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Rola dzieci w transmisji SARS-CoV-2 i leczenie COVID-19 w populacji pediatrycznej

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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Wykaz publikacji stanowiących pracę doktorską

1. Okarska-Napierała M, **Mańdziuk J**, Kuchar E. SARS-CoV-2 Cluster in Nursery, Poland. Emerging Infectious Diseases. 2021 Jan;27(1):317–319. doi: 10.3201/eid2701.203849. Epub 2020 Oct 19.

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2. **Mańdziuk J**, Okarska-Napierała M, Woźniak W, Hryniewicka A, Radziński P, Gambin A, Podsiadły E, Demkow U, Kuchar E. Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave. Pediatric Infectious Disease Journal. 2023 Dec 1;42(12):1086-1092. doi: 10.1097/INF.0000000000004079. Epub 2023 Sep 7.

Punktacja MNiSW: 100 pkt, Impact Factor: 2.9

3. **Mańdziuk J**, Kuchar E, Okarska-Napierała M. How international guidelines recommend treating children who have severe COVID-19 or risk disease progression. Acta Paediatrica. 2024 Nov;113(11):2345-2353. doi: 10.1111/apa.17354. Epub 2024 Jul 10.

Punktacja MNiSW: 100 pkt, Impact Factor: 2.4

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Spis treści

Wykaz stosowanych skrótów (w kolejności alfabetycznej)

CDC - ang. Centers for Disease Control and Prevention

COVID-19 - choroba koronawirusowa 2019

DSK UCK WUM - Dziecięcy Szpital Kliniczny Uniwersyteckie Centrum Kliniczne Warszawskiego Uniwersytetu Medycznego

IDSA – ang. Infectious Diseases Society of America

NICE - ang. National Institute for Health and Clinical Excellence

NIH - ang. National Institutes of Health

OITD – Oddział Intensywnej Terapii Dziecięcej

PCR - reakcja łańcuchowa polimerazy

SARS-CoV-2 (ang. severe acute respiratory syndrome coronavirus 2) - drugi koronawirus ciężkiego ostrego zespołu oddechowego

WHO (ang. World Health Organization) – Światowa Organizacja Zdrowia.

Streszczenie w języku polskim

Rozprawę doktorską stanowią trzy publikacje w języku angielskim, których tematyka dotyczy COVID-19 u dzieci. Tematy prac badawczych odzwierciedlają zagadnienia, które stanowiły przedmiot zainteresowania zarówno naukowców, jak i lekarzy praktyków w miarę postępu pandemii. W pierwszych miesiącach pandemii dominował pogląd, że dzieci prawdopodobnie rzadko zakażają inne dzieci i dorosłych wirusem SARS-CoV-2, a na COVID-19 chorują rzadziej i łagodniej niż dorośli. W piśmiennictwie pojawiały się doniesienia o znikomej roli dzieci w przenoszeniu wirusa m.in. w środowisku szkolnym. W pierwszej publikacji z cyklu, pt. „*SARS-CoV-2 Cluster in Nursery, Poland*", która ukazała się w czasopiśmie agencji rządu Stanów Zjednoczonych *Centers for Disease Control and Prevention (CDC)* opisaliśmy ognisko COVID-19 wśród dzieci w żłobku. Po dochodzeniu epidemiologicznym, z pomocą lokalnej Stacji Sanitarno-Epidemiologicznej oraz po zapoznaniu się z zasadami dotyczącymi zapobiegania zakażeniu w żłobku wykazaliśmy, że dzieci musiały być źródłem infekcji w swoich domach, czyli zakaziły osoby dorosłe. W kolejnych miesiącach pandemii badano rozprzestrzenianie się wirusa SARS-CoV-2 w środowisku domowym. Szukano czynników, które mogą przyczyniać się do zwiększenia transmisji pomiędzy członkami rodzin. Przypuszczano, że zaraźliwość wirusa może zmieniać się wraz z pojawianiem się jego nowych wariantów oraz rozpowszechnieniem szczepionek przeciwko COVID-19. W drugiej publikacji z cyklu, pt. „*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*" oceniliśmy, jak często dzieci były pierwszymi zakażonymi osobami w swoim domu oraz przy użyciu metody Monte-Carlo zidentyfikowaliśmy czynniki ryzyka bycia pierwszym zakażonym domownikiem. Uczęszczanie dzieci do placówek edukacyjnych korelowało z byciem pierwszym zakażonym domownikiem we wszystkich grupach wiekowych. Taką samą korelację zaobserwowaliśmy w podgrupie rodzin, w których przeważającym wariantem był SARS-CoV-2 Delta, w przeciwieństwie do podgrupy rodzin z dominującymi pozostałymi wariantami wirusa. Od początku pandemii trwały również intensywne prace nad leczeniem przyczynowym COVID-19. Wytyczne dotyczące leczenia dzieci są głównie ekstrapolowane z wytycznych dla dorosłych i opierają się na doświadczeniu klinicznym. W ostatniej publikacji z cyklu, pt. „*How international guidelines recommend treating children who have severe COVID-19 or risk disease progression*" podsumowaliśmy wytyczne dotyczące leczenia COVID-19 u dzieci opublikowane przez gremia naukowe o międzynarodowym zasięgu. Porównaliśmy brytyjskie wytyczne *National Institute for Health and Clinical Excellence (NICE)*, amerykańskie

wytyczne *National Institutes of Health (NIH)* oraz wytyczne *Infectious Diseases Society of America (IDSA)* i wytyczne australijskie. Przedstawiliśmy je w formie przyjaznej praktykom. Podsumowując, w toku prowadzonych prac wykazaliśmy, że dzieci mogą pełnić istotną rolę w transmisji zakażenia SARS-CoV-2 do środowiska domowego. Rola dzieci w pandemii COVID-19 prawdopodobnie zmienia się wraz z kolejnymi wariantami wirusa. Wytyczne leczenia COVID-19 są zgodne, że należy rozważyć leczenie przeciwko COVID-19 u dzieci z ciężkim przebiegiem choroby oraz u dzieci z wysokim ryzykiem ciężkiego przebiegu choroby. Wybór właściwego leczenia jest uzależniony od czasu, który upłynął od rozpoczęcia choroby do wdrożenia leczenia oraz przebiegu klinicznego choroby.

Streszczenie w języku angielskim

Title: The Role of Children in SARS-CoV-2 Transmission and COVID-19 Treatment in the Pediatric Population

The doctoral dissertation consists of three publications in English, all focused on COVID-19 in children. The topics of the research reflect issues that were of interest to both scientists and practicing physicians as the pandemic progressed. In the early months of the pandemic, it was believed that children were unlikely to infect other children or adults with SARS-CoV-2 and develop COVID-19 less frequently and with milder symptoms than adults. Reports in the literature suggested that children play a minimal role in virus transmission, particularly in school settings. The first publication in the series, entitled '*SARS-CoV-2 Cluster in Nursery, Poland*', published by the U.S. *Centers for Disease Control and Prevention (CDC)*, describes a COVID-19 outbreak among children in a nursery. After an epidemiological investigation, in collaboration with the local sanitary-epidemiological office, and an analysis of infection prevention measures at the nursery, we demonstrated that children were the source of infection in their households, meaning they transmitted the virus to adults. In the following months of the pandemic, the spread of SARS-CoV-2 in the household environment was studied, and researchers explored factors that could increase transmission between family members. It was hypothesized that SARS-CoV-2 infectivity might change with the emergence of new variants and the widespread use of COVID-19 vaccines. In the second publication, entitled '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*', we assessed how often children were the first infected individuals in their households and, using the Monte Carlo method, we identified risk factors of being the first infected household member. Children's attendance at educational facilities was correlated with being the first infected household member in all age groups. We observed the same correlation in the subset of families where the Delta variant was predominant, as opposed to the subset where other variants were dominant. Since the beginning of the pandemic, significant efforts have also been made to develop effective treatments for COVID-19. Guidelines for treating children are primarily extrapolated from adult treatment protocols and based on clinical experience. In the final publication of the series, entitled '*How international guidelines recommend treating children who have severe COVID-19 or risk disease progression*', we summarized international guidelines concerning the treatment of COVID-19 in children. We compared the British guidelines from the *National Institute for Health and Clinical Excellence*

(NICE), the U.S. guidelines from the *National Institutes of Health (NIH)*, the guidelines from the *Infectious Diseases Society of America (IDSA)*, and Australian guidelines. We presented them in a format that is practitioner-friendly. In conclusion, our research showed that children can play a significant role in the transmission of SARS-CoV-2 within households. The role of children in the COVID-19 pandemic likely changes with the emergence of new virus variants. COVID-19 treatment guidelines recommend considering treatment for pediatric patients with severe COVID-19 and for children at high risk of severe disease. The treatment choices depend on the clinical course of the disease and the time since the disease's onset.

Wstęp uzasadniający połączenie wskazanych publikacji w jeden cykl, jak i komentujący osiągnięcie naukowe kandydata na tle dotychczasowego stanu wiedzy

1. Wstęp

W marcu 2020 roku Światowa Organizacja Zdrowia (WHO) ogłosiła stan pandemii choroby koronawirusowej 2019 (COVID-19). W ciągu 3 lat trwania pandemii ponad 7 milionów ludzi na całym świecie zmarło z powodu COVID-19 (1). W ciągu ostatnich kilku lat trwały intensywne prace nad patogenezą zakażenia SARS-CoV-2, nad drogami transmisji oraz środkami zapobiegającymi rozprzestrzenianiu się wirusa, a także nad leczeniem COVID-19. Co istotne, wraz z pojawianiem się kolejnych wariantów wirusa, a także zmieniającym się stanem uodpornienia społeczeństwa, zaraźliwość COVID-19 oraz przebieg kliniczny choroby zmieniały się. Rozprawę doktorską stanowią trzy publikacje w języku angielskim, których tematyka dotyczy COVID-19 u dzieci. Tematy prac odzwierciedlają zmieniające się pytania badawcze, jakie stawiano sobie w kolejnych latach pandemii.

2. Transmisja SARS-CoV-2 w placówkach opiekuńczych dla dzieci

W pierwszych miesiącach pandemii dominował pogląd, że dzieci prawdopodobnie sporadycznie zakażają inne dzieci i dorosłych wirusem SARS-CoV-2 (2, 3). W piśmiennictwie pojawiały się doniesienia o znikomej roli dzieci w przenoszeniu wirusa m.in. w środowisku szkolnym (4, 5). Kwestionowano zasadność odgórnego zamykania placówek edukacyjnych dla dzieci (6, 7). Należy jednak brać pod uwagę, że prace publikowane na początku pandemii miały pewne ograniczenia. Dane pozyskiwane były w okresie „lockdownu", w którym kontakty towarzyskie dzieci były ograniczone głównie do członków rodziny. Trudno więc było wyciągać pewne wnioski co do roli dzieci w przenoszeniu zakażenia. Kolejnym ograniczeniem powyższych badań był fakt, że odnosiły się głównie do populacji dzieci w wieku szkolnym. Pomijano w badaniach dzieci małe, pozostające w placówkach opiekuńczych, tj. przedszkolach czy żłobkach, gdzie charakter kontaktów społecznych sprzyja przenoszeniu infekcji. Tymczasem w badaniu Heald-Sargent i wsp. wykazano, że stężenie SARS-CoV-2 w nosogardle jest najwyższe właśnie u najmłodszych dzieci, z czym początkowo wiązano możliwą większą zaraźliwość małych dzieci (8).

