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Early Impact of Severe Acute Respiratory Syndrome Coronavirus 2 on Pediatric Clinical Research: A Pan-European and Canadian Snapshot in Time

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Objective To capture the early effects of the coronavirus disease 2019 (COVID-19) pandemic on pediatric clinical research.

Study design Pediatric clinical research networks from 20 countries and 50 of their affiliated research sites completed two surveys over one month from early May to early June 2020. Networks liaised with their affiliated sites and contributed to the interpretation of results through pan-European group discussions. Based on first detection dates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), countries formed 1 early detecting and 1 late detecting cluster. We tested the hypothesis that this clustering influenced clinical research.

Results Research sites were first impacted by the pandemic in mid-March 2020 (March 16 ± 10 days, the same date as lockdown initiation; $P = .99$). From first impact up until early June, site initiation and feasibility analysis processes were affected for >50% of the sites. Staff were redirected to COVID-19 research for 44% of the sites, and 75.5% of sites were involved in pediatric COVID-19 research (only 6.3% reported COVID-19 cases in their other pediatric trials). Mitigation strategies were used differently between the early and late detecting country clusters and between countries with and without a pediatric COVID-19 research taskforce. Positive effects include the development of teleworking capacities.

Conclusions Through this collaborative effort from pediatric research networks, we found that pediatric trials were affected and conducted with a range of unequally applied mitigations across countries during the pandemic. The global impact might be greater than captured. In a context where clinical research is increasingly multinational, this report reveals the importance of collaboration between national networks. (*J Pediatr* 2021;239:67-73).

The coronavirus disease 2019 (COVID-19) pandemic has impacted healthcare in many ways. Yet the impact on clinical research^{1,2} is unclear, even more so because different medical specialties might have been affected in different ways. For instance, although there have been reports in oncology³⁻⁵ (including pediatric oncology^{6,7}), there have been none of comparable extent in the broad field of pediatrics, where recent work includes calls to mitigate the impact on ongoing and future trials.^{8,9} This is perhaps because children are less directly impacted by COVID-19. Nonetheless, the organization of pediatric clinical research has been greatly affected by the pandemic. European pediatric clinical research national networks (Table I; available at www.jpeds.com) are part of conect4children, a pan-European network aimed at facilitating the development of pediatric therapies (<https://conect4children.org/>).^{10,11}

Like other organizations, national networks were facing the unknown when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected. This report is a joint effort from 19 European national networks and 2 Canadian networks to assess the impact on pediatric clinical research. This effort to capture and give meaning to information is a learning process for the global pediatric clinical research network and contributes to shaping its organization.

This study aimed to assess the early impact of the SARS-CoV-2 pandemic on the conduct and organization of pediatric clinical research on a multinational scale. Data were gathered from research centers across Europe and Canada and analyzed and interpreted collaboratively to comprehensively depict the situation. After observing that the countries formed 2 clusters differing in the timing of the pandemic and potentially in national attitudes to managing it, we tested the hypothesis that clinical research was more impacted where the virus had been present for longer. We also sought further evidence of inconsistency among countries in the mitigation strategies used to ensure trial continuity.

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COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Methods

This study was conducted in 20 countries. Information on the national networks involved (name and number of affiliated research sites) is provided in [Table I](#). A data collection phase using surveys was followed by an interpretation phase in which the data were analyzed and reviewed collaboratively by the national networks to provide a global perspective.

Surveys at the National Network and Research Site Levels

Two web-based surveys ([Appendix 2](#); available at www.jpeds.com) were designed by the French pediatric clinical research network (PEDSTART) ([Table I](#)) and administered in Google Forms (Google LLC). A first survey was developed and used to identify at the national and national network level (1) the composition of the national networks in terms of the number of affiliated research centers; (2) how countries were currently affected by the pandemic and the measures undertaken at the national, regional, and network levels; and (3) the impact on pediatric clinical research networks' activities. A second site-focused web-based survey then had to be disseminated by e-mail from the networks to their affiliated research sites. This latter survey was used to evaluate directly the impact of the pandemic on pediatric clinical research at the research site level.

