located in the different Basic Health Areas (BHA) and territorial areas will be ensured taking into account tertiles of SARS-CoV-2 accumulated incidence and tertiles of socio-economic deprivation index[32]
- Representation of schools with different characteristics:
    - Sociodemographic indicators. At least two-to-five high complexity schools characterized by low socioeconomic level and specific educational needs
    - Some schools located in rural areas[33]
    - Schools with all levels of education, small school size and school centres with professional training courses
    - Public, charter and private schools

The sentinel surveillance is carried out by means of serial cross-sectional and longitudinal school-based studies, direct observation, index case study and participatory research approach in children, adolescent and school staff from the selected sentinel schools. In a subset of schools (n=5), a cohort of students from first grade of secondary school to high school (12->18 years) and school staff has been stablished in order to monitor the COVID-19 incidence and the feasibility and acceptability of different periodical screening practices for COVID-19 confirmation. All the study interventions will be carried out in two academic years starting from January 2021 to June 2022 and the analysis will take place from June 2022 until the end of 2022.

Study population (Inclusion criteria)

- Students attending sentinel schools will be eligible for the study, from preschool (3-years-old) to high school (approximately 18-years-old)
- School staff of the sentinel schools, including teachers, administrators, canteen and cleaning staff, and other adults working in the educational settings such as extracurricular education instructors

Informed consent

Informed consent will be obtained from school staff, parents of children under 16 and pupils of 16 years-old or older. Participants will be free to decline/withdraw consent at any time without providing a reason and without being subject to any resulting detriment.

Study procedures

Summary information of questionnaires, biological samples and other information to be collected is provided in Table 1.

<u>Knowledge, attitudes and behaviours regarding COVID-19 (KAB) questionnaires and impact of preventive and control measures</u>

Each headteacher will send the study information pack (a study leaflet and the information sheet) and the link to the online informed consent and the baseline questionnaires by e-mail to the parents/guardians, school staff and older students (when necessary, on paper). We will send follow-up questionnaires twice a year. Three different questionnaire models will be designed: for teachers and other school staff (Questionnaire A); for students under 16, which will be answered by parents/guardian (Questionnaire B), and for students over 16 (Questionnaire C). The variables included in the KAB survey will be mainly based on the WHO recommendations, as described in WHO/Europe (2020)[34].

<u>Prevalence of SARS-CoV-2 active infection and seroprevalence of antibodies against SARS-CoV-2</u>

Cross-sectional study: A field team (FT) made up of three nurses and a field coordinator will visit each school equipped with personal protective equipment to collect the samples for testing.

They will schedule the number of intervention days with each participating school depending on school size. The following samples in the baseline and the following cross sectionals (twice yearly) will be collected from all participants: i) Nasal swabs to perform a transcription-mediated amplification assay (TMA) for detection of SARS-CoV-2; ii) Finger prick blood sample to assess with a quick anti SARS-CoV-2 IgM/IgG antibody test.

Longitudinal study: Follow-up interventions will be scheduled twice monthly during the school year as an alternative testing strategy. In each intervention, the FT will collect saliva and nasal specimens for the detection of SARS-CoV-2 by molecular or antigenic tests, respectively. The cohort participants will fill in an additional online epidemiological survey with information related to SARS-CoV-2 infection, their symptomatology, exposure and vaccine status.

Secondary attack rate and SARS-CoV-2 variants

This part of the study will be carried by the Paediatric Infectious Diseases and Immunodeficiencies Unit at Hospital Universitari Vall d'Hebron (HUVH). Data on COVID-19 index cases will be collected with appropriate social and geographical distribution. These cases will be detected by the routine data provided by the Catalan Public Health Department or detected during the study interventions and analysed in depth from then on. Data on demographic, social and clinical features, vaccination status, comorbidities and clinical outcome will be collected. School and household contacts will also be studied in depth to detect secondary cases. Samples from the index case and all COVID-19 confirmed contacts will be sequenced using whole genome sequencing (WGS) following the ARTIC Network protocol[35] for the characterization of SARS-CoV-2 (lineage and mutations), molecular tracing of sequences, and measurement of the viral load in these respiratory samples to assess its role in the transmission dynamics.

Environmental determinants and barriers

The environmental evaluation will be carried out by the ISGlobal team to obtain information on the structural characteristics of each participating sentinel school, ventilation practices and other environmental prevention measures using the KKmoon carbon dioxide detector device. This intervention will include: i) A structural evaluation by a field technician in at least one classroom for each grade; ii) Online twice yearly surveys addressed to teachers and headteachers regarding ventilation and other prevention practices; iii) Twice yearly 15-day assessment of CO_2, temperature and humidity – seven days assessed by the field technician and the remainder as an experimenting tool for students – in 5 to 8 previously chosen classrooms.