W pierwszej pracy z cyklu, zatytułowanej „*SARS-CoV-2 Cluster in Nursery, Poland*" opisaliśmy ognisko zachorowań na COVID-19 w żłobku, w którym wirusa przenosiły małe dzieci zakażając siebie nawzajem oraz członków swoich rodzin. W tamtym czasie, zgodnie z ogólnokrajowymi zasadami testowania ludzi na COVID-19, badano osoby objawowe oraz skontaktowane z osobą z potwierdzonym zakażeniem. W opisanym ognisku zbadano łącznie 106 osób, z których 29 (27%) miało dodatni wynik testu reakcji łańcuchowej polimerazy (PCR) w kierunku zakażenia SARS-CoV-2. Odsetek pozytywnych testów na terenie kraju wynosił wówczas jedynie 0,01, można więc przyjąć założenie, że osoby dodatnie zakaziły się w tym ognisku. Dodatni wynik badania w kierunku SARS-CoV-2 miało 8 dzieci ze żłobka oraz 12 członków ich rodzin (9 osób dorosłych i 3 dzieci, rodzeństwa). Kontakty pracowników żłobka z rodzicami dzieci były bardzo ograniczone – rodzice odbierali dzieci przed budynkiem żłobka; dzieci były wyprowadzane na zewnątrz przez pracowników, którzy nosili maski chirurgiczne. Między tymi dwoma grupami dorosłych – pracownikami żłobka oraz rodzicami dzieci – zachodził jedynie kontakt pośredni poprzez dzieci uczęszczające do placówki. Opisane przez nas ognisko stanowiło dowód na to, że wbrew dotychczasowym doniesieniom w piśmiennictwie, dzieci przeniosły zakażenie na rodziców i swoje rodzeństwo. Wyjaśnieniem tej sytuacji mogły być szczególnie bliskie kontakty, jakie zachodzą między małym dzieckiem a jego opiekunem, niemożność pełnego stosowania się do zasad higieny wśród tak małych dzieci, jak również przedłużony kontakt między dziećmi w zamkniętym pomieszczeniu. Publikacja była opisem sytuacji epidemiologicznej w jednym ośrodku, ale zakwestionowała ówczesny stan wiedzy. Wyniki pracy opublikowane w amerykańskim czasopiśmie *Centers for Disease Control and Prevention (CDC)* spotkały się z dużym zainteresowaniem, nie tylko ze strony innych badaczy (18 cytowań w bazie Scopus), ale również mediów (opis badania został opublikowany w amerykańskim wydaniu Newsweeka). Wyniki pracy zostały uwzględnione w opisie wpływu Warszawskiego Uniwersytetu Medycznego na funkcjonowanie społeczeństwa i gospodarkę w okresie 2017-2021. Publikacja została również zacytowana w raporcie UNICEF '*The Evolving Epidemiologic and Clinical Picture of SARS-CoV-2 and COVID-19 Disease in Children and Young People*'(9).

3. Transmisja SARS-CoV-2 w środowisku domowym

W pierwszych miesiącach pandemii zakładano, że dzieci zwykle zakażają się wirusem SARS-CoV-2 w środowisku domowym, od dorosłych członków swojej rodziny. Rzadziej

obserwowano zakażenie dziecka w placówce edukacyjnej lub z innych źródeł. W związku z tym zakładano, że dzieci rzadko chorują jako pierwsze spośród domowników i „wprowadzają" SARS-CoV-2 do swoich domów (10-12). Niemniej przypuszczano, że sytuacja mogła ulec zmianie po zniesieniu ograniczeń kontaktów międzyludzkich związanych z „lockdownem" oraz w związku z pojawianiem się nowych wariantów wirusa SARS-CoV-2 (13-15). Szczególnie podczas wzrostu zakażeń wariantem B.1.1.529 (Omikron) zauważono, że dzieci przyczyniły się do zachorowania innych członków rodziny w swoich domach (16).
Ocena transmisji SARS-CoV-2 i precyzyjne prześledzenie kolejności zakażeń wśród domowników są trudne. Przyczyniają się do tego stosunkowo długi okres inkubacji, duży odsetek bezobjawowych zakażeń oraz złożona sieć interakcji międzyludzkich. W celu określenia, kto był pierwszą zakażoną osobą w danym środowisku (np. domowym), badacze musieli przyjąć pewne założenia, które my również wykorzystaliśmy w swojej analizie (opisane poniżej).

W drugiej publikacji z cyklu, „*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*" oceniliśmy, jak często dzieci były pierwszymi zakażonymi osobami w swoim domu oraz zidentyfikowaliśmy czynniki ryzyka bycia pierwszym zakażonym domownikiem. Grupą badaną były dzieci hospitalizowane lub testowane w kierunku zakażenia SARS-CoV-2 w Dziecięcym Szpitalu Klinicznym Uniwersyteckiego Centrum Klinicznego Warszawskiego Uniwersytetu Medycznego (DSK UCK WUM) od września 2021 do stycznia 2022 z potwierdzonym zakażeniem SARS-CoV-2 (badaniem PCR lub testem antygenowym) oraz członkowie ich rodzin. Do badania włączaliśmy dzieci testowane przed planowymi hospitalizacjami, dzieci pracowników szpitala testowane w naszym ośrodku, jak również dzieci hospitalizowane w Szpitalnym Oddziale Ratunkowym i oddziałach szpitala. W przypadku zakażeń potwierdzonych testem PCR, wykonaliśmy serotypowanie wariantu wirusa (Delta lub nie-Delta). Zebraliśmy informacje dotyczące każdego domownika: data pierwszych objawów COVID-19, jeśli były obecne; rodzaj i wynik testu w kierunku COVID-19, jeśli był wykonany; dane demograficzne: wiek i płeć; status zaszczepienia oraz kontakty społeczne przez dwa ostatnie tygodnie przed zachorowaniem (uczęszczanie do pracy/placówki edukacyjnej lub hospitalizacje). U każdego domownika z zakażeniem SARS-CoV-2 ustalaliśmy datę początku zachorowania zdefiniowaną jako wcześniejszą z następujących dat: data początku objawów lub data wykonania testu w kierunku COVID-19 z wynikiem pozytywnym. Jako pierwszego zakażonego domownika („*index case*") uznawaliśmy osobę, która miała najwcześniejszą datę początku zachorowania. Do badania

włączyliśmy rodziny, w których możliwe było ustalenie, kto był pierwszym zakażonym domownikiem. Ostatecznie badaniem objęliśmy 515 rodzin. Dziecko było pierwszym zakażonym domownikiem w 359 domach (prawie 70%). Użyliśmy metody Monte Carlo w celu oceny czynników predykcyjnych bycia pierwszym zakażonym domownikiem w rodzinie. Uczęszczanie do placówek edukacyjnych i opiekuńczych było skorelowane z byciem pierwszym zakażonym domownikiem we wszystkich grupach wiekowych. Ponadto, starszy wiek dziecka również okazał się istotnym predyktorem bycia pierwszym zakażonym domownikiem.

W celu uwiarygodnienia naszych wyników analizę przeprowadziliśmy także w podgrupie 234 rodzin, w których wszyscy domownicy zostali przetestowani w kierunku zakażenia SARS-CoV-2. Co interesujące, w grupie rodzin z zawężonymi kryteriami włączenia starszy wiek dziecka okazał się nieistotny statystycznie, a uczęszczanie do placówek opiekuńczych w każdej grupie wiekowej wciąż pozostało czynnikiem ryzyka bycia pierwszym zakażonym domownikiem. Wynik dotyczący wieku należy więc interpretować z ostrożnością. Płeć, status zaszczepienia oraz hospitalizacje w ciągu 2 tygodni przed zachorowaniem nie miały znaczenia dla bycia „*index case*".

Wśród pacjentów przetestowanych do końca 2021 roku 87% zostało zakażonych przez wariant Delta wirusa SARS-CoV-2, natomiast od stycznia 2022 roku 91% pacjentów przez wariant nie-Delta. To pozwoliło nam na podzielenie rodzin na 2 podgrupy: z dominującym wariantem Delta (rodziny włączone w 2021 roku) i z dominującym wariantem innym niż Delta (rodziny włączone w 2022 roku). Przeprowadziliśmy analizę osobno wśród tych 2 podgrup rodzin. Uczęszczanie do placówek edukacyjnych i opiekuńczych korelowało z byciem pierwszym zakażonym domownikiem we wszystkich grupach wiekowych w podgrupie rodzin, w których Delta była przeważającym wariantem, w przeciwieństwie do podgrupy rodzin z dominującymi innymi wariantami wirusa.

Dodatkowym wynikiem naszej pracy było scharakteryzowanie przebiegu zakażenia SARS-CoV-2 wśród dzieci włączonych do badania. Większość dzieci miała zakażenie o łagodnym przebiegu. Połowa dzieci z dodatnim wynikiem testu w kierunku SARS-CoV-2 nie wymagała pobytu w szpitalu. Spośród dzieci przyjętych do szpitala prawie 45% zostało przyjętych z innych powodów niż COVID-19. Jedynie 13% hospitalizowanych wymagało swoistego leczenia przeciwko COVID-19, w tym 1 chory był leczony na Oddziale Intensywnej Terapii Dziecięcej (OITD). Wyniki zgadzają się z danymi z literatury o stosunkowo łagodnym przebiegu COVID-19 w populacji dziecięcej.

Szczególnym atutem naszej pracy było zastosowanie metody Monte Carlo w analizie danych uzyskanych w toku badania. Aby określić „cechy" dziecka, które było pierwszym zakażonym domownikiem (np. czy uczęszczało do placówki opiekuńczej czy nie) napotkaliśmy na trudności związane z zależnością dzieci w rodzinie, tzn., jeśli dziecko A było „*index case*" w danej rodzinie, to jego rodzeństwo nie mogło już być pierwszym zakażonym domownikiem, mimo że mogłoby teoretycznie posiadać identyczne „cechy" jak dziecko A. W celu uniknięcia wpływu tych zależności, zastosowaliśmy metodę Monte Carlo, która umożliwia ich wyeliminowanie. Najpierw losowo wybrano dziecko z każdej rodziny. W ten sposób wszystkie dzieci były „niezależne" od innych (swojego rodzeństwa). Następnie wykonano analizę regresji liniowej, aby określić cechę, która predysponuje do bycia „*index case*" w rodzinie. W kolejnym etapie powtórzono tę procedurę 10 000 razy, wybierając za każdym razem losowo "próbkę" innych dzieci. Oprócz wykluczenia opisanych wyżej zależności między dziećmi w rodzinie, metoda Monte Carlo pozwoliła nam również zidentyfikować niezależne czynniki ryzyka bycia „*index case*" w środowisku domowym, w oparciu o dane pozyskane na stosunkowo niewielkiej grupie badanej. Dzięki temu byliśmy również w stanie określić różnice między falą Delta a kolejną falą w kontekście roli dzieci w transmisji SARS-CoV-2. Nasza praca była pierwszą publikacją, w której skorzystano z metody Monte Carlo w celu oceny roli dzieci w pandemii COVID-19. Potencjalne zastosowanie tej metody nie ogranicza się jedynie do oceny czynników ryzyka rozprzestrzeniania się SARS-CoV-2 - metodę Monte Carlo można wykorzystać również przy badaniu innych zakażeń, w kolejnych przyszłych epidemiach.

Na podstawie uzyskanych wyników można sformułować wniosek, iż uczęszczanie przez dzieci do placówek edukacyjnych i opiekuńczych może być znaczącym predyktorem bycia pierwszym zakażonym domownikiem w rodzinie. Kolejnym wnioskiem, który wynika z naszej pracy jest to, że rola dzieci w pandemii COVID-19 prawdopodobnie zmienia się wraz z kolejnymi wariantami wirusa.

4. Leczenie COVID-19 u dzieci

Według dostępnego piśmiennictwa przebieg COVID-19 u dzieci jest łagodniejszy niż u dorosłych (3, 17-19). Większość dzieci choruje bezobjawowo lub ma łagodne objawy infekcji dróg oddechowych (katar, kaszel, stan podgorączkowy, ogólne złe samopoczucie). Leczenie opiera się na postępowaniu objawowym – odpowiednim nawodnieniu, obniżaniu gorączki i odpoczynku. U części dzieci COVID-19 przebiega pod postacią charakterystycznego zespołu objawów np. podgłośniowego zapalenia krtani czy ostrego zapalenia oskrzeli. W tych

przypadkach wskazane jest stosowanie się do rekomendacji dotyczących leczenia tych chorób (20).