After being pilot tested, the surveys were disseminated by e-mail to the national networks on May 5, 2020. The national networks and associated research sites initially had 10 days (May 5 to May 15, 2020) to complete the online surveys. More time was then allotted to maximize the number of respondents, resulting in the last submission of the site survey on June 11. (The average date of site survey completion was $May\ 15 \pm 9$ days). No answers were mandatory except contact details. Respondents could modify their responses by completing the questionnaire again and sending an e-mail notification.

Data Analyses and Pan-European Group Discussions

The data gathered during this initiative were curated by the French national network (PEDSTART). Raw data were first presented to the other national networks, and subsequent dedicated pan-European group discussions were organized. Pan-European group discussions with national networks were used to refine data interpretation by considering cultural, semantic, and other differences among countries. These discussions, in groups of approximately 10 national network representatives, allowed for a multinational interpretation of the results.

Dates were converted to number of days elapsed since January 1, 2020, for graphical representation and statistical analyses. Country clusters based on the date on which a first case of SARS-CoV-2 infection was detected were confirmed using Bayesian information criterion and optimal univariate *k*-means clustering.¹² Differences between clusters not related to clinical research are shown in [Table II](#) (available at www.jpeds.com). Nonbinary survey questions were

collapsed to binary outcomes for statistical analyses. Differences between clusters and between countries with or without a dedicated pediatric COVID-19 research taskforce were analyzed using the *t* test and the Fisher exact test for proportions. A significance level of 0.05 was used, and numerical data are presented as mean \pm SD.

Results

Pediatric Clinical Research National Networks Evaluating the Impact of the Pandemic

The 21 networks involved in this study ([Table I](#)) reported coordinating an average of 12 research sites in their countries (median, 10.5; range, 3-25). Values used for descriptive statistics are presented in [Table I](#). [Figure 1](#), A shows the number of pediatric clinical research sites from each national network that contributed to this study. There were an average of 3 research sites per national network. [Figure 1](#), B shows how many pediatric clinical studies each site was undertaking before the SARS-CoV-2 outbreak.

Different National Responses as Reported by the Networks

Countries were impacted and responded differently according to their pediatric clinical research networks. [Figure 2](#), A shows the delay from the first detected case of SARS-CoV-2 infection until the initiation of lockdown for each country. An early detecting cluster ($n = 7$ countries) detected a first case of SARS-CoV-2 infection significantly earlier than a late detecting cluster ($n = 11$ countries) ($P < .001$) ([Figure 2](#), A and [Table II](#)). The early detecting country cluster had a longer delay before going into lockdown ($P < .001$) ([Figure 2](#), A), and clusters did not differ with respect to lockdown initiation date and other metrics not related to pediatric research except population ([Table II](#)). Only 6 countries (5 shown in [Figure 2](#) and Czechia) reported that a pediatric COVID-19 taskforce was in place to help catalog current initiatives and predict consequences. Only German, Canadian, Polish, and British networks reported regional differences in the measures taken at this stage of the pandemic. National networks reported that recommendations for pediatric clinical research during the pandemic were issued by national societies for 39% of the countries (7 of 18).

Impacts of the SARS-CoV-2 Pandemic on Pediatric Clinical Research

A total of 50 pediatric clinical research sites ([Figure 1](#)) were involved in this study. The moment when the outbreak started affecting each pediatric research site's activity is plotted in [Figure 2](#), B. On average, pediatric research sites were first affected on $March\ 16 \pm 10$ days (median, March 16; range, February 3 to April 4), the same average date as initiation of lockdown. There was no significant difference between the dates of lockdown initiation reported by the networks and the dates of first impact on the activity reported by the sites ($P = .99$) ([Figure 2](#)). There was no