Participatory research

The project is conceived as a collaborative and transdisciplinary research project where the education community and families participate in different phases of the research process. They will act as co-researchers evaluating the prevention and control measure implementation of SARS-CoV-2 infection in the school environment with a systemic perspective, as well as elaborating their recommendations to improve the prevention and control strategy. This approach will be implemented in collaboration with the EC funded project CONNECT, which aims to improve science learning and increase students' motivation towards science careers by engaging schools, scientists and families to solve local challenges.

Participation will entail discussion groups: i) Online focus groups with teachers. Preliminary results of the bio-behavioural surveys will be shared and, based on these, they will be invited to analyse problems, opportunities and needs, and to develop proposals for improvement of prevention measures following a protocol; ii) Teachers conducting focus groups with their class-group students and then families, reproducing a similar protocol; iii) The edited list of recommendations will be presented by students to scientists and policy makers in an online conference; iv) Elaboration of the final list of recommendations; v) Capital science survey: a pre-

and post-intervention survey addressed to pupils regarding the science learning and students' attitudes and motivation, and a pre- and post-intervention survey addressed to teachers regarding the education process.

Sample management, microbiological analysis and test result communication

As described above, diverse biological samples will be collected during the study.

The finger prick blood collected at the baseline and the follow-up will be processed at the time of collection to perform a quick SARS-CoV-2 serological test (COVID-19 IgG/IgM Rapid Test Kit, Lambra, Spain) with sensitivities of 97,2% (IgG) and 87,9% (IgM), and specificities of 100% for both immunoglobulins as the manufacturers describe. This approach will be used to assess the exposure to SARS-CoV-2 infection or vaccination by the presence of antibodies. In addition, the nasal swab sample collected in the longitudinal study will be processed at the time of collection for detection of SARS-CoV-2 antigen using the Panbio COVID-19 Ag Rapid Test (Abbot, USA) with a sensitivity of 93.3% (95% CI: 83.8-98.2%) and specificity of 99.4% (95% CI: 97.0-100%) as the manufacturers describe. The nursing team will upload the rapid test results on an online research database using electronic tablets. These results will be introduced afterwards to the electronic health record of all participants, who will be able to consult them in the online patient health portal (La Meva Salut app). In case of Ag positive with IgG negative, the COVID-school manager, a new sanitary staff role acting as a liaison between the primary care team and the school centres, will activate the public health protocol established by the Catalan Ministry of Health[36].

Nasal swabs and saliva samples will be maintained at 4ºC during sampling procedures and transport to laboratory facilities. A molecular assay based on the transcription mediated amplification assay (Procleix SARS-CoV-2, Grifols) will be conducted in HUVH for detection of SARS-CoV-2 in nasal swabs, and RT-PCR assay (Allplex SARS-CoV-2/FluA/FluB/RSV, Werfen) will be conducted at the Hospital Universitari Germans Trias i Pujol (HUGTiP) laboratories to determine SARS-CoV-2 infection in saliva specimens. If the TMA assay (HUVH) or RT-PCR assay (HUGTiP) is positive, an active infection will be confirmed. Once the nasal samples have been tested, all positive specimens will be stored in sample collection C.0001145 on the *Instituto de Salud Carlos III* register. On the other hand, saliva samples with positive SARS-CoV-2 results will be frozen and stored at the IGTP-HUGTiP Biobank and conserved for two years. TMA/PCR results will be uploaded by the microbiology laboratories to the electronic health record, and the participants and their general practitioners or paediatricians will be able to check them.

Regarding the transmissibility study, nasopharyngeal or nasal swab samples from index cases and positive secondary cases will be sent to the HUVH laboratory for genetic SARS-CoV-2 characterisation, to measure the viral load and to detect other respiratory viruses. The genetic characterisation of SARS-CoV-2 will be performed through WGS according to the ARTIC Network protocol[35] by using MiSeq and NextSeq 2000 platforms (Illumina, CA, USA). Other respiratory viruses will be detected by a real-time multiplex RT-PCR assay (Allplex Respiratory Panel Assay, Seegene); total nucleic acids will be extracted using NucliSENS EasyMAG (bioMérieux, Marcy l'Etoile, France) or Microlab STARlet System (Hamilton, CA, USA) according to the manufacturer's instructions. Additionally, to measure the SARS-CoV-2 viral load, an in-house quantitative RT-PCR assay using the primer/probe set targeting the nucleocapsid protein (N1) and the human RNase P (housekeeping gene) from the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel will be carried out. The Ct values of the viral target will be normalized to a housekeeping gene based on the ΔCt method (Ctsample − Cthousekeeping gene) in order to minimize the variations due to the non-standardized collection of a heterogenous specimens.

