What do we know about COVID-19 in children in the 3rd year of the pandemic in Catalonia?

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Summary

The coronavirus 2019 disease (COVID-19) pandemic forced health-care professionals to join their effort of sharing real time data in coordinated research projects. Also, there was an initial concern, particularly among paediatricians, to know how this disease would affect children and adolescents. The aim of this article is to show the feasibility and the main results of a successful multidisciplinary paediatric research strategy, the COPEDI-CAT group, that integrates primary care along with hospitals and other non-medical professionals in Catalonia, Spain. The research group, with more than 170 professionals, has already published more than a dozen articles in high-impact factor journals, has participated in several national and international webinars and conferences, and has created a real-time space of debate to follow-up the COVID-19 pandemic. There are still ongoing studies and new collected data are reviewed, new projects are proposed, and punctual interventions in weekly meetings are made by professional experts on this disease (local and from other areas or countries). The COVID-19 pandemic has represented a unique opportunity to conduct a quality multidisciplinary research in pediatrics, and COPEDI-CAT could serve as a model for future research in other diseases that affect children and adolescents in our country.

Key words:
COVID-19. SARS-CoV-2. Paediatrics. Epidemiology. Children.

¿Qué sabemos de la COVID-19 pediátrica en el tercer año de la pandemia en Cataluña?

Resumen

La pandemia de la enfermedad por coronavirus 2019 (COVID-19) obligó a los profesionales de la salud a unir sus esfuerzos para compartir datos en tiempo real en proyectos de investigación coordinados. Además, hubo una inquietud inicial, sobre todo entre los pediatras, por saber cómo afectaría esta enfermedad a los niños y adolescentes. El objetivo de este artículo es mostrar la viabilidad y los principales resultados de una exitosa estrategia de investigación pediátrica multidisciplinar, el grupo COPEDI-CAT, que integra atención primaria junto con hospitales y otros profesionales no médicos en Catalunya, España. El grupo de investigación, con más de 170 profesionales, ya ha publicado más de una docena de artículos en revistas de alto factor de impacto, ha participado en varios webinars y congresos nacionales e internacionales, y ha creado un espacio de debate en tiempo real para el seguimiento de la pandemia de COVID-19. Todavía hay estudios en curso y se revisan nuevos datos recopilados, se proponen nuevos proyectos y se realizan intervenciones puntuales en reuniones semanales por parte de profesionales expertos en esta enfermedad (locales y de otras áreas o países). La pandemia de COVID-19 ha representado una oportunidad única para realizar una investigación multidisciplinar de calidad en pediatría, y COPEDI-CAT podría servir de modelo para futuras investigaciones en otras enfermedades que afectan a niños y adolescentes de nuestro país.

Palabras clave:
COVID-19. SARS-CoV-2. Pediatría. Epidemiología. Niños.

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Introduction

The outbreak of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Wuhan (China) at the end of 2019 was the starting point of the Coronavirus 2019 disease (COVID-19) pandemic in Europe in March 2020. At the same time as this was happening, there was a need for communication and joint research between health professionals, particularly among paediatricians in Catalonia (Spain), to know how this disease would affect children and adolescents. As a consequence, the COVID-19 paediatric research in Catalonia (COPEDI-CAT) was created as a network of paediatricians from Primary and Hospital health-care centres aiming to answer some of the research questions related to COVID-19 in children. The COPEDI-CAT research group was gradually expanded to other specialists from different research areas including epidemiology, microbiology, immunology, computational biology and also paediatricians from abroad working with SARS-CoV-2 infection.

The first published international studies about paediatric COVID-19 demonstrated a lower household SARS-CoV-2 transmission when the index cases were children[1]. In addition, SARS-CoV-2 seroprevalence studies demonstrated that this infection was proportionally increasing with the age[2]. On the other hand, children with SARS-CoV-2 infection were mostly asymptomatic or had mild symptoms, especially fever and cough, and a low percentage were hospitalized with a general good prognosis[3]. However, after the first pandemic wave, children diagnosed with a severe multisystem inflammatory syndrome (MIS-C) temporally associated with COVID-19 and long-COVID paediatric cases were reported.