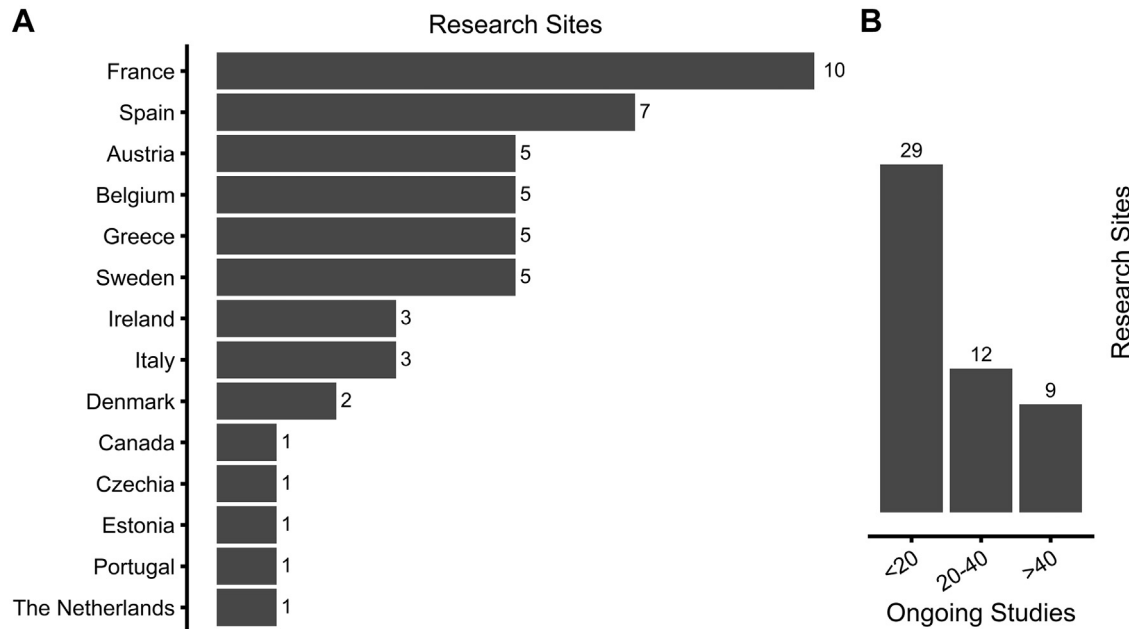


Figure 1. Pediatric clinical research sites that contributed to this study. **A**, Pediatric clinical research sites that contributed to this study, by national network and **B**, reported numbers of ongoing pediatric clinical studies in which these sites were involved before the outbreak. No sites associated with the following networks contributed to this study: Finland, Germany, Norway, Poland, Switzerland, and the United Kingdom. More than one-half of the sites (58%) were involved in less than 20 pediatric clinical studies, 24% of the sites in 20 to 40 studies, and 18% in more than 40 studies.

difference between the early detecting and late detecting country clusters (**Figure 2**, A) in the date of first impact on site activity ($P = .30$) (**Figure 2**, B and **Table II**), not supporting the hypothesis that clinical research was impacted differently in these countries.

Table III describes COVID-19 research at the various sites, how pediatric clinical research was impacted, and the mitigations used to ensure continuity of clinical trials during the pandemic. There again were no differences in the impacts on clinical research and COVID-19 research at sites between the early detecting and late detecting country clusters and between countries with a taskforce and those without a taskforce. Close to one-half (44%) of the research sites reported that some of their staff were redirected to COVID-19 research projects. Although 75.5% of the sites were involved in pediatric COVID-19 research projects, only 6.3% reported SARS-CoV-2 infections in children participating in non-COVID clinical trials. Sixty-six percent of the sites involved in this study reported that clinical research site initiation visits were cancelled, and 54.3% reported that the clinical trial feasibility analysis process was affected. There were reports of studies being temporarily or permanently discontinued. Fewer clinical research visits were performed during the pandemic at 36.7% of sites, a figure perhaps decreased by the involvement of some sites in COVID-19 projects. **Figure 3** shows the documented effect of the pandemic on pediatric clinical research visits at a French site (1 with more than 40 ongoing studies; **Figure 1**, B). Compared with 2019, there was an abrupt decrease in the number of visits performed during the first 2020 lockdown and an abrupt overshoot

afterward (**Figure 3**), resulting in a similar total annual number of visits performed.