COVID-19 u dzieci sporadycznie może przebiegać ciężko. Ciężki przebieg choroby (obejmujący m. in.: ostrą niewydolność oddechową, ostre uszkodzenie nerek, ostrą niewydolność wątroby, encefalopatię, zapalenie mięśnia sercowego, zapalenie osierdzia, sepsę, wstrząs, chorobę zakrzepowo-zatorową) początkowo występował u około 2% dzieci z COVID-19 (21). Odsetek dzieci z ciężkim przebiegiem COVID-19, które wymagały hospitalizacji w OITD zmniejszał się wraz z kolejnymi falami, natomiast odsetki dzieci w wieku < 5 lat, które wymagały tlenoterapii biernej lub wsparcia oddechowego, pozostawały podobne przez całą pandemię (22). Najczęstszym objawem w trakcie ciężkiego zachorowania jest stan zapalny dolnych dróg oddechowych, który może prowadzić do rozwoju niewydolności oddechowej wymagającej wentylacji mechanicznej (23). Dysfunkcja wielonarządowa jest prawdopodobnie spowodowana „burzą cytokinową", stresem oksydacyjnym i rozsianym wykrzepianiem wewnątrznaczyniowym (24, 25). Ciężki przebieg COVID-19 może wystąpić u każdego dziecka, istnieją jednak grupy pacjentów, którzy są zagrożeni większym prawdopodobieństwem ciężkiego zachorowania. W populacji dziecięcej dane dotyczące czynników ryzyka ciężkiego przebiegu COVID-19 są ograniczone i niepewne. Niemowlęta i nastolatki prawdopodobnie cechują się największym ryzykiem hospitalizacji w OITD i śmierci (26). Przynależność do rasy innej niż biała była również opisywana jako czynnik ryzyka ciężkiego przebiegu COVID-19 (27, 28). Ponadto dzieci z określonymi chorobami są bardziej predysponowane do ciężkiego zachorowania, m.in dzieci w immunosupresji, otyłe, z poważnymi chorobami układu oddechowego, chorobą neurologiczną, metaboliczną, genetyczną lub istotną hemodynamicznie chorobą serca (29-31). Czynnikiem obniżającym ryzyko progresji do ciężkiego COVID-19 jest szczepienie przeciwko COVID-19 (32, 33). U dzieci z ciężkim przebiegiem COVID-19 i wysokim ryzykiem ciężkiego przebiegu należy rozważyć leczenie przeciwwirusowe przeciwko COVID-19. Wybór właściwego leczenia jest uzależniony od przebiegu choroby i czasu, jaki upłynął od pierwszych objawów. Wybór optymalnego leczenia jest znacznie utrudniony przez fakt, że odbyło się bardzo mało badań klinicznych, w których uczestniczyły dzieci. Rekomendacje dotyczące leczenia COVID-19 u dzieci są więc pochodną zaleceń dla dorosłych.

Celem trzeciej publikacji z cyklu, pt. „*How international guidelines recommend treating children who have severe COVID-19 or risk disease progression"* było podsumowanie czterech międzynarodowych wytycznych dotyczących leczenia COVID-19 u dzieci. Porównaliśmy

brytyjskie wytyczne *National Institute for Health and Clinical Excellence (NICE),* amerykańskie wytyczne *National Institutes of Health (NIH)*, amerykańskie wytyczne *Infectious Diseases Society of America (IDSA)* oraz wytyczne australijskie (20, 34-36). Chcieliśmy przedstawić je w formie przyjaznej lekarzom-praktykom. Wytyczne są zgodne, że należy rozważyć leczenie COVID-19 u dzieci z ciężkim przebiegiem COVID-19 lub z wysokim ryzykiem ciężkiego przebiegu. Wybór właściwego leczenia jest uzależniony od czasu od rozpoczęcia choroby do wdrożenia leczenia oraz przebiegu choroby. U dzieci z ryzykiem ciężkiego przebiegu choroby można zastosować nirmatrelwir z ritonawirem lub remdesiwir. Leczenie powinno być włączone jak najszybciej, najlepiej w ciągu pierwszych dni choroby. Remdesiwir znajduje również zastosowanie u dzieci hospitalizowanych, które wymagają tlenoterapii. Suplementacja tlenu jest także wskazaniem do zastosowania glikokortykosteroidów systemowo. W razie braku skuteczności leczenia, należy rozważyć włączenie immunomodulatorów – baricitinibu lub tocilizumabu – szczególnie u dzieci z objawami uogólnionego zapalenia. Należy jednak podkreślić, że decyzje dotyczące leczenia dzieci z COVID-19 muszą być podejmowane indywidualnie, z uwzględnieniem bilansu potencjalnych korzyści i ryzyka. Nasz artykuł w zwięzły sposób podsumowuje aktualny stan wiedzy i stanowi pomocne źródło przy podejmowaniu takich decyzji.

Założenia i cel pracy

Celem pracy było zbadanie roli dzieci w transmisji SARS-CoV-2 w środowisku żłobkowym i domowym oraz podsumowanie wytycznych dotyczących leczenia COVID-19 w populacji dziecięcej. Założeniem pracy była próba odpowiedzi na pytania stawiane przez badaczy i lekarzy w kolejnych miesiącach pandemii.

Cele szczegółowe:

1. Opracowanie epidemiologiczne ogniska COVID-19 w żłobku, w którym dzieci prawdopodobnie zakaziły swoich dorosłych domowników i inne dzieci – wbrew panującemu wówczas przekonaniu, że dzieci nie przenoszą efektywnie wirusa SARS-CoV-2. Opisanie roli dzieci w transmisji zakażenia w żłobku (publikacja nr 1).
2. Scharakteryzowanie rodzin dzieci zakażonych SARS-CoV-2 hospitalizowanych w DSK UCK WUM od września 2021 do stycznia 2022: określenie, jak często dzieci były zakażane jako pierwsze w rodzinie i zidentyfikowanie czynników ryzyka bycia pierwszym zakażonym domownikiem w rodzinie przy użyciu metody Monte Carlo. Zbadanie roli dzieci w transmisji zakażenia w środowisku domowym (publikacja nr 2).
3. Podsumowanie wytycznych dotyczących leczenia COVID-19 u dzieci (na podstawie wytycznych NICE, NIH, IDSA oraz wytycznych australijskich) i przedstawienie ich w formie przyjaznej lekarzom-praktykom (publikacja nr 3).

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SARS-CoV-2 Cluster in Nursery, Poland

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We report a cluster of surprisingly high spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with a single nursery in Poland. Our findings contrast with the presumed negligible role of children in driving the SARS-CoV-2 pandemic. Children 1–2 years of age might be effective SARS-CoV-2 spreaders.

Despite robust research, knowledge about coronavirus disease (COVID-19) spread and effective control measures is still limited. Until recently, research has indicated that children rarely spread the infection to adults and are not the primary drivers of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission (*1*).

We describe characteristics of the cluster of SARS-CoV-2 cases that emerged in a single nursery in Poland within 2 weeks of its reopening. We anonymized all data and collected no sensitive data. The Bioethics Committee of the Medical University of Warsaw approved the study protocol.

The nursery at issue was reopened after a nationwide lockdown on May 18, 2020. On May 31, a nursery worker reported family contact with a symptomatic SARS-CoV-2–infected person, and the nursery was closed. During the 14 days the nursery was open, a mean of 25 children attended the nursery daily. Children spent ≈8 hours there, divided into 3 groups, each cared for by 2 caregivers (Appendix, https://wwwnc.cdc.gov/EID/article/27/1/20-3849-App1.pdf). Neither children nor caregivers moved across multiple classes. Caregivers wore facemasks when in contact with children. Parents did not enter the building when dropping off and picking up children. Contacts between parents and nursery workers lasted <15 minutes, with facemasks on. Family members of different children did not mix.

The index case of SARS-CoV-2 infection (in a nursery worker with family contact) was confirmed on June 4. Subsequent PCR testing of nursery staff, children attending the facility, and family members (2 initial case-patients plus 104 other persons) (Appendix) revealed positive results in an additional 4 nursery workers (of whom 1 was also a parent of a child attending the facility), 3 children of the nursery workers, 8 children attending the facility, 3 siblings of those children, 8 parents, and 1 grandparent. The cluster involved a total of 29 persons; 8 were children attending the nursery, and 12 were children's family members who did not enter the facility (Table). One child with a negative result had 2 parents with positive results. One child's parent tested negative in this cluster but had tested positive within the previous 2 weeks, involved in another cluster.

The overall positivity rate in our cluster was 27%. COVID-19 prevalence in Poland is low. The number of tests conducted in the country was 124,194 in June, whereas the number of positive cases was 1,374, which corresponded to a positivity rate of 1% (2). Thus, local SARS-CoV-2 circulation in society is not sufficient to explain the positivity rate in our cluster.

Table. Severe acute respiratory syndrome coronavirus 2 testing outcomes of potentially infected persons in a nursery setting, Poland, 2020

Person	No. tested	No. positive by PCR	% Positive
Children attending the nursery	28	8	29
Parents of children attending nursery*	31	8	26
Siblings of children attending nursery	16	3	19
Grandparent of children attending nursery	1	1	100
Nursery workers	25	5	20
Spouses of nursery workers	2	1	50
Children of nursery workers	3	3	100
Total	106	29	27

*One of the parents of children attending the nursery was also a nursery worker; she is counted as a worker in this table.

The case of the COVID-19–negative child with positive parents could have been a false-negative result or a negative result after being infected. The result might also have been a true negative, and the parents were infected from another source. However, other potential exposures could not explain infections in all parents involved in our cluster.

We depict probable chains of transmission in the Figure. Of note, physical contact between nursery workers and children's family members who were infected was strictly limited, and the only close contacts for these groups of adults were children. Given that most COVID-19–positive persons were asymptomatic and tested on the same day, determining with certainty whether children transmitted the virus to their parents or the workers is not possible. Nevertheless, children seemed to be effective mediators of infection between adults.

Several reports concerning clusters of COVID-19 in childcare settings imply little to no SARS-CoV-2 transmission among children and from children to adults (1,4,5; A. Fontanet, unpub. data, https://doi.org/10.1101/2020.06.25.20140178; R.M. Viner, unpub. data, https://doi.org/10.1101/2020.05.20.20108126). However, such estimations are open to bias, given that most published data were obtained at the time of lockdown, when children's social contacts were limited to family members. Another limitation of those publications is that they applied mostly to school-age children.

The high infection attack rate among children in our cluster could be explained by prolonged close contact between very young children, who are less able to adjust to control measures. Similarly, specific intimate contact between toddlers and their family members could have led to effective spread within families. This observation might be particularly important in light of novel findings that nasopharyngeal SARS-CoV-2 levels are the highest in the youngest children (6). Moreover, the airborne transmission route in the nursery rooms' confined environment could have played an important role (7).

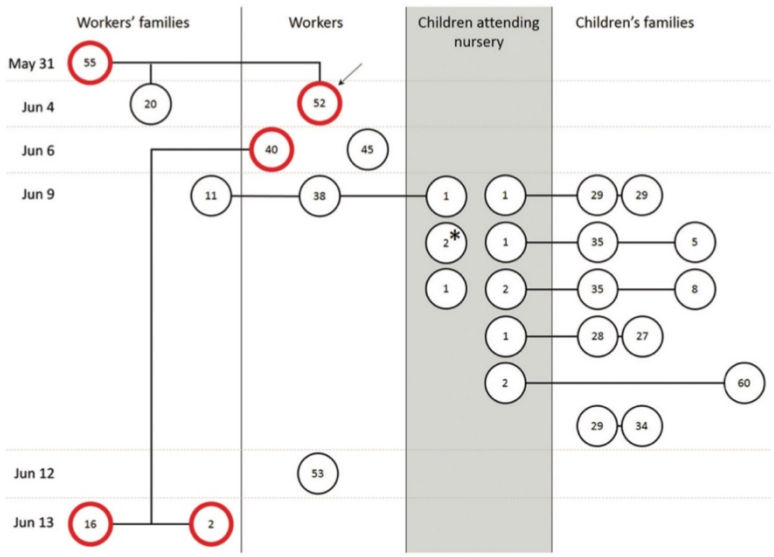

Figure. All persons testing positive for severe acute respiratory syndrome coronavirus 2 infection in a cluster associated with a nursery, Poland 2020. Dates to left indicate first positive results in consecutive case-patients. Circles indicate infected case-patients; numbers in circles indicate age in years. Red circles indicate infected case-patients with symptoms. Circles connected by lines indicate case-patients who are members of the same household. Arrow indicates the probable index case-patient. Asterisk indicates child whose parent tested negative in this cluster but tested positive within the previous 2 weeks.