In this context, COPEDI-CAT has focused its research in the following studies: SARS-CoV-2 household transmission, building up clinical predictive models for paediatric COVID-19 disease, long-COVID in children and adolescents, analysis of MIS-C cases in Catalonia to determine incidence and prevalence among the paediatric population, SARS-CoV-2 dynamics transmission in the schools (Sentinel Schools project), SARS-CoV-2 interaction with other respiratory viruses affecting children, and the report of possible adverse effects of the COVID-19 vaccine on children and adolescents.

The aim of this article is to show the feasibility of a successful multidisciplinary quality research strategy in COVID-19 that integrates primary care along with hospitals and other areas of research work in Catalonia.

Material and method

COPEDI-CAT research group was launched in July 2020. A secure digital database (REDCap©, Vanderbilt University, Nashville, USA) was initially used to collect all the paediatric COVID-19 cases diagnosed in the participating Catalan Primary Care centres and hospitals. In addition, other data was obtained from public administration agencies such as the Catalan Agency for Health Quality and Assessment (AQuAS), Primary Care Information Systems (SISAP) and Traçacovid website from the Department of Education of the Generalitat de Catalunya. Subsequently, as the pandemic was going on, and given the need for a multidisciplinary approach, the computational biology research group of the Department of Physics of the Universitat Politècnica de Catalunya (BIOCOM-SC, UPC) joined us, as well as the departments of Microbiology and Immunology of the Hospital Universitari Vall d'Hebron. Thus, the COPEDI-CAT group is currently made up of more than 170 professionals, paediatricians from Primary Care (n=111), paediatricians from public and private hospitals (n=55), microbiologists and immunologists (n=5), biophysics and bioengineers of the BIOCOM-SC research team, and international paediatric collaborators from Italy, UK, Chile, Costa Rica and other Latin American countries. This research initiative has received the institutional support of the Catalan Society of Paediatrics (SCP) since its launch.

There are weekly meetings where the ongoing studies are updated, data collected are reviewed, proposals for new projects are discussed, and journal club sessions, given by local and international paediatricians and professionals from other disciplines, are presented. In addition, a COPEDI-CAT website has been created (https://www.copedicat.cat/inici) with the aim of disseminating the research to all interested professionals. Moreover, due to the scientific production, it has been possible to create the Emerging Group of Paediatric Infectious Diseases (ReCaVip) at the IDIAP-Jordi Gol Institute, and an agreement has also been signed between Vall d'Hebron Research Institute (VHIR) and IDIAP-Jordi Gol with the aim of developing different projects in a coordinated manner between hospital and primary care.

Results

During last two years, the COPEDI-CAT network has participated in different national and international congresses and webinars (Table 1), and has led and published several studies around COVID-19 and children that are summarized in Table 2. The first study aimed to analyse epidemiological and clinical features and viral household transmission dynamics in COVID-19 patients aged <16 years. The secondary attack rate (SAR) was calculated, and logistic regression was used to assess associations between transmission risk factors and SARS-CoV-2 infection. The study included 1,040 COVID-19 patients, almost half

Table 1. Oral communications in congresses and webinars or courses of the COPEDI-CAT research group.