In this context, mitigation strategies were used by research sites but inconsistently among countries. Some clinical research visits were reported to be replaced by phone calls for 85.7% of the surveyed sites and by home nurse interventions for 22.4% of them (**Table III**). Other procedures were put in place to ensure continuity of care and safety of enrolled patients and included sending study drug to patients' homes, performing biological safety assessments at patients' homes or at a nearby laboratory, and administering questionnaires and standard tests via telephone or videoconference (**Table III**). There were no differences between the early detecting and late detecting country clusters and between countries with and those without a taskforce on the mitigation strategies used except for sending study drugs to patients' homes that occurred more often in the early detecting cluster ($P < .01$) and in countries with a taskforce, with a difference close to statistically significant for the latter ($P = .06$) (**Table III**). Takeaway themes from group discussions and open-ended survey questions are presented in **Table IV** (available at www.jpeds.com), along with other mitigation strategies, concerns of research sites, and potentially positive effects of the pandemic.

Discussion

The present study is a multinational effort by pediatric clinical research national networks from Europe and Canada and their affiliated research sites to capture the acute effect of the outbreak on clinical research efforts. Although the extent of

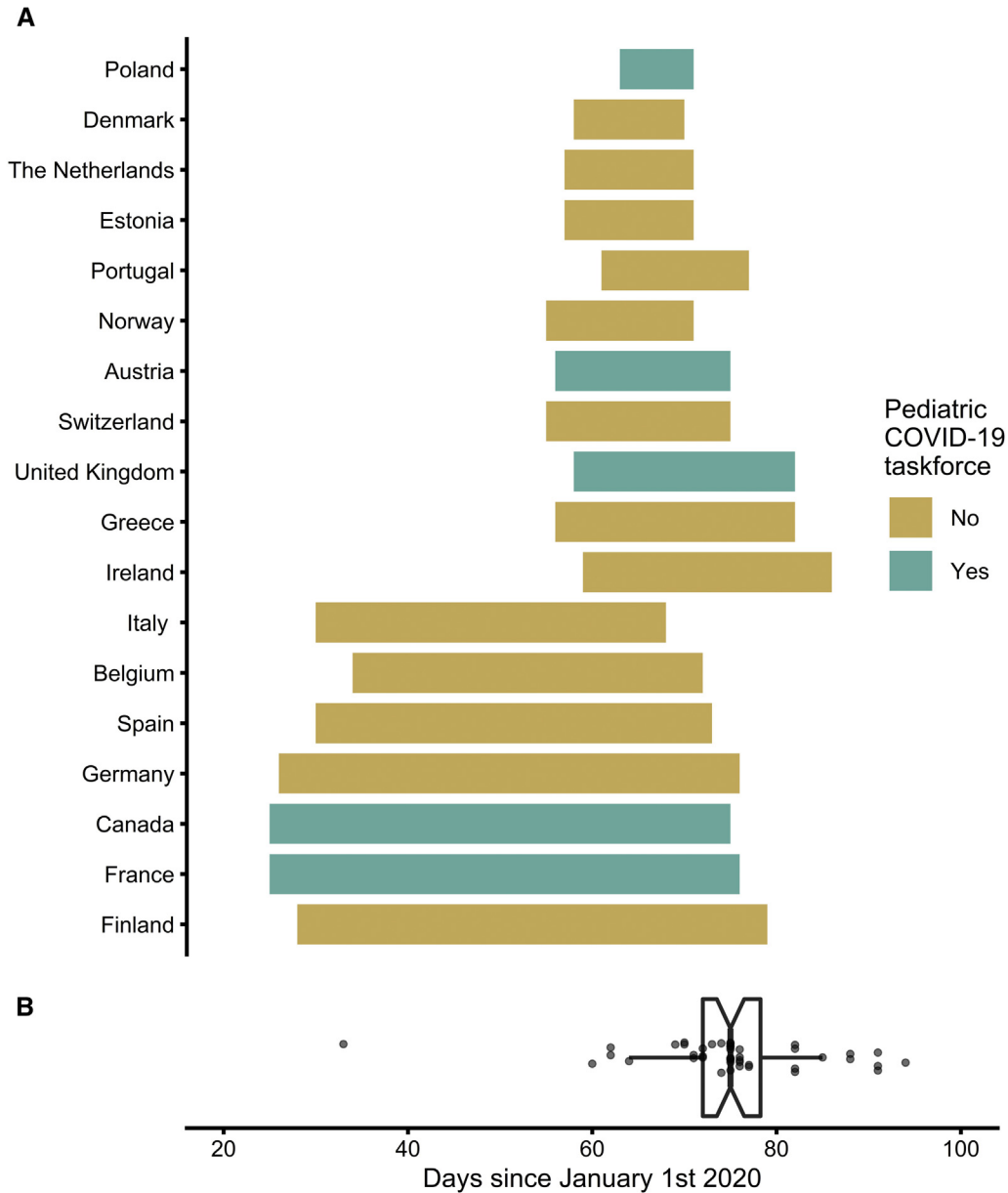


Figure 2. A, Delay per country from the first detected case of SARS-CoV-2 infection until lockdown initiation as reported by the pediatric clinical research National Networks. Bars start, the day the first case was detected, end the day of lockdown initiation, and are colored according to whether there was a pediatric COVID-19 taskforce put in place by the networks. Countries are sorted according to the length of the bars. No lockdown initiation date was provided by the Swedish network, no data on the first detected case was provided by the Czech network, and the values for Canada are the average for the 2 networks that contributed. Differences between country clusters are reported in [Table 2](#). Ten sites in [Figure 1](#) (20%) located in Austria (2 sites out of 5, 40%), Greece (3 sites out of 5, 60%), Italy (1 site out of 3, 33%), and Sweden (4 sites out of 5, 80%) reported not be in lockdown when they completed the survey. **B**, Date of first impact on the activity as reported by the pediatric clinical research sites. The box represents the interquartile range (IQR), the dark line represents the median, whiskers extend to 1.5 times the IQR, and notches give an estimate of the 95% CI around the median.