Our study has some potential limitations. We could not determine whether the infection in the nursery worker was the real index case because one of the children's parents had tested positive within the previous 2 weeks and that child could also have been the primary case. Moreover, we could not verify the information we obtained from the nursery about the facility's prevention methods.

Our report questions the role of young children in driving the COVID-19 pandemic. Of note, most children in our study were asymptomatic, and this cluster would likely not have been detected without subsequent testing of persons who had direct contact with the index case-patient. We believe further studies are needed to clarify young children's role in the transmission of SARS-CoV-2.

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Dr. Okarska-Napierała works as an attending physician and professor in the Department of Pediatrics with the Clinical Assessment Unit, Medical University of Warsaw. Her research is focused on Kawasaki disease.

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Developing Endemicity of Schistosomiasis, Corsica, France

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Urogenital schistosomiasis was diagnosed in a man from Germany who had never traveled outside Europe. He likely acquired the infection in Corsica, France, but did not swim in the Cavu River, which was linked to a previous outbreak. This case highlights that transmission of schistosomiasis in Corsica is ongoing.

A 49-year-old man from Germany experienced macrohematuria in June 2020 and underwent cystoscopy in August 2020. Histologic analysis of a bladder biopsy specimen showed ova of *Schistosoma* spp. He was referred to the outpatient department for tropical medicine at LMU Hospital Munich.

The patient had never traveled outside Europe. He had, however, traveled twice to Corsica, France, in 2013 and 2019. He never swam in the Cavu River, which has been associated with cases of schistosomiasis in recent years (*1*–*3*).

The patient visited Corsica during August 22–September 4, 2019. By using GPS data from his smartphone and camera, he reconstructed his bathing sites precisely. During August 22–24, he swam

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Appendix

Detailed Characteristics of Children's Groups and Testing Sequence

Children in the nursery were divided into 3 groups according to age (group A, the youngest; group B, medium; group C, the oldest). The mean number of children attending the nursery every day was 10–12 for group A, and 5–7 for groups B and C. The total number of children attending group A was 16, and 12 in both groups B and C.

When the first COVID-19 cases were identified among the nursery workers, children were split into "direct contact" and "indirect contact" groups. Children from group A were considered "direct contacts" and thus were tested together with all their household members. Children from groups B and C were "indirect contacts," and only children were tested. Of note, 1 nursery worker was a parent of a child from group A and worked with children from group B. She tested positive, but all children with whom she worked tested negative, and thus their families were not tested.

The sequence of testing was as follows.

1. The index case, who was a caregiver in group A, tested positive on June 4, together with her adult child.
2. Two more nursery workers working in close contact with the index case tested positive on June 6 (one of them was another caregiver in group A).
3. On June 9, all children from group A (16 children) and all their household members (32 parents, 16 siblings, and 1 grandparent) were tested.
4. The rest of children attending the nursery (groups B and C, 12 children) were tested on consecutive days, and none of them tested positive. Their family members were not tested. Similarly, the rest of the nursery workers, who did not have direct contact with the first 3 cases, were tested on consecutive days.

5. Two more children of one nursery worker were tested 7 days after she tested positive, and they were positive.

Testing practices implemented in the nursery by a local sanitary-epidemiological station complied with standard testing procedures in the country at that time. They involved testing symptomatic people and contacts of confirmed COVID-19 cases.

PCR Testing

The testing was done in a single validated laboratory at the local sanitary-epidemiological station.

The isolation phase of the reaction was performed on Veri-Q Prep M16 Nucleic Acid Extraction Device using Viral DNA/RNA Prep/kit-Airway Sample (Humanitas Global Logistics, https://hglmedical.com/). The amplification phase was performed on Veri-Q PCR 316 Gene Amplification Device using nCoV19 Detection PCR Kit.

Clinical Picture

There were no symptomatic cases among children attending the facility and their family members. A total of 5 people had COVID-19 symptoms. The family member of the index case was diagnosed and treated in the hospital. Two nursery workers and 2 children of 1 of them had mild symptoms of the disease.

Seven children attending the nursery and 2 of their siblings were evaluated in the hospital. Laboratory testing and chest x-ray revealed no abnormalities except for an 11-year-old girl who had elevated transaminase levels (alanine transaminase 297 U/I, aspartate transaminase 167 U/I) that normalized within 1 week.

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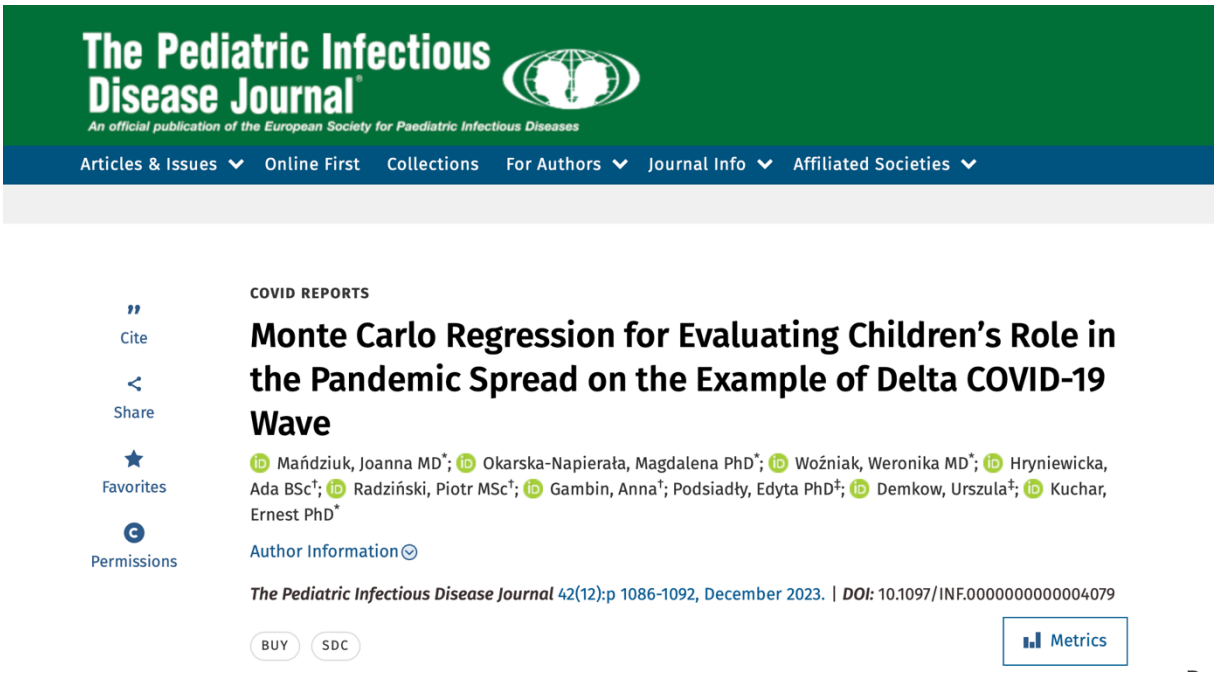

Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave

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Key Words: nursery, kindergarten, school, transmission, SARS-CoV-2

Cover title: Monte Carlo Regression for Children's Role in COVID Spread

Running head: Children's Role in COVID-19 Spread

Abstract

Background: The children's role in transmitting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the familial settings is uncertain. We aimed to assess how often children were the index cases transmitting SARS-CoV-2 into their households during the Delta wave, and to identify risk factors of children being the index case.

Methods: In this prospective survey study we collected information regarding household members of SARS-CoV-2 positive children tested in a single tertiary hospital. Some patients were tested with polymerase chain reaction and those samples were typed and classified as Delta or non-Delta variant. We have used the Monte Carlo approach to assess predictors of children being the index case in the household.

Results: We surveyed 629 families and 515 of them fulfilled inclusion criteria. The child was the index case in 359 (69.71%) households. Attending childcare facilities in all age groups was positively associated with being the index case in the household (nursery, estimate = 1.456, 95% CI [1.456, 1.457], *p* value <0.001; kindergarten, estimate = 0.899, 95% CI [0.898, 0.900], *p* value = 0.003; school, estimate = 1.23, 95% CI [1.229, 1.231], *p* value = 0.001). The same association was present in the subgroup of the families with predominant Delta variant, but not in the subgroup with predominant non-Delta variant.

Conclusions: Attending childcare and educational facilities might be a significant predictor of a child being the SARS-CoV-2 index case in their household. Children's role in driving the SARS-CoV-2 pandemic changes in consecutive waves. The Monte Carlo approach can be applied to assess risk factors of infectious agents' spread in future epidemics.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.617.2 (Delta) variant was first detected in December 2020 in India.[1] Due to higher transmissibility than the previous variants, it had quickly become the dominant variant in Europe.[2] The corresponding coronavirus disease 2019 (COVID-19) wave in Poland emerged between October 2021 and December 2021.[3]

So far, little research has focused on children's role in transmitting SARS-CoV-2 in the familial settings. Early in the pandemic, it was believed that children usually got infected with SARS-CoV-2 from adult family members rather than from exposure in educational settings or elsewhere. Accordingly, it was assumed that children rarely transmitted SARS-CoV-2 into the household.[4–6] However, this could have changed after the physical distancing measures were lifted, and consecutive variants of SARS-CoV-2 emerged.[7–9] Particularly during B.1.1.529 (Omicron) variant surge it was demonstrated that children notably contributed to spreading infection to their households.[10]

Evaluating SARS-CoV-2 transmission is challenging. Long incubation period, high percentage of asymptomatic cases, and complex net of social interactions make it difficult to reconstruct the precise chains of transmission. Moreover, the clustered structure of the population leads to unavoidable dependencies between variables measured within households.

The Monte Carlo approximation is a method of assessing probability distribution. It is a computational technique which estimates the behavior of a complex system, by repeating much simpler simulations repeatedly and taking a simple statistic as the estimation result. Thus, the Monte Carlo approach allows to assess risks and make accurate predictions despite input data being interdependent.

We aimed to assess how often children were the index cases transmitting SARS-CoV-2 into their households during the Delta variant wave and to identify risk factors of children being the index case, with the use of the Monte Carlo regression.

MATERIALS AND METHODS

Families' recruitment

In this prospective survey study, we collected information regarding the families of children who were hospitalized and/or tested for COVID-19 in the Pediatric Teaching Hospital in Warsaw, Poland, and had positive SARS-CoV-2 test result (either reverse transcription polymerase chain reaction [RT-PCR] or antigen test) between September 2021 and January 2022. We included children who were routinely tested before planned hospitalizations, children of healthcare workers, patients consulted in the Emergency Department and children admitted to the hospital wards. After informed consent, parents of children were interviewed using a questionnaire regarding information about each household member. The survey contained questions about demographic data, the date of first symptoms if present, the type and result of the COVID-19 test if performed, and social contacts within two weeks preceding the illness onset in the index case (including in-office working, attending childcare facilities, and hospitalizations preceding infection).

Our goal was to select those households in which it was clear, who was the first SARS-COV-2 infected person (index case). To achieve that, we applied following inclusion and exclusion criteria to whole households.

The inclusion criterion for the family was a complete information about infection status (as described below) in all household members. The exclusion criteria for the family were i) >1 index case; ii) ≥2 cases co-exposed to COVID-19 outside the household (e.g., during family meeting); iii) cases who lived outside the household within 14 days before COVID-19

infection; iv) cases with confirmed SARS-CoV-2 contact in a hospital; v) >14 days between any two consecutive positive cases.

The study was approved by the Bioethical Committee of the Medical University of Warsaw (No. AKBE/224/2020).

Study definitions

The adult was defined as a person ≥18 years old and the child as <18 years old.

The positive and negative cases were defined as follows:

1) **A positive case**
   a) Positive or inconclusive COVID-19 test result,

   OR

   b) Symptoms present AND either:
      a. person not tested,
      b. person tested negative before the symptom onset,
      c. person tested negative >14 days after the symptom onset.

2) **A negative case**
   a) Negative COVID-19 test result within 14 days since the symptom onset,

      OR

   b) Symptoms absent, AND person tested negative or not tested.

An inconclusive COVID-19 test result applied only to RT-PCR results in household members, tested outside our hospital, reported by our respondents. We considered an inconclusive test result to be positive because it was combined with a contact with COVID-19-positive family member.