Oral communications in congresses		
Title	**Date**	**Congress**
Estudio COPEDI-CAT. Enfermedad pediátrica COVID-19 en Cataluña. Papel de los niños en la dinámica de la transmisión intradomiciliar del SARS-CoV-2	5-7/11/2020	I Congreso digital Asociación Española de Pediatría (AEP)
Papel de los niños en la transmisión del SARS-CoV-2. Estudio multicéntrico colaborativo entre atención primaria y hospitalaria	10/3-15/05/2021	Curso online de actualización en pediatría de la Asociación española de pediatría de atención primaria (AEPap)
La COVID a pediatria. No tot està als protocols	27-28/05/2021	I Reunió Anual Virtual de la SCP
Transmissió intradomiciliar del SARS-CoV-2 a Catalunya: quin paper tenen els nens?	27-28/05/2021	I Reunió Anual Virtual de la Societat Catalana de Pediatria
Característiques clíniques de la COVID-19 en nens a Catalunya	27-28/05/2021	I Reunió Anual Virtual de la Societat Catalana de Pediatria
Es pot dur a terme investigació d'alt nivell a pediatria d'atenció primària?	27-28/05/2021	I Reunió Anual Virtual de la Societat Catalana de Pediatria
Household SARS-CoV-2 transmission and children: a network prospective study	25-29/05/2021	The 39th Annual Meeting of the European Society of Paediatric Infectious Diseases ESPID 2021
Aplicación de modelos predictivos en el diagnóstico clínico de la infección por SARS-CoV-2 en población pediátrica	3-5/06/2021	II Congreso digital AEP
COVID-19 persistente pediátrico	3-5/06/2021	II Congreso digital AEP
Migraciones y pandemia: Impacto en salud	13-15/10/2021	XIX Congreso latinoamericano de Infectología pediátrica (SLIPE 2021)
Oral presentations in webinars and courses		
Title	**Date**	**Webinar or course**
Projecte COPEDI-CAT: COVID-19 pediàtrica a Catalunya	10/02/2020	IRSI Vall d'Hebron Institut de recerca (HVIR)
Manifestaciones pediátricas en la COVID-19. Kawasaki	23-25/09/2020	Actualización en el diagnóstico y tratamiento del COVID-19. Universidad Internacional Menéndez Pelayo Tenerife
COVID-19 in children: what's their role in viral transmission?	3/11/2020	King's Health Partner. European University Hospital Alliance
Projecte viu col·laboratiu Hospitalària i Atenció Primària	17/03/2021	XXXVIII Curs de Formació Continuada Pediatres de ponent
COPEDI-CAT	5/10/2021	Actualització Grup de Recerca. GT Malalties infeccoses. SCP
Lesiones aprendidas y consecuencias de la pandemia por SARS-CoV-2 en la edad pediátrica	7/10/2021	I Encuentro con el pediatra. Hospital Universitario Quirónsalud Madrid
Afectación por el virus del SARS-CoV-2 en el paciente pediátrico	7/10/2021	I Encuentro con el pediatra. Hospital Universitario Quirónsalud Madrid
Recerca catalana en la xarxa	8/10/2021	V Jornada catalana d'actualització en Infectologia pediàtrica
Novetats en vacunes en temps de COVID	8/10/2021	V Jornada catalana d'actualització en Infectologia pediàtrica
Sumant esforços per donar respostes a la COVID pediátrica a Catalunya	21/10/2021	Sessió Inaugural XXXIV Curs de Formació Continuada Dr. Riera. Consorci Sanitari de l'Anoia

(47.2%) were asymptomatic, 10.8% had comorbidities and 2.6% required hospitalization. Viral transmission was common among household members (62.3%), more than 70% (756/1,040) of paediatric cases were secondary to an adult, whereas 7.7% (80/1,040) were index cases. The SAR was significantly lower in households with COVID-19 paediatric index cases during the school period relative to summer (p=0.02) and compared to adults (p=0.006). We concluded that children were unlikely to

Table 2. Publications of the COPEDI-CAT research group.