the impact and the measures undertaken have varied widely across countries and research sites, we provide a global overview of how pediatric clinical research was affected and reorganized in the early stage of the outbreak. Direct overload from COVID-19 was limited, but changes in pediatric research activities were substantial, with feasibility and site initiation processes impacted at >50% of the surveyed sites

([Table III](#)). This is in line with site initiation visit cancellations reported by the Innovative Therapies for Children with Cancer consortium.⁶

Twenty countries were involved ([Table I](#)). The average participation rate of 25% of national networks-affiliated research sites ([Figure 1, A](#)) is encouraging for follow-up studies. The data that we have gathered suggests the different

Table III. COVID-19 research at sites, impact on pediatric clinical research, and mitigation strategies used to ensure continuity of clinical trials

Variables	All sites, % (n/N)	Clusters			Taskforce		
		EDC, % (n/N)	LDC, % (n/N)	P	Negative, % (n/N)	Positive, % (n/N)	P
COVID-19 research at sites							
Staff redirection to COVID-19 research	44 (22/50)	50 (13/26)	33 (6/18)	.36	45 (15/33)	41 (7/17)	1.0
Staff involvement in pediatric projects	76 (37/49)	80 (20/25)	67 (12/18)	.48	82 (27/33)	63 (10/16)	.17
Impact on clinical research							
Initiation visit cancellations	66 (31/47)	68 (17/25)	71 (12/17)	1.0	72 (23/32)	53 (8/15)	.32
Feasibility process impacted	54 (25/46)	63 (15/24)	53 (9/17)	.75	56 (18/32)	50 (7/14)	.75
Less research visits on site	37 (18/49)	44 (11/25)	22 (4/18)	.20	39 (13/33)	31 (5/16)	.75
Mitigation strategies*							
Visits by phone call	86 (42/49) (100)	92 (24/26)	78 (14/18)	.21	88 (28/32)	82 (14/17)	.68
Visits by home nurse intervention	22 (11/49) (57)	27 (7/26)	11 (2/18)	.27	19 (6/32)	29 (5/17)	.48
Biological safety assessments at the patient's home or a nearby laboratory	23 (9/39) (36)	30 (7/23)	17 (2/12)	.45	15 (4/26)	38 (5/13)	.13
Questionnaires and standard tests by telephone or videoconference	72 (28/39) (79)	65 (15/23)	75 (9/12)	.71	77 (20/26)	62 (8/13)	.45
Sending study drug to the patient's home	26 (10/39) (29)	43 (10/23)	0 (0/12)	<.01	15 (4/26)	46 (6/13)	.06

EDC, early detecting cluster; LDC, late detecting cluster.