Data management, data protection and patient confidentiality

Informed consents and the different surveys will be designed and published by means of the EUSurvey management system, an official online survey management tool of the European Commission. For those participants for whom online access is not possible, printed surveys will be distributed by the field team and afterwards digitalized. The periodical surveys from the cohort study will be published by means of the OpenTIC software.

After giving their consent to participate (or allow their child to participate), each participant will be allocated a unique participant ID number on enrolment to the study. This unique identifier will serve as a link to all the data needed for the study (questioners, biological samples). The file that relates the identifier or pseudonym to the personally identifiable data will be encrypted and the access to this file will be restricted to a very small number of authorized persons (EM, YD, JA, LA). The process will comply with the General Data Protection Regulation (GDPR) requirements.

Study definitions:

Given that all the participants attending the school should be asymptomatic, a confirmed COVID-19 case will be defined as any individual testing SARS-CoV-2 positive by molecular assays (PCR or TMA-based) or COVID-19 Ag Rapid Test (RAT) in a respiratory or saliva specimen[37].

A paediatric index case will be established when the child is the first confirmed COVID-19 case in the classroom noticed by health authorities or the research team[26]. A secondary case will be defined as a classmate or household contact subsequently testing positive for SARS-CoV-2 by molecular assay or RAT. Close contacts will be defined as all people who have shared space with a positive COVID-19 less than 2 metres away, for more than 15 minutes, without protection and from the 48 hours prior to the onset of symptoms. If the positive person has not had symptoms, onset will be defined as the date of performing the diagnostic test.

Variables collected

i) Individual data

- Sociodemographic and socioeconomic indicators: age, gender, ethnic origin, household and career, economic status, job situation of their parents in the case of pupils
- Clinical data and infection by SARS-CoV-2: symptoms, COVID-19 chronic symptoms, the duration of symptoms, reinfection of COVID-19, hospitalization, exposure, contact with positive cases
- Attitude, behaviour and knowledge regarding COVID-19 and preventive measures
- Pandemic impact indicators such as changes on mental and physic health and the purchasing power of parents and school staff
- Vaccination data: manufacturer, number of doses, date of doses, side effects of COVID-19 vaccine, refusal to vaccinate (date and reason)
- Attitude and usability of focus groups regarding scientific contribution

ii) Collective data

Number of classrooms, number of tables/classroom, number of pupils/m^2, school surface, schoolyard surface, concentration of CO_2, temperature and humidity in the classrooms.

iii) Ecological data

These data will be collected and provided by the Primary Care Services Information System (SISAP) and the Data analytics program for health research and innovation (PADRIS) and will include data from different data sources in order to obtain the information mentioned below:

- Number of new COVID-19 confirmed cases or tested positive for SARS-CoV-2 by TMA/PCR or RAT /total of residents.
- Number of new COVID-19 confirmed cases or tested positive for SARS-CoV-2 by TMA/PCR or RAT/total of tested people.
- Number of new COVID-19 confirmed cases or tested positive for SARS-CoV-2 by TMA/PCR or RAT/total of suspected cases.
- Number of confined classrooms/total number of classrooms.

Data analysis plan and sample size

We estimate a participation of 50-70% among the total of 11,000 individuals who are on the census at the 26 sentinel schools since not all potential participants are aware of the public health concern and due to other barriers. A descriptive analysis will be performed for all the main aforementioned variables collected: participant's sociodemographic characteristics, SARS-CoV-2 infection characterization, its associated factors, behaviour information and other outcomes of interest. For quantitative variables, we will use measures of central tendency and dispersion (mean, standard deviation, median, interquartile range, 95% confidence interval). For qualitative variables, we will calculate absolute frequencies and percentages. To estimate the statistical significance of time trends in SARS-CoV-2 laboratory confirmed cases we will use multivariate logistic regression analysis with robust standard errors clustered at the individual-level and school-level, adjusting for sociodemographic, environmental and school structural variables.

In order to address the fourth objective related to the transmissibility study, a descriptive analysis will be performed for all cases and contacts identified in school clusters. Analyses will include chi-square and independent sample t-test procedures to assess differences between super-spreaders and non-spreaders for index cases and secondary cases using socio-demographics, number of classmates and household contacts, clinical and environmental variables. Finally, we will use univariate and multivariate logistic regression models to assess the association between transmission risk factors and SARS-CoV-2 infection among index cases and close contacts. All models will be adjusted for gender, age, vaccination status, number of classmates, and household contacts and whether or not the index cases are symptomatic.