Title	Journal	Reference
Household Severe Acute Respiratory Syndrome Coronavirus 2 Transmission and Children: A Network Prospective Study	Clinical Infectious Diseases Journal	*Clin Infect Dis.* 2021 Sep 15;73(6):e1261-e1269. doi: 10.1093/cid/ciab228.
Fever without source as the first manifestation of SARS-CoV-2 infection in infants less than 90 days old	European Journal of Pediatrics	*Eur J Pediatr.* 2021 Jul;180(7):2099-2106. doi: 10.1007/s00431-021-03973-9. Epub 2021 Feb 19.
Papel de los niños en la transmisión del SARS-CoV-2. Estudio multicéntrico colaborativo entre Atención Primaria y Hospitalaria	Revista Pediatria de Atención Primaria	*Rev Pediatr Aten Primaria.* Supl. 2021(30):58-61.
Los menores de 16 años apenas son relevantes en la evolución global de la pandemia por SARS-CoV-2	Revista Pediatria de Atención Primaria	*Rev Pediatr Aten Primaria.* 2021;23:91.
Conocimientos y retos sobre COVID-19 y población pediátrica	Revista Pediatria de Atención Primaria	*Rev Pediatr Aten Primaria* 2021;23:91.
Prevalence of thrombotic complications in children with SARS-CoV-2	Archives of Diseases in Childhood	*Arch Dis Child.* 2021 Nov;106(11):1129-1132. doi: 10.1136/archdischild-2020-321351. Epub 2021 Apr 30.
Treatment of Multisystem Inflammatory Syndrome in Children	New England Journal Medicine	*N Engl J Med.* 2021 Jul 1;385(1):11-22. doi: 10.1056/NEJMoa2102968. Epub 2021 Jun 16.
Reply to Darcis et al	Clinical Infectious Diseases Journal	*Clin Infect Dis.* 2022 Mar 1;74(4):747-749. doi: 10.1093/cid/ciab572.
A Bayesian Model to Predict COVID-19 Severity in Children	The Pediatric Infectious Disease Journal	*Pediatr Infect Dis J.* 2021 Aug 1;40(8):e287-e293. doi: 10.1097/INF.0000000000003204.
Age-dependency of the Propagation Rate of Coronavirus Disease 2019 Inside School Bubble Groups in Catalonia, Spain	The Pediatric Infectious Disease Journal	*Pediatr Infect Dis J.* 2021 Nov 1;40(11):955-961. doi: 10.1097/INF.0000000000003279.
Schools as a Framework for COVID-19 Epidemiological Surveillance of Children in Catalonia, Spain: A Population Based Study	Frontiers in paediatrics	*Front Pediatr.* 2021 Sep 8;9:754744. doi: 10.3389/fped.2021.754744. eCollection 2021.
Prevalence of asymptomatic SARS-CoV-2 infection in children undergoing hospital screening.	Enfermedades Infecciosas y Microbiología Clínica	*Enferm Infecc Microbiol Clin* (Engl Ed). 2021 Oct;39(8):415-416. doi: 10.1016/j.eimce.2020.10.008
Clinical spectrum of COVID-19 and risk factors associated with severity in Spanish children	European Journal of Pediatrics	*Eur J Pediatr.* 2022 Mar;181(3):1105-1115. doi: 10.1007/s00431-021-04306-6. Epub 2021 Nov 5.
Symptom-Based Predictive Model of COVID-19 Disease in Children	Viruses	*Viruses.* 2021 Dec 30;14(1):63. doi: 10.3390/v14010063.
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	BMJ Open	*BMJ Open*. 2022 Jan 25;12(1):e055649. doi: 10.1136/bmjopen-2021-055649.

cause household COVID-19 clusters or be major drivers of the pandemic, even if attending school[4].

Later on, our aim, as a COVID-19 paediatric research network, was to study the SARS-CoV-2 transmission within the schools in Catalonia collaborating with the BIOCOM-SC from the UPC. As a result of this collaboration we published the results of two studies[5,6]. In the first one[5], we analysed contagions of COVID-19 inside school bubble groups in Catalonia in the presence of strong non-pharmaceutical interventions from September to December 2020. We found that propagation inside of the bubble group was small. Among 75% index cases, there was no transmission to other members in the classroom, with an average specific reproductive number across all ages of 0.4. We found a significant age-trend in the secondary attack rates, concluding that the SAR depends on the school level and therefore on the age[5]. In the second study[6], we analysed the childhood (<18 years) COVID-19 incidence in Catalonia during the first 36 weeks of the 2020-2021 school-year comparing it with the incidence in adults. Despite a great diagnostic effort among children, the relative incidence of SARS-CoV-2 for <18 years was slightly lower than for the general population, and it increased with the age of the children. We concluded that a great diagnostic effort, including mass screening and systematic whole-group contact tracing, was associated with childhood SARS-CoV-2 incidence and lower positivity rate in the 2020-2021 school year, and schools were a key tool in epidemiological surveillance rather than being main drivers of SARS-CoV-2 incidence in Catalonia[6]. On the other hand, to evaluate and establish the diagnostic performance of the symptoms and signs (isolated and

in combination) in community-based children with suspected COVID-19, we aimed to propose a machine learning (ML) model to assess the need for a SARS-CoV-2 test in children, depending on their clinical symptoms[7]. The use of ML demonstrated an AUROC of 0.65 to predict a COVID-19 diagnosis in children, being the absence of high-grade fever the major predictor of COVID-19 in younger children, whereas loss of taste or smell was the most determinant symptom in older children. We concluded that although the accuracy of the models was lower than expected, they can be used to help paediatricians to provide a diagnosis when epidemiological data on the risk of exposure to COVID-19 is unknown[7].