Population data were obtained from the World Bank (World Development Indicators, 2020). EDC, early detecting cluster (n = 7 countries); LDC, late detecting cluster (n = 11 countries).

*Percentages of countries in Figure 1 are also shown in parentheses for mitigation strategies.

countries were initially impacted at different rates by the pandemic (Figure 2, A and Table II). Previous nonpediatric reports have noted country-specific impacts of the pandemic on clinical research^{3,13}; for instance, at the time when a previous survey was administered, there was a smaller effect on enrollment in oncology trials in Asia compared with Europe and the US.³ This reinforces the dynamic nature of the pandemic and demonstrates that these differences between countries at one point in time could be the main caveat of the current analysis. Yet we found no difference on the impact on clinical research between the early detecting and late detecting country clusters and between countries with and those without a taskforce. The 28-day difference in

the initiation of lockdown between the early detecting and late detecting country clusters (Table II) could reflect national attitudes toward managing the pandemic. The extent to which this clustering is meaningful, besides reflecting population differences (Table II), is uncertain, given that the alternative of using 1 detected case per million inhabitants¹⁴ does not cluster countries in a similar way. Taken together, our data suggest that what impacts clinical research—and what did not differ much here between countries (Figure 2 and Table II)—is the timing of containment measures.

The impact of the pandemic was on average first felt by pediatric clinical research sites (Figure 1) in mid-March 2020 (Figure 2, B). Staff were mobilized to COVID-19 research in

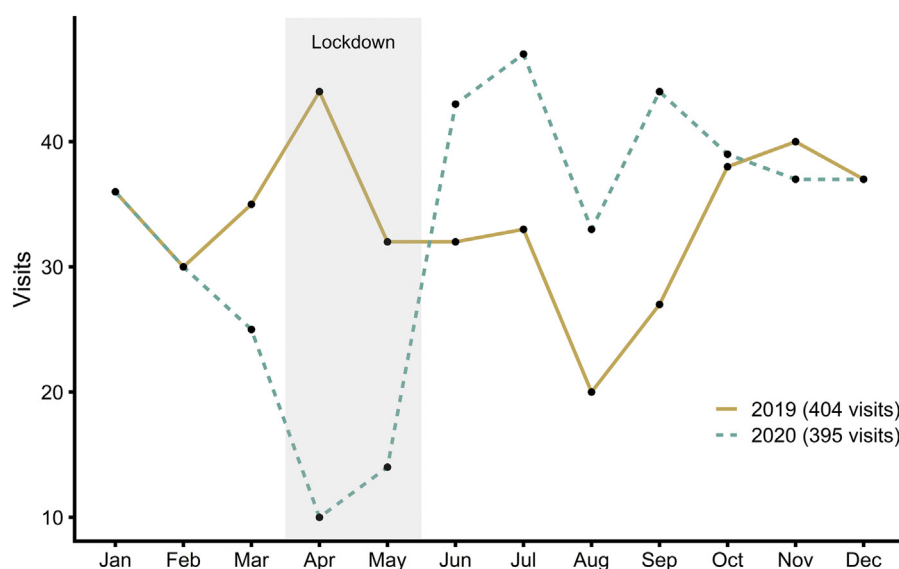


Figure 3. Effect of the pandemic on pediatric clinical research visits. Total visits per month documented at a French site (Lille University Hospital) in 2019 (solid line; 404 visits in total) and 2020 (dotted line; 395 visits in total). The gray-shaded area indicates the first 2020 lockdown (March 17-May 10).