In each positive case, we established the date of illness onset, defined as the date of the symptom onset or the positive COVID-19 test result, whichever was first.

The index case was defined as the first positive case (with the earliest illness onset date) in the household.

Persons vaccinated with one dose of adenovirus 26 vector vaccine (Ad26.COV2.S) or two doses of any other anti-SARS-CoV-2 vaccine were considered fully vaccinated. Those who were vaccinated with one dose of a vaccine other than Ad26.COV2.S were considered incompletely vaccinated.

Childcare and educational facilities were categorized as nurseries (for <3-year-olds), kindergartens (for 3-6-year-olds), and schools (for 7-17-year-olds).

Delta variant typing

Depending on individual indications, upon clinicians' decisions, a proportion of patients were tested for SARS-CoV-2 with real-time RT-PCR in our hospital.

To determine the SARS-CoV-2 variant, we examined the presence of genetic mutations P681R, L452R, and E484Q in the *S* gene, in all positive SARS-CoV-2 nasopharyngeal samples. The test Vitassay qPCR SARS-CoV-2 Variants II (Vitassay, Spain) was applied. Both P681R and L452R mutations in the S gene are present in lineages B.1.617.1 and B.1.671.2, whereas E484Q mutation is detected only in lineage B.1.617.1. The samples were classified as Delta variant if both genetic mutations P681R and L452R in *S* gene were detected with concurrent absence of E484Q mutation.[1]

The distribution of Delta and non-Delta cases is presented in Figure 1. In patients tested until December 2021, 87% had Delta variant, whereas, since January 2022, 91% of patients had non-Delta variant. This observation allowed us to divide all families into two subgroups: those with index cases from 2021 – with a predominant Delta variant, and those with index cases from 2022 – with non-Delta variant predominance.

Statistical methods

Monte Carlo regression approach

Since we aimed to characterize children who were the index case in the household, we encountered the problem of dependencies between children within the same household. Namely, if a given child was the first infected family member, their siblings could not be the first. Therefore, we applied the Monte Carlo approach to eliminate these dependencies. First, we randomly picked a child from each family. This way, all children in such a limited dataset were independent of each other. Then, we performed a linear regression analysis to predict being the index case. Finally, we repeated this procedure 10000 times, sampling different children each time. To deal with a question of causation, not only correlation, we considered such use of Monte Carlo approach more suitable than commonly used methods like multilevel models or generalized estimating equation. The only assumption required for our Monte Carlo regression was that all expected values in the computations were finite.

In some cases, sampling led to data separation issues, i.e., situations when an outcome variable separated a predictor variable completely. This resulted in a high standard error (SE) estimate. To deal with this problem, we accepted only regressions where all SE were <1 or, in cases where results <1 were absent, we used the threshold value of 1.5. If there were no results with SE <1.5, the predictor was removed from the analysis. The final results were obtained by taking the average results of individual draws.

Linear regressions

We performed linear regression to establish factors (age [as a continuous variable], sex, attending childcare facility, hospitalization within two weeks preceding illness onset, and vaccination against COVID-19) that may predict children being the index case.

Then, we performed the same regression on the families in which all family members were SARS-CoV-2 tested. It allowed us to verify our initial results on a smaller group, in which the infection status of all family members was more certain.

Finally, we repeated the regression in two subgroups of the families: those with a predominant Delta variant and those with a predominant non-Delta variant, as described above. In the analysis of the families with predominant Delta variant, we removed 'vaccination against COVID-19', due to high SE in all regressions. In the analysis of the families with non-Delta variant predominance, two factors: 'vaccination against COVID-19' and 'previous hospitalization' were removed.

RESULTS

Characteristics of the children hospitalized and/or tested in the hospital

From September 22, 2021, to January 23, 2022, 748 children with confirmed SARS-CoV-2 infection were tested and/or hospitalized in our hospital. Parents of 637 children agreed to participate in the study, and we collected data from 629 families (some of the children belonged to the same household). Finally, 515 families were included in the analysis (Figure 2).

Demographic and clinical characteristics of children hospitalized and/or tested in our facility, including COVID-19 complications and treatment details, are presented in Supplemental Digital Content 1 (table).

Characteristics of the families included in the study

Within 515 households included in the final analysis, there were 883 children (478 boys; 54.1%) and 1060 adults (487 men, 45.9%). In nearly 70% of the families, the child was the index case (359 families, 69.7% of all families). Table 1 shows the characteristics of the families included in the analysis.

Results of Monte Carlo regression

All families included in the analysis

Among children from 515 families included in the analysis, attending childcare and educational facilities in all age groups was positively associated with being the index case

(attending nursery, estimate = 1.456, 95% CI [1.456, 1.457], *p* value <0.001; attending kindergarten, estimate = 0.899, 95% CI [0.898, 0.900], *p* value = 0.003; attending school, estimate = 1.23, 95% CI [1.229, 1.231], *p* value = 0.001). Moreover, the age of children was a positive predictor of being the index case (estimate = 0.106, 95% CI [0.106, 0.106], *p* value = 0.002). Sex, vaccination status or previous hospitalizations were not statistically significant predictors for being the index case. The number of regressions with SE <1 was 7473.

Families in which all members were tested for SARS-CoV-2

In 234 households, all family members were tested for SARS-CoV-2. In 137 (58.6%) of them, a child was the index case. In this subgroup of the families, the results of Monte Carlo regression were like the ones presented above, except for older age being a positive predictor. Still, attending childcare and educational facilities in all age groups was positively associated with being the index case (attending nursery, estimate = 1.625, 95% CI [1.625, 1.626], *p* value = 0.002; attending kindergarten, estimate = 1.253, 95% CI [1.252, 1.255], *p* value = 0.003; attending school, estimate = 1.513, 95% CI [1.510, 1.515], *p* value = 0.012). The number of regressions with SE <1 was 7488.

Families surveyed in 2021 (Delta variant predominant)

In 410 families, the index case had illness onset in 2021. In this subset of the families, the results of Monte Carlo regression were also consistent with the results obtained in all families. Attending childcare and educational facilities in all age groups was positively associated with being the index case (attending nursery, estimate = 1.655, 95% CI [1.654, 1.655], *p* value <0.001; attending kindergarten, estimate = 0.932, 95% CI [0.931, 0.933], *p* value = 0.008; attending school, estimate = 1.605, 95% CI [1.603, 1.606], *p* value <0.001). Also, as previously, the age of children was a positive predictor of being the index case (estimate = 0.092, 95% CI [0.092, 0.092], *p* value = 0.017). The number of regressions with SE <1 was 10000.

Families surveyed in 2022 (non-Delta variant predominant)

In 105 families, in which the index case had illness onset in 2022, the age was a significant positive predictor of a child being the index case in the household (estimate = 0.174, 95% CI [0.173, 0.174], *p* value = 0.027), whereas all other analyzed factors were insignificant. The number of regressions with SE <1.5 was 7459.

The results of the Monte Carlo regressions are presented in Table 2.

DISCUSSION

Clinical course of SARS-CoV-2 infection in children

According to the literature, the course of COVID-19 in children is usually asymptomatic or mild, which we also saw in our study.[11,12] Half of the children hospitalized and/or tested in our facility were discharged home after a consultation. Of those hospitalized, nearly 45% were admitted for reasons other than COVID-19 and hospitalized children were mostly young. The latter can be explained by the fact that young children have a lower hospital admission threshold than older ones. COVID-19 course in those hospitalized was usually mild as well, with only 13% of the children receiving specific treatment and one patient requiring intensive care.

Children being the first COVID-19 case in the household

The most surprising result of our study was that in most families, a child was the index case, which implied that children got infected outside the household and transmitted infection into the family. This finding contrasts sharply with the results from other studies.[13–15] It can be partially explained by several limitations of our study. Firstly, the data were gathered in a pediatric hospital, so in all families included in the study at least one child was SARS-CoV-2 positive (in other words, we did not include families where children did not get infected). Secondly, by including families with only one person infected, we involved a group of families with the child being the first (and only) positive case (these families, with second

attack rate = 0, comprised 32% of all households). Finally, some COVID-19 cases were omitted due to an assumption that an asymptomatic person who was not tested was negative. The latter applies particularly to adults, as more adults than children were not tested (so there were more false-negative cases among adults). Nevertheless, when we analyzed the subset of the families in which all family members were tested, children were still the index cases in nearly 60% of the families.

At the beginning of the pandemic, the general belief was that children rarely transmit SARS-CoV-2 to other children or adults.[16,17] Household transmission studies showed that children usually got infected by an adult family member and rarely were the index case of COVID-19 in their families.[6,13–15] Several reports about COVID-19 clusters in childcare and educational settings also described minimal transmission among children or from children to adults.[18–20] Most of the published data, however, were gathered at the time of lockdown, when social contacts, especially children's social contacts, were very limited. Of note, a few papers at that time reported a high spread of SARS-CoV-2 associated with childcare settings.[21,22] Since then, social distancing measures have been gradually withdrawn, including step-by-step re-opening of children's facilities. At the time of our study, nurseries and kindergartens in Poland were open; schools were also open except from December 20, 2021, to January 9, 2022.[23] Moreover, with time, new, more transmissible variants of SARS-CoV-2 have emerged.[24–26] In particular, reports concerning B.1.1.529 (Omicron) variant have suggested significantly higher risk of household transmission compared to previous variants.[27,28] The vital role of children in contributing to the household transmission during Omicron wave has also been noticed.[10] These factors may have also influenced our finding that children were the index cases in more than ⅔ of the families.

The age and attending nurseries, kindergartens, or schools predicted children being the index case in the household

The main finding of our study is that attending childcare facilities and older age were significant factors predicting the child being the index SARS-CoV-2 case in the household during the Delta COVID-19 wave. These two factors: age and attending childcare facility, could be linked. The ratio of children attending childcare facilities increased with their age. Only 18% of children <3 y.o. attended nursery, whereas 88% of children ≥7 y.o. went to school. Thus, the older the child, the higher the probability they attended a childcare facility. On the other hand, the influence of age applied to all children, including a broad group of those attending school (from 7 to 17 y.o.). This argues for age to be an independent risk factor. It could be hypothesized that age influences social activities other than attending school, which are probably more common in older children compared to younger ones. Interestingly, in the subset of families with more strict inclusion criteria (all family members tested for SARS-CoV-2), the age of children was not a significant predictor of being the index case, whereas attending childcare facilities remained significant. Thus, our finding that age influences the risk of a child being the index case, must be interpreted with caution.

Our findings emphasize the role of nurseries, kindergartens, and schools in SARS-CoV-2 transmission. They contrast with the evidence gathered early in the pandemic, suggesting the limited role of childcare and educational settings in driving the virus circulation.[18,20,29,30] Importantly, most studies regarding this issue were conducted before B.1.1.7. (Alpha) variant emergence, and so they do not apply to new, more transmissible variants of SARS-CoV-2. During autumn 2021, when the Delta variant was predominant in Europe, Galocic et al.[31], who monitored the transmission of SARS-CoV-2 in childcare and educational facilities, found more outbreaks in those settings compared to earlier variants. However, at this pandemic stage, when community transmission was high, it was not easy to state whether transmission occurred in childcare and educational settings or elsewhere.

Interestingly, after separating families with predominant Delta variant from those with predominant non-Delta variant, we reproduced our results concerning the role of childcare facilities only for the Delta wave. It cannot be explained by the smaller sample size in the non-Delta subgroup, as the Monte Carlo approach overcomes this issue. Thus, our results suggest that the role of childcare facilities in driving the COVID-19 pandemic change in consecutive waves, which might be due to constant changes in the virus transmissibility and social distancing measures.

Sex, vaccination status, and previous hospitalization did not predict children being the index case in the household

We found no proof that sex, vaccination status, or preceding hospitalization predicted children being the index case in the household. To our knowledge, studies examining the influence of the abovementioned factors on children being the index case in the household have not been published yet. It has been found that being vaccinated against COVID-19 reduced the risk of being the index case and transmitting SARS-CoV-2 to other household members. However, this effect was smaller for the Delta variant than the Alpha variant.[32,33]

Monte Carlo approach

To our knowledge, this is the first study to evaluate the role of children in COVID-19 pandemic with the use of Monte Carlo technique. Random multiple sampling of children from the families included in our analysis allowed us to both: clear our results from dependencies unavoidable within the family and identify independent risk factors of children spreading SARS-CoV-2, based on a relatively small sample. With the access to the same set of variables, we were able to reveal a significant difference between the Delta and the subsequent COVID-19 wave in terms of children's role in SARS-CoV-2 transmission. The Monte Carlo approach presented in this work can be further used for assessment of infection spread in the clustered population.