We were awarded by the Fundació La Marató de TV3 2021 for the project "SARS-CoV-2 and other respiratory viruses in childhood: different approaches to define predictive models for their diagnosis and epidemiological evolution" with the expedient number 202134-30-31, with the aim to study epidemiological and clinical predictive models for SARS-CoV-2 and other respiratory viruses. The results of this study will serve for a thesis of a pre-doctoral student at the UPC. We also were awarded by the Fundación Prandi de Pediatría Extrahospitalaria for the project "Risk and Predictive Factors of Persistent COVID-19 in children and adolescents in Catalonia", to study the long-COVID syndrome in children and adolescents, and a guide for the management of persistent paediatric COVID-19 was launched in 2021 http://www.scpediatria.cat/?p=page/html/detallnoticia/4817. Finally, there are several ongoing studies about COVID-19 in children within the Sentinel Schools project (https://escolessentinella.cat), launched by the Departament de Salut i Educació de la Generalitat de Catalunya coordinated by the Centre d'Estudis Epidemiològics sobre el VIH/SIDA de Catalunya (CEEISCAT)[8].

Discussion

COPEDI-CAT has represented a great achieve in qualitative paediatric research in COVID-19 in Catalonia. The multidisciplinary network with primary care and hospital paediatricians working together with other professionals from different scientific and medical areas is crucial to explain the final result of these studies. In this sense, the BIOCOM-SC research team has been one of the pillars of the group with their modelling and analytical approach of the tackled studies. On the other hand, the departments of microbiology and immunology of the Vall d'Hebron University Hospital have provided the network with their expertise on the microbiological and genetic determinations and on the design and set-up of sentinel surveillance systems.

Networking for the study of paediatric COVID-19 disease has also been carried out in hospital-based settings, such as the EPICO-AEP group in Spain, which described risk factors associated to severe paediatric COVID-19 disease[9,10], described the clinical and epidemiology of MIS-C cases[11], and reviewed the characteristics of thrombotic complications of SARS-CoV-2 in the paediatric population[12], among other studies. In Europe, the European paediatric tuberculosis research group (ptbnet), formed by paediatricians working with paediatric tuberculosis since 2009, studied the characteristics of severe paediatric COVID-19 cases admitted to 82 hospitals in 25 European countries during the first pandemic wave[13]. The main findings of this study were that COVID-19 is generally a mild disease in children. However, a small proportion developed severe disease requiring ICU admission and prolonged ventilation, although fatal outcome was overall rare[13]. And finally, high-impact studies have been conducted in United Kingdom thanks to government incentives with population-based surveillance[14,15].

From the beginning of the COVID-19 pandemic to late-March 2022, 2,598,940 individuals under 20 years of age have been diagnosed in Spain (22.5% of a total of 11,532,101 cases), and 52 have died (15 since October 2021)[16]. In Catalonia, we have diagnosed 148 MIS-C cases and the prevalence of long-COVID in children is being studied, although it appears to be lower than in adults. Despite the low severity of COVID-19 in paediatrics, the long COVID-19 in children and the MIS-C cases have caused concern to the families and their paediatricians. For this reason, the COPEDI-CAT group has lastly focused on the research of these areas, with several ongoing projects. Globally, MIS-C outbreaks are infrequent, have declined along the time of the pandemic, and can give clinical spectrum ranging from fever and inflammation to myocarditis, shock, and aneurysms[17,18]. COPEDI-CAT preliminary results on the MIS-C cases in Catalonia point to a similar direction. On the other hand, long COVID-19 disease in children has an unknown prevalence and can limit the daily lives of the affected children and adolescents[19, 20]. These issues are being investigated by COPEDI-CAT, with a long COVID-19 study that includes a control group that should facilitate the assessment of its incidence.

We are convinced that the successful COPEDI-CAT model can persist over time with the aim to be replicated in other areas of the paediatric research. The active participation of primary care paediatricians has been and will keep being the key: their proximity to the community allows for a higher quality approach to children's health. Their collaboration with hospital paediatricians gives coverage to the whole clinical progress of infectious diseases in children, from mild infections to most serious cases.

We want to highlight the great value of the multidisciplinary and multicentric research networks, such as COPEDI-CAT, to achieve results that can impact in public health policies, applicable not only in the paediatric field but also in other medical research specialities. In fact, the transversality of this network offers a great example to the society to counteract potential fake-news that have been used to generate disinformation across the pandemic.

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