some, but not all, sites (Table III). A substantial proportion of surveyed sites (76%) were involved in pediatric COVID-19 research as well. Non-COVID-19 studies that were perturbed and reorganized during the first lockdown were not disturbed much by SARS-CoV-2 infections in children. In parallel, it was reported that the lockdown appreciably reduced pediatric admissions and visits for viral and nonviral infections.¹⁵ Main pandemic hurdles for pediatric clinical research concerned the feasibility and site initiation processes for trials that had not yet started and patient visits to research centers for the ongoing trials (Table III). This is corroborated by more granular data from a French site showing patient visit cancellations during the early stage of the pandemic and the lockdown and a subsequent overshoot, with more visits than usual being performed after restrictive measures were lifted (Figure 3). More data to confirm whether this is generalizable are required, but this is in line with the decrease in new subject enrollment in many therapeutic areas in Europe and Asia reported for the same period.¹³ Sites' involvement in COVID-19 studies might explain why few sites reported performing fewer patient visits onsite (Table III).

Nonetheless, consistent with some special considerations formulated elsewhere,¹³ research sites applied mitigation strategies to ensure continuity of clinical trials but heterogeneously among countries (Tables III and IV). We found that the early detecting country cluster and countries with a pediatric COVID-19 taskforce were more prone to sending study drugs to the patients' homes. Given that the early detecting country cluster was ~3 times more populous (Table II), perhaps this mitigation strategy is more conceivable in larger countries. Understanding the underlying reason could help broaden its future use. Although mitigation ensured the continuity of clinical trials during the pandemic, questions also could be raised about the delivery of medicinal products to patients' homes and about the impact of visits performed remotely (as opposed to face-to-face) on the quality of clinical research. It could be argued that the latter are less reliable for gathering some types of data.

Owing to less travel, teleworking and teleconferencing decreased transportation and maintenance costs and reduced the environmental impact. Meetings were easier to organize. However, the involvement of network stakeholders is difficult to maintain by teleconference. It is also harder for newcomers to find their place (Table IV), and teleconferences do not allow for potentially important networking and exchange of ideas as in face-to-face meetings.

We acknowledge some limitations of this study, including the small sample size in terms of number of research sites within some national networks and differences among countries at the time of the survey, as well as potential semantic and cultural differences affecting interpretation of survey questions. The involvement of pediatric clinical research national networks (Table I) should have helped minimize the impact of the latter. The participation rate was lowered by national networks for which no affiliated site contributed (networks in Switzerland, Finland, Germany, and Norway).

Networks in the United Kingdom and Poland were excluded from the calculation because they did not disseminate the survey to their affiliated sites. The British network decided to not distribute the survey considering the level of COVID-19 research that was ongoing at the time of the survey and the pressure on the sites to deliver key COVID-19 research. Canada was also excluded because there is no official national network there. Two networks from Canada contributed to the current study, compared with 1 network in European countries (Table I); however, only 1 research site from Canada was involved (Figure 1, A). The assumption that each site survey respondent represents what national networks consider a distinct research site also could bias our estimate of the participation rate. Compared with lockdown initiation dates reported elsewhere,¹⁴ dates reported by the national networks differ slightly for some countries.

COVID-19 has brought unity across and within countries in pediatric clinical research. We have shared practices, which has allowed us to pinpoint potential areas of improvement. With this study, we show how pediatric clinical trials were impacted and reorganized in the early stage of the outbreak, with the major finding that a range of mitigation strategies was used, but these strategies were applied inconsistently in different countries. This crisis allowed us to develop and reflect on different ways of working. Above all, in a context in which clinical research is increasingly multinational, with both academic and industrial stakeholders, this work shows the value of collaboration among national networks. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Developmental Screening: The Value of Direct Observation of Skills

Frankenburg WK, Goldstein AD, Camp BW. The revised Denver Developmental Screening Test: its accuracy as a screening instrument. *J Pediatr* 1971;79:988-95.

Although developmental screening is commonplace today in medical settings, the concept was novel in 1971. The Denver Developmental Screening Test (DDST) was the first instrument and the most popular for 25 years. What happened?