Limitations

This study has several limitations. Some were mentioned above (see section 4.2.): recruiting only families of SARS-CoV-2-positive children; recruiting a subset of families with only one person (a child) infected; and assuming that asymptomatic and non-tested persons were negative. The former two limited generalizability of our results, whereas the latter one could have resulted in false-negative cases. Moreover, children included in the study were mainly young, usually symptomatic and consulted in the hospital, which further limited the generalizability of our findings. However, it is worth noticing that most of the children had benign COVID-19 course and were not hospitalized due to SARS-CoV-2 infection. In addition, COVID-19 testing was entirely dependent on family members' decisions. Finally, COVID-19 symptoms, type and results of the SARS-CoV-2 tests, and vaccination status were based solely on self-report.

CONCLUSIONS

Attending childcare and educational facilities in all age groups might be a significant predictor of a child being the SARS-CoV-2 index case in their household. Children's role in driving the COVID-19 pandemic changes in consecutive waves. The Monte Carlo approximation can be applied in assessing children's role in the infection spread.

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Table1

Table 1. The characteristics of the families (*n*=515)

Children (n; %)	883 children
Boys	478, 54.1%
Girls	405, 45.9%
Age of the children [median (Q1-Q3)] [years]	5.00 (1.00-11.00)
Adults (n; %)	1060
Men	487, 45.9%
Women	573, 54.1%
Age of the adults [median (Q1-Q3)] [years]	37.00 (32.00-43.00)
Family structure*	
'2+1'	153, 29.7%
'2+2'	178, 34.6%
other	184, 35.7%
Attending childcare facilities (n, % of children in a respective age group)	
In total	542/883, 61.4%
Nursery	57/310, 18.4%
Kindergarten	152/197, 77.2%
School	333/376, 88.6%
In-office working (n, % of adults of a respective sex)	
In total	542/1060, 51.1%
Men	332/487, 68.2%
Women	210/573, 36.6%
Families with 'no contacts' (n, %)**	55, 10.7%

Preceding hospitalization* (n, % of respective groups)**	
In total	70, 3.6%
Children	35, 4%
Adults	35, 3.3%
Vaccinated (n, % within respective age group)	
a) **Completed primary series****	
Adults	718, 67.7%
Children	72/456, 15.8%
5-11 y.o.	9/270, 3.3%
≥12 y.o.	63/186, 33.9%
b) **At least one dose**	
Adults	745, 70.3%
Children	88/456, 19.3%
5-11 y.o.	16/270, 5.9%
≥12 y.o.	72/186, 38.7%
Positive cases among children and how they were identified (n, % of positive cases among children)	
In total	663, 75.1%
RT-PCR	373, 56.3%
Antigen	250, 37.7%
Unknown type of the test	1, 0.2%
Solely symptoms	39, 5.9%
Children, symptomatic (n, % of positive cases among children)	589/663, 88.8%

Positive cases among adults and how they were identified (n, % of positive cases among adults)	
In total	509, 48%
RT-PCR	331, 65%
Antigen	87, 17.1%
Unknown type of the test	3, 5.9%
Solely symptoms	88, 17.3%
Adults, symptomatic (n, % of positive cases among adults)	444/509, 87.2%
The second attack rate = 0 (n, % of all families)	165, 32%
The second attack rate = 1 (n, % of all families)	143, 27.8%

* Number of the people living in the household; the first number = number of adults, the second number = number of children

** Families with no children attending childcare facilities and no adults working in an office

*** Applies to hospitalization within two weeks preceding infection in the index case

**** Persons vaccinated with one dose of adenovirus 26 vector vaccine (Ad26.COV2.S) or two doses of any other anti-SARS-CoV-2 vaccine

Table2

Table 2. The results of Monte Carlo regressions

All families						
	Estimate	**SE**	**z value**	**p value**	**%p ***	**95% CI**
(Intercept)	-0.820	0.194	-4.228	<0.001	100%	[-0.821,-0.820]
Male sex	0.015	0.204	0.075	0.891	0%	[0.015,0.016]
Age	0.106	0.034	3.143	0.002	100%	[0.106,0.106]
Attending nursery	1.456	0.409	3.565	<0.001	100%	[1.456,1.457]
Attending kindergarten	0.899	0.296	3.038	0.003	100%	[0.898,0.900]
Attending school	1.230	0.370	3.32	0.001	100%	[1.229,1.231]
Fully vaccinated	1.09	0.744	1.451	0.155	0%	[1.08, 1.09]
Previous hospitalizations	0.284	0.453	0.627	0.532	0%	[0.283,0.285]
Families in which all members were tested for SARS-CoV-2						
(Intercept)	-1.170	0.300	-3.91	<0.001	100%	[-1.170,-1.170]
Male sex	0.038	0.296	0.129	0.880	0%	[0.037, 0.039]
Age	0.048	0.055	0.885	0.381	0%	[0.048, 0.049]
Attending nursery	1.625	0.526	3.088	0.002	100%	[1.625, 1.626]
Attending kindergarten	1.253	0.413	3.033	0.003	100%	[1.252, 1.255]
Attending school	1.513	0.597	2.533	0.012	100%	[1.510, 1.515]
Fully vaccinated	1.361	0.844	1.598	0.175	0%	[1.355, 1.366]
Previous hospitalizations	0.328	0.626	0.523	0.603	0%	[0.327, 0.330]
Families surveyed in 2021 (Delta variant predominant)						
(Intercept)	-1.137	0.232	-4.910	<0.001	100%	[-1.138, -1.136]
Male sex	0.106	0.231	0.457	0.653	0%	[0.105, 0.107]
Age	0.092	0.038	2.424	0.017	100%	[0.092, 0.092]
Attending nursery	1.655	0.445	3.718	<0.001	100%	[1.654, 1.655]

Attending kindergarten	0.932	0.346	2.694	0.008	100%	[0.931, 0.933]
Attending school	1.605	0.430	3.734	<0.001	100%	[1.603, 1.606]
Previous hospitalizations	0.515	0.472	1.091	0.277	0%	[0.514, 0.516]
Families surveyed in 2022 (non-Delta variant predominant)						
(Intercept)	-0.064	0.394	-0.163	0.871	0%	[-0.065, -0.063]
Male sex	-0.008	0.492	-0.014	0.868	0%	[-0.010, -0.006]
Age	0.174	0.078	2.217	0.027	100%	[0.173, 0.174]
Attending nursery	1.214	1.160	1.047	0.295	0%	[1.213, 1.215]
Attending kindergarten	0.784	0.647	1.212	0.227	0%	[0.783, 0.785]
Attending school	1.163	1.162	0.988	0.330	0%	[1.157, 1.170]

Abbreviations: SE, Standard Error; %p, percent of Monte Carlo runs with p value <0.05; 95% CI, 95% confidence interval.

*The following voting procedure was used to assess the statistical significance of predictors. For each predictor we counted the number of Monte Carlo runs for which the given predictor was statistically significant (*p* value <0.05). We considered the predictor significant if the percent of positive runs (votes) exceeded the predefined threshold (80%).

Figure1

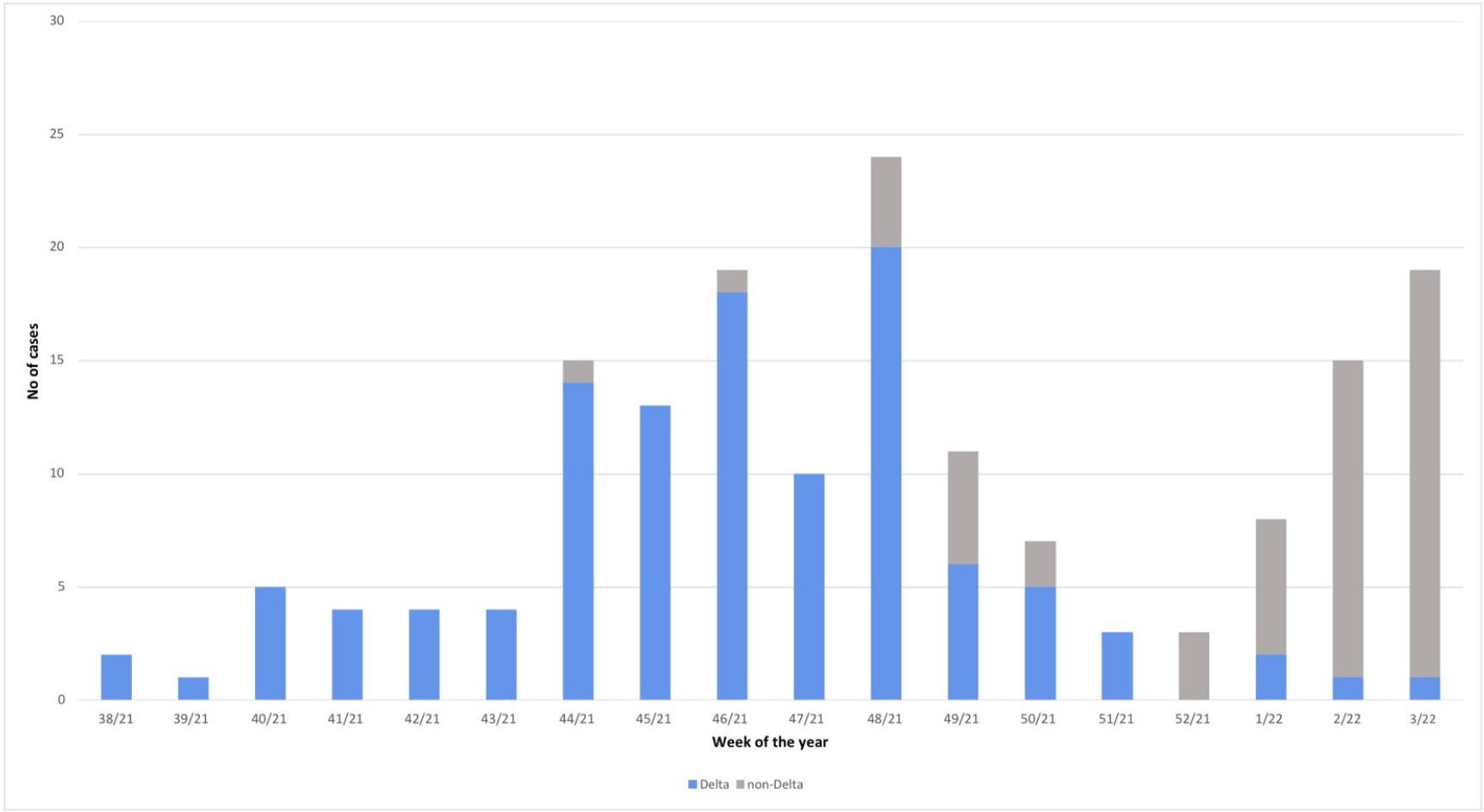

FIGURE 1. The time distribution of Delta and non-Delta variants from children who were tested with RT-PCR in our hospital. Among 167 samples, 113 (67.7%) were Delta cases and 54 (32.3%) were non-Delta cases. RT-PCR indicates reverse transcription polymerase chain reaction.

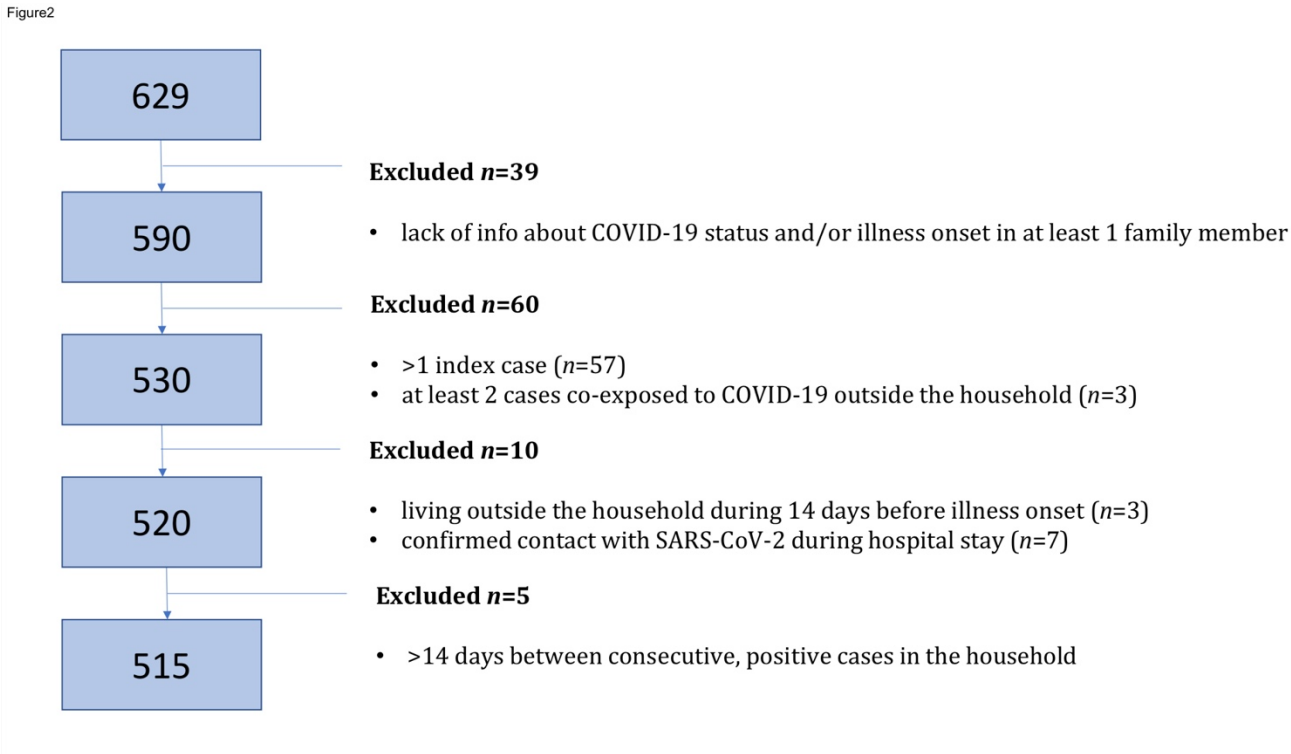

FIGURE 2. Families' selection based on exclusion criteria.

Supplemental Digital Content 1. The characteristics of children hospitalized and/or tested

All children hospitalized and/or tested in the hospital (n=637)	
Sex (n, % of all)	
Boys	350, 55%
Girls	287, 45%
Age (median; Q1-Q3) [years]	3.00; 1.00-10.00
Patients' recruitment site (n, % of all)	
Hospitalization	243, 38.1%
Emergency department visit	320, 50.3%
Child of the hospital worker	12, 1.9%
Swab collection point*	62, 9.7
Type of positive SARS-CoV-2 test (n, % of all)	
RT-PCR	368, 57.8%
Antigen test	269, 42.2%
Vaccinated ** (n, % of children in this age group)	
5-11 y.o.	5, 5%
≥12 y.o.	35, 28.9%
COVID-19 clinical course (n, % of all)	
Symptomatic	558, 87.6%
Asymptomatic	61, 9.6%
Symptoms not clear, might be attributed to a concomitant illness	18, 2.8%
COVID-19 symptoms (n, % of symptomatic patients)	
Cough	383, 68.6%

Coryza	354, 63.4%
Fever	325, 58.2%
Tiredness	279, 50%
Loss of appetite	237, 42.5%
Patients hospitalized (*n*=243)	
Sex (n, % of hospitalized patients)	
Boys	141, 58%
Girls	102, 42%
Age (median; Q1-Q3) [years]	2.00; 1.00-11.00
Cause of hospitalization (n, % of hospitalized patients)	
COVID-19	137, 56.4%
Other than COVID-19	106, 43.6%
Causes of hospitalization other than COVID-19 (n, % of hospitalized patients)	
Diabetes	8, 3.3%
Foreign body ingestion	8, 3.3%
Nephrotic syndrome	8, 3.3%
Epilepsy	7, 2.9%
Febrile seizures	6, 2.5%
Chronic diseases of children hospitalized due to COVID-19 (n, % of hospitalized patients)	
Allergy, excluding asthma	9, 3.7%
Asthma	5, 2.1%
Epilepsy	4, 1.7%
Cerebral palsy	3, 1.2%

Hypothyroidism	2, 0.8%
COVID-19 complications (n, % of hospitalized patients)	
Abnormalities in the chest X-ray	54, 22.2%
Desaturation	21, 8.6%
Treatment for COVID-19 (n, % of hospitalized patients)	
Systemic steroids	18, 7.4%
Remdesivir	10, 4.1%
Tocilizumab	3, 1.2%
Low-dose oxygen therapy	17, 7%
High flow oxygen therapy	5, 2.1%
Invasive ventilation	1, 0.4%
Stay in PICU	1, 0.4%

* COVID-19 routine screening in patients before planned hospitalizations

** Children vaccinated with at least one dose of COVID-19 vaccine

Abbreviations: COVID-19, coronavirus disease 2019; y.o., years old; PICU, pediatric intensive care unit; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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REVIEW ARTICLE

How international guidelines recommend treating children who have severe COVID-19 or risk disease progression

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Abstract

Aim: This study reviewed the current knowledge and guidelines on managing COVID-19 in children and proposed a practical approach to drug treatment.

Methods: We analysed international guidelines from four prominent scientific bodies on treating COVID-19 in children. These were the UK National Institute for Health and Care Excellence, the American National Institutes of Health, the Infectious Diseases Society of America and the Australian National Clinical Evidence Taskforce COVID-19.

Results: Most paediatric patients with COVID-19 only require symptomatic treatment. There was limited evidence on treatment recommendations for children with severe COVID-19 or at risk of disease progression. However, several drugs are available for children and we have summarised the guidelines, in order to provide a concise, practical format for clinicians. All the guidelines agree that nirmatrelvir plus ritonavir or remdesivir can be used as prophylaxis for severe COVID-19 in high-risk patients. Remdesivir can also be used for severe COVID-19 cases. Glucocorticosteroids are recommended, particularly in patients requiring oxygen therapy. Tocilizumab or baricitinib should be reserved for patients with progressive disease and/or signs of systemic inflammation.

Conclusion: The guidelines provide useful advice and a degree of consensus on specific drug treatment for children with severe COVID-19 or at risk of progression.

KEYWORDS
baricitinib, pandemic, remdesivir, steroids, tocilizumab

1 | INTRODUCTION

COVID-19 has contributed to more than seven million deaths worldwide.[1] Older age and specific underlying medical conditions have been recognised as risk factors for severe disease. According to the literature, COVID-19 is usually asymptomatic or mild in children. However, a small subset of paediatric patients, particularly those with underlying chronic conditions, might have severe COVID-19 that requires specific treatment.

Our aim was to review the current knowledge on managing COVID-19 in children, by focusing on four guidelines from the United Kingdom, United States and Australia. The COVID-19 rapid guideline: managing COVID-19, by the UK National Institute for Health and Care Excellence (NICE), was last updated on 8 May 2024.[2] The COVID-19 Treatment Guidelines, by the American National Institutes of Health (NIH), was last updated on 29 February 2024.[3] The Guidelines on the Treatment and Management of Patients with COVID-19, by the Infectious

Abbreviations: ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; IDSA, Infectious Diseases Society of America; NICE, National Institute for Health and Care Excellence; NIH, National Institutes of Health.

Diseases Society of America (IDSA), was last updated on 26 June 2023.[4] The Australian guidelines for the clinical care of people with COVID-19, by the National Clinical Evidence Taskforce COVID-19, was last updated on 30 May 2023.[5]

Most of the recommendations for managing COVID-19 in children are based on guidelines for adults or expert opinions. There have been few randomised controlled trials that included children as participants. It is important to note that children have significantly milder disease courses and lower mortality risks than adults. Thus, effect sizes for children may be smaller, requiring higher numbers needed to treat.[3] Therefore, clinicians should carefully weigh the risks and benefits of paediatric pharmacologic interventions.

Key Notes

- We analysed four international guidelines on treating COVID-19 in children, from prominent scientific bodies in the United Kingdom, America and Australia.
- These suggest that symptomatic care is sufficient for most children, but treatment is needed for more severe cases and where there is a risk of disease progression.
- Several drugs are recommended for children and we have summarised the guidelines, to provide a concise, practical format for clinicians.

2 | WHO TO TREAT

Most children with COVID-19 are asymptomatic or have mild symptoms, such as fever, cough, congestion or malaise. They typically need ambulatory care and supportive treatment, including adequate hydration, fever and cough management and rest. Some children with COVID-19 present with similar symptoms to other respiratory syndromes, such as croup or bronchiolitis. In these cases, treatment should follow the respective guidelines.[3] However, some children develop severe COVID-19 and this is an independent indication for specific treatment, regardless of their underlying conditions. In addition, children at risk of severe COVID-19 may benefit from treatment. Specific COVID-19 treatment should be considered for these two groups.

2.1 | Severe COVID-19

Severe COVID-19 is rare in paediatric populations. Initially, it affected about 2% of infected children, who developed acute respiratory distress, kidney injury, liver failure, encephalopathy, myocarditis, shock and thromboembolism. Some died.[6] The prevalence of severe disease among children decreased to below 0.1% with subsequent shifts in the virus that causes COVID-19.[7] In addition, the number treated in paediatric intensive care units decreased with successive COVID-19 waves. However, the number of children under 5 years of age who required oxygen or ventilatory support remained constant throughout the pandemic.[8]

Symptoms that indicate severe and critical COVID-19 include respiratory failure, shock and multiorgan dysfunction. Lower respiratory involvement, leading to the need for mechanical ventilation, has been the most common.[9] Multiorgan dysfunction probably stems from cytokine storm, oxidative stress and disseminated intravascular coagulation. Cytokine storm has been associated with the severity of COVID-19 and mortality.[10,11]

Importantly, even asymptomatic COVID-19 may lead to multisystem inflammatory syndrome in children. This rare late complication, which occurs approximately 4 weeks after the acute infection, has typically affected otherwise healthy children.[12] Some of the children have presented with symptoms and signs similar to acute, severe COVID-19, but the treatment required differs markedly.[12] Specific recommendations regarding multisystem inflammatory syndrome in children treatment are beyond the scope of this review.

2.2 | Risk factors for severe COVID-19

Severe COVID-19 can develop in individuals of any age or health status. However, there are specific risk factors for the severe course of COVID-19. In adults, these include advanced age, certain underlying medical conditions and lack of COVID-19 vaccination.[13] According to the American Centers for Disease Control and Prevention, age has been the strongest predictor of severe COVID-19 outcomes.[13]

There is limited evidence to support the risk factors for severe COVID-19 in children. Infants and teenagers may have a higher risk of paediatric intensive care unit admission and death.[14] Non-White race/ethnicity and certain comorbidities may also increase severity.[13,15–18] The list of comorbidities that may lead to severe COVID-19 in children, as proposed by the NIH, is presented in Table 1. However, the association between comorbidities and progression to severe COVID-19 in children remains uncertain. Vaccination against COVID-19 has been shown to reduce the risk of severe disease.[19,20]

3 | HOW TO TREAT

The choice of treatment depends on the clinical course and time since disease onset. One challenge is recommending medication for paediatric patients with COVID-19, due to the shortage of randomised trials. We provide a list of medications authorised for COVID-19 management in adults and some that are also used in children. Details on treating COVID-19 in children, according to the various guidelines, are presented in Table 2. Table 3 outlines the recommended management of COVID-19 in children based on their clinical condition.

TABLE 1 The association between specific underlying conditions and risk of progression to severe COVID-19 in children, according to COVID-19 Treatment Guidelines by National Institutes of Health.[3]

Risk level	Comorbidities
High risk[a] Strong or consistent association with progression to severe COVID-19.	• Immunosuppression • Obesity, defined as a body mass index >95th percentile for age and sex • Medical complexity, with dependence on respiratory technology • Severe neurological, genetic, metabolic or other disability that results in impaired airway clearance or limitations in self-care or daily activities • Severe asthma or other severe chronic lung disease requiring ≥2 inhaled or ≥1 systemic medications daily • Severe cardiac disease • Multiple moderate to severe chronic diseases
Intermediate risk[a] Moderate or inconsistent association with progression to severe COVID-19.	• Aged <1 year • Prematurity in children aged ≤2 years • Sickle cell disease • Poorly controlled diabetes mellitus • Non-severe cardiac, neurological, or metabolic disease
Low risk[a] Weak or unknown association with progression to severe COVID-19.	• Mild asthma • Overweight • Well-controlled diabetes mellitus

[a]The associations between comorbidities and progression to severe COVID-19 in children are uncertain.

3.1 | Remdesivir

Remdesivir is an intravenously administered antiviral, which inhibits viral replication by binding to ribonucleic acid polymerase. Initially approved by the American Food and Drug Administration (FDA) for hospitalised adults with COVID-19, it has showed effectiveness in shortening the time to recovery.[21] However, the World Health Organization Solidarity randomised trial found that remdesivir had no significant effect on ventilated patients with COVID-19. It had a small effect against death or progression to ventilation among other hospitalised patients.[22] This led to a recommendation from the World Health Organization against using remdesivir in patients with COVID-19, due to insufficient evidence. Conversely, in April 2022, the World Health Organization recommended remdesivir within 7 days of symptom onset in patients with non-severe COVID-19 at risk of hospitalisation. This recommendation applied to individuals at least 12 years old and weighing at least 40 kilograms. In the same month, the FDA approved remdesivir for children with COVID-19 aged at least 28 days, and weighing at least 3 kg, at risk of progressing to severe disease. This recommendation followed the preliminary results of a study on using remdesivir for children under 18 years of age with COVID-19.[23]

According to all four guidelines, remdesivir may be used to prevent progression to severe COVID-19 and to treat COVID-19. Detailed recommendations are presented in Table 2.

Remdesivir can be used as prophylaxis for severe COVID-19 and may be administered within 7 days of symptom onset for individuals with a high risk of progressing to severe disease.[2–5] The guidelines vary with regard to the minimum age recommendations: the NIH guidelines suggest at least 12 years,[3] while the Australian guidelines suggest at least 28 days.[5] The Australian guidelines particularly recommend remdesivir for unimmunised children with COVID-19.[5] However, it must be emphasised that the association between risk factors and severe COVID-19 in children remains uncertain. Hence, routine remdesivir prophylaxis should be considered with caution.

The guidelines agree that remdesivir should be provided for hospitalised individuals with COVID-19 who need supplemental oxygen. However, the criteria for using oxygen therapy differ. The NICE guidelines recommend only using remdesivir for patients on low-flow oxygen,[2] whereas the Australian guidelines also include those on high-flow oxygen therapy.[5] The NIH and the IDSA guidelines broaden the indications further by adding patients requiring non-invasive ventilation.[3,4] All recommendations unanimously state that remdesivir is not recommended for individuals requiring mechanical ventilation. In addition, the IDSA guidelines specifically mention extracorporeal membrane oxygenation (ECMO) as a contraindication.[4] Meanwhile, the NIH and Australian guidelines restrict remdesivir administration to patients on glucocorticosteroids.[3,5] The recommended dose of remdesivir in the NIH and IDSA guidelines is 5 mg/kg/dose on day one, followed by 2.5 mg/kg/dose once daily. For children who weigh 40 kg or more, the dose is 200 mg on day one, followed by 100 mg once daily.[3,4] The recommended treatment duration varies among the guidelines and depends on the indications and the patient's condition. In the NICE, NIH and IDSA guidelines, it ranges from 3 days, to prevent deterioration, to 5 days for severe COVID-19 treatment.[2–4] The NIH recommends that treatment may be extended for up to 10 days if there is no clinical improvement.[3]

TABLE 2 Details on treating COVID-19 in children, according to the NICE, NIH, IDSA and Australian guidelines.[2–5]

		NICE[2]	NIH[3]	IDSA[4]	Australian[5]
Nirmatrelvir plus ritonavir (to prevent progression[a])		Adults ≥18 years only	People ≥12 years old within 5 days of symptom onset and at high risk[b]	People ≥12 years old and ≥ 40 kg within 5 days of symptom onset and at high risk	Children ≥12 years old and ≥ 40 kg within 5 days of symptom onset and at high risk, particularly those who are not immunised against COVID-19[c]
Remdesivir	To prevent progression[a]	People ≥12 years old. and ≥ 40 kg within 7 days of symptom onset and at high risk[d]	People ≥12 years old. within 7 days of symptom onset and at high risk[b]	People within 7 days of symptom onset and at high risk	Children ≥28 days old and ≥3 kg within 7 days of symptom onset and at high-risk, particularly those who are not immunised against COVID-19[c]
	To treat	Children ≥28 days old and ≥3 kg with COVID-19 pneumonia who are hospitalised and need supplemental oxygen[d] Not to be used in people who need high-flow oxygen, non-invasive or mechanical ventilation	Hospitalised children who need supplemental oxygen: either conventional or high-flow[e] or non-invasive ventilation[e]	People with SpO2 ≤ 94% on room air, including those who need supplemental oxygen Not to be used in people who need mechanical ventilation or ECMO	Children ≥28 days old and ≥3 kg with severe COVID-19[f] who need oxygen and glucocorticosteroids Not to be used in children who need non-invasive or mechanical ventilation
Systemic glucocorticosteroids		People who need supplemental oxygen[g] Not to be used in people who don't need supplemental oxygen	People with increasing oxygen needs, particularly those who need high-flow therapy, non-invasive or mechanical ventilation or ECMO Not to be used in people who don't need supplemental oxygen	People with SpO2 ≤ 94% on room air, including those who need supplemental oxygen, and those who need mechanical ventilation or ECMO Not to be used in people who don't need supplemental oxygen	Children who need supplemental oxygen[d] Not to be used in children who don't need supplemental oxygen[d]
Immunomodulation	Baricitinib	People ≥2 years old. who are hospitalised, need supplemental oxygen and glucocorticosteroids and have no infection which could worsen due to baricitinib[d]	People ≥2 years old. who are hospitalised, need high-flow oxygen therapy, non-invasive or mechanical ventilation or ECMO and have no rapid improvement after glucocorticosteroids	People who need glucocorticosteroids (as described above), but cannot receive them because of a contraindication[h]	Children ≥2 years old who require non-invasive or mechanical ventilation
	Tocilizumab	Adults ≥18 years only		Adults ≥18 years only	Children who require supplemental oxygen, particularly where there is evidence of systemic inflammation[d]

Abbreviations: ECMO, extracorporeal membrane oxygenation; IDSA, Infectious Diseases Society of America; NICE, National Institute for Health and Care Excellence, NIH, National Institutes of Health.

[a]Applies to people with mild-to-moderate COVID-19 and no new or increased supplemental oxygen requirement attributable to COVID-19.

[b]Not enough evidence to recommend either for or against routine use in children <12 years old.

[c]Not immunised include: immunosuppressed or those who did not receive a vaccine dose nor had a *severe acute respiratory syndrome coronavirus 2* infection within past 6 months.

[d]Consider use (conditional recommendation).

[e]Only in combination with glucocorticosteroids.

[f]Likely to progress to ventilation.

[g]Recommended.

[h]Only in combination with remdesivir.

TABLE 3 Recommended management of COVID-19 in children, based on their clinical condition, in line with the NICE, NIH, IDSA and Australian guidelines.[2–5]

Clinical condition	Management
• Within 5–7 days of symptom onset • AND mild-to-moderate course • AND no need for oxygen supplementation	• Consider remdesivir (within 7 days of disease onset) or nirmatrelvir plus ritonavir (within 5 days since disease onset) in high-risk groups, particularly children ≥12 years old
• Need conventional oxygen supplementation	• Consider glucocorticosteroids (the higher oxygen needs the more likely to benefit) • Consider remdesivir (the earlier in the course of disease the more likely to benefit)
• Need high-flow oxygen therapy or non-invasive ventilation	• Give glucocorticosteroids • Consider remdesivir (the earlier in the course of disease the more likely to benefit) • Consider tocilizumab or baricitinib (particularly if no rapid improvement after glucocorticosteroids and/or signs of inflammation)
• Need for mechanical ventilation or extracorporeal membrane oxygenation • AND/OR critical disease • AND/OR cytokine storm	• Give glucocorticosteroids • Consider tocilizumab or baricitinib (particularly if no rapid improvement after glucocorticosteroids and/or signs of inflammation)

Abbreviations: IDSA, Infectious Diseases Society of America; NICE, National Institute for Health and Care Excellence, NIH, National Institutes of Health.

3.2 | Nirmatrelvir plus ritonavir

Nirmatrelvir plus ritonavir, an oral antiviral, inhibits the virus that causes COVID-19 replicating. Nirmatrelvir is a 3Cl protease inhibitor, while ritonavir is a CYP3A4 inhibitor. Hammond et al. studied symptomatic, unvaccinated adults with mild-to-moderate COVID-19 at high risk of progression to severe disease in ambulatory settings. They were randomised to receive either nirmatrelvir plus ritonavir or a placebo. The nirmatrelvir plus ritonavir group had an 89% lower risk of progression to severe COVID-19.[24] However, another study by Hammond et al. found that there was no difference in the recovery time between adults with COVID-19 who received nirmatrelvir plus ritonavir or a placebo.[25] A study by Liu et al.[26] reported that nirmatrelvir plus ritonavir did not significantly reduce all-cause mortality risk in hospitalised adults with COVID-19 and severe comorbidities.

In December 2021, the FDA authorised nirmatrelvir plus ritonavir for mild-to-moderate COVID-19 in patients aged 12 years or older, weighing at least 40 kg, at high risk of severe disease.

All guidelines, except the NICE guidelines, recommend nirmatrelvir plus ritonavir for individuals who are least 12 years of age, within 5 days of symptom onset, if they have mild-to-moderate COVID-19 and a high risk of disease progression.[3–5] The NICE guidelines recommend nirmatrelvir plus ritonavir for adults only.[2] The Australian guidelines particularly advise its use for non-immunised patients.[5] The NIH guidelines state that nirmatrelvir plus ritonavir should be administered cautiously in patients concurrently taking CYP3A4 inducers, due to the risk of potentially life-threatening elevations in drug concentration.[3] The recommended doses are 300 mg of nirmatrelvir with 100 mg of ritonavir, orally, twice daily for 5 days.[3]

3.3 | Glucocorticosteroids

Glucocorticosteroids have anti-inflammatory and immunosuppressive properties that are likely to mitigate immune system overstimulation present in severe or critical COVID-19 cases. The randomised evaluation of COVID-19 therapy trial demonstrated that dexamethasone reduced mortality in patients with COVID-19 who were receiving oxygen therapy.[27] Subsequent studies confirmed lower mortality rates in severely and critically ill patients with COVID-19 who were treated with systemic corticosteroids versus usual care or a placebo.[28,29] Conversely, Crothers et al. found that when dexamethasone was administered within 48 h of hospital admission, it increased mortality among patients with COVID-19 who did not require oxygen or were on low-flow oxygen.[30] Dexamethasone is the most extensively studied glucocorticosteroid for COVID-19. Other steroids, including methylprednisolone and hydrocortisone, have also been assessed, but the trials that included these had insufficient sample sizes, resulting in inconclusive evidence.[31–33] Limited data exist on using dexamethasone for children with COVID-19, but its licences and established safety in paediatric populations support its use for specific scenarios.

All the guidelines agree that systemic glucocorticosteroids are indicated for patients with COVID-19 who require oxygen supplementation, irrespective of age. The NIH specifically advises their use in patients who need high-flow oxygen therapy, non-invasive ventilation, mechanical ventilation or ECMO. However, all the guidelines recommend against administering dexamethasone to patients with COVID-19 who do not require supplemental oxygen. The dose of dexamethasone recommended by the NICE, NIH and Australian guidelines is 0.15 mg/kg orally or intravenously once daily for up to 10 days or until the patient is discharged from