Global data on the COVID-19 epidemic in Catalonia and the school basic health area (BHA) will be collected to contextualize the current epidemic situation. Data will be provided globally and stratified by age groups and collectives. This data will be provided by the Catalan Agency for Quality and Health Assessment (AQuAS) and SISAP. Analysis of the interrupted time series of SARS-CoV-2 seroprevalence and COVID-19 confirmed cases will be performed to assess the public health implemented measures including vaccination programmes. The confirmed cases will be modelled as ARIMA processes to estimate the expected numbers to be compared to those observed and estimate the impact of the different analysed measures, to do this we will calculate absolute and relative changes between expected-observed confirmed cases in each time point of the implemented measures. Analysis will be conducted in R (R Core Team, 2014).

PATIENT AND PUBLIC INVOLVEMENT (PPI)

We will convene a virtual PPI panel, who will contribute to the dissemination of findings.

ETHICS AND DISSEMINATION

The ethical aspects of the present study include:

- Recruitment of participants with informed consent
- Collection and storage of biological samples
- Questionnaires with non-anonymized data
- Collection and storage of personal data

The confidentiality of data and other ethical considerations will be managed in accordance with the recommendations of the Spanish Law 14/2007 of 3 July, on Biomedical Research and the Spanish Royal Decree RD 1716/2011 of 18 November, which lays down the basic requirements for the authorisation and operation of biobanks for purposes of Biomedical Research and the treatment of biological samples of human origin. Informed consent is required for this project as is established in article 59 of the law.

The necessary measures will be taken to ensure the protection of personal data and their confidentiality, in accordance with EU Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (RGPD), and in the Spanish Organic Law 3/2018 of 5 December, for the protection of personal data and Guarantee of digital rights (LOPD-GDD).

The data protection office of the Ministry of Health of the Government of Catalonia has reached an agreement signed by all the organizations in the research team to align with all the ethical considerations mentioned above and recommended by the same office.

The data and results provided by this project will be valuable in the current context of the public health emergency of international concern declared by the WHO for the COVID-19 pandemic and taking into account the urgent need for information coming from COVID-19 studies.

The CEEISCAT research team will generate a quarterly report with qualitative and quantitative data to give feedback to the stakeholders. Findings from this study will be disseminated at national and international conferences, reported on the public webpage of the project and published in peer-reviewed journals.

Study registration

Ethical approval was obtained from the Foundation University Institute for Research in Primary Health Care Jordi Gol i Gurina (IDIAPJGol) ethics committee with code 20/192-PCV on 17 December 2020 and the Hospital Universitari Vall d'Hebron ethics committee with code PR(AMI)668/2020.

AUTHORS' CONTRIBUTIONS

All authors have read, reviewed and agreed to the finalized submitted version of the manuscript. Conceptualisation: JC. Design study: JC, CF, AS, AB, JR, JS, PS, AS and MG. Operational procedures: JC, JR, AB, CF, AC, JS, MG, AA, TP, IB, JF, RM, PS, AS, MS and JB. Resources: RF, JM, JMA, CC and JB. Writing and draft preparation: AB, CF, AC, AS, MS and RM. Writing, review and edition; all authors.

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COMPETING INTEREST STATMENT

All of the authors declare that they have no conflicts of interest.

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Table 1. Summary information of study procedures.

Type of intervention	Determination	Type of Test	Coordination	Frequency
Bio-behavioural questionnaires			CEEISCAT	
- Questionnaire A (teaching and non-teaching staff) - Questionnaire B (parents or foster parents of students under 16 years old) - Questionnaire C (16-years-old or older students)				Once during 2020-2021 school year and twice during 2021-2022 school year
Biological sampling			CEEISCAT	
Baseline - Blood from finger prick - Nasal swab sample Longitudinal study (> 1st grade of middle school and school staff) - Saliva sample - Nasal swab sample	Ab anti-SARS-CoV-2 Viral RNA (SARS-CoV-2) Viral RNA (SARS-CoV-2) SARS-CoV-2 Ag rapid test	LFA TMA RT-PCR LFA		Once during 2020-2021 school year and twice during 2021-2022 school year Bi-monthly
Environmental and structural evaluation in each sentinel school			ISGlobal	
- Environmental questionnaires (Directors and teachers) - Structural and environmental evaluation by a field technician - CO_2, humidity and temperature measurements	Prevention measures (e.g. ventilation practices)			Once during 2020-2021 school year and twice during 2021-2022 school year
Transmissibility study			HUVH	
- COVID-19 index cases - Household and classmate contacts evaluation - Secondary attack rate	Viral coinfections Viral RNA (SARS-CoV-2) SARS-CoV-2 characterisations Viral load measurement	RT-PCR TMA/PCR Whole genome sequencing Quantitative PCR assay		
Participatory research			Living lab (IRSICaixa)	
- Scientific capital surveys - Focus groups - List of recommendations - Annual school conference				Once during 2020-2021 school year and twice during 2021-2022school year

Ab: antibodies; Ag: antigens; LFA: Lateral flow assay; TMA: Transcription mediated amplification assay

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.