The DDST was introduced by Frankenburg and Dodds in 1967 as an instrument to ascertain whether a child was demonstrating developmental delays. It relied on direct testing of the child in 4 developmental domains by trained individuals. Concerns arose that the DDST resulted in excessive over-referrals. In this article, a “conservative interpretation” of test scores was introduced wherein some who would have originally received a score of “abnormal” indicating the need for evaluation were now classified as “questionable” and some “questionable” results as “normal.” This new interpretation was validated on “the indigent population of Denver.” Greater validity was reported, with increased agreement (97% specificity, 92% sensitivity) between abnormal, questionable, and normal DDST ratings and criterion tests (the Bayley Infant Scales for children under 2 years; the Stanford-Binet, L-M for 2+) leading to only a 3.2% over-referral rate.

Fifty years later, developmental screening is commonplace, but the Denver has fallen out of favor due to concerns regarding over-referrals and cultural biases. Most current screenings use parent-completed questionnaires (eg, Ages and Stages, Parents’ Evaluation of Developmental Status [PEDS]) rather than direct testing. Although parent-report results have been found to align with direct testing, the value of multiple sources of information is stressed by professionals in the field,¹ who have long advocated for the importance of eliciting parental concerns and directly observing skills.

It seems the field has come full circle on the value of direct observation. Screening instruments for autism have begun incorporating videos of parents eliciting behaviors at home. Recently, the Food and Drug Administration approved Cognoa, a machine-learning vehicle for autism risk, using uploaded videos by parents.

In our collective mission to identify developmental delays early and initiate timely intervention, information from all sources, including parents, school/daycare, and direct observation, is valuable. As a result, we still use the Denver II in the Bronx.

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Appendix 1

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Table I. Pediatric clinical research national networks that contributed to this study

Country	National network	Affiliated sites
Austria	OKIDS GmbH	6*
Belgium	Safepedrug-BPCRN	9*
Canada	TARGet Kids!	12
Canada	Maternal Infant Child Youth Research Network	17
Czechia	CUNI	4*
Denmark	DanPedMed (Trial Nation)	16*
Estonia	University of Tartu (ELAV)	3*
Finland	HUS	10*
France	PEDSTART	15*
Germany	RBMF/GermanNetPaeT	23*
Greece	HELpnet	13*
Ireland	in4kids	11*
Italy	INCIPIIT	12*
Norway	NorPedMed	6*
Poland	Childrens Memorial Health Institute	10*
Portugal	STAND4Kids	10*
Spain	RECLIP	25*
Sweden	SwedPedMed	8-15*
Switzerland	SwissPedNet	9*
The Netherlands	Pedmed-NL	17*
United Kingdom	National Institute for Health Research (NIHR)	223†

*Values used for descriptive statistics.

†The network reported that there are 223 National Health Service trusts that are automatically affiliated with the NIHR.

Table IV. Takeaway themes from group discussions and open-ended survey questions

Main themes	Subthemes
Network sustainability	Concerns that the absence of face-to-face interactions combined with a high rate of staff turnover would weaken the networks and affect the integration of new members
Mitigation strategies at sites	Other mitigation strategies than reported in Table III ; blood sampling at home; rescheduling patients visits when clinical activity was lower; delivering more than usual medication to prevent visits to the hospital; using both visits by phone call and home nurse intervention for some protocols
Concerns of research sites	Financial issues because COVID-19 studies are prioritized; delays for future and ongoing pediatric clinical research
Development during the pandemic	Teleworking, teleconsulting, teleconferencing; communication capabilities; team cohesion and collaboration

Table II. Differences among country clusters

Variables	EDC	LDC	P value
First detected case	29/01 ± 3 d	27/02 ± 2 d	<.001
Delay to lockdown, d	46 ± 6	18 ± 6	<.001
Lockdown initiation	15/03 ± 4 d	16/03 ± 6 d	.52
Population, × 10 ⁶ inhabitants	44.6 ± 28.6	16.2 ± 19.5	<.05

EDC, early detecting cluster; LDC, late detecting cluster.

Population data were obtained from the World Bank (World Development Indicators, 2020). EDC, early detecting cluster (n = 7 countries); LDC, late detecting cluster (n = 11 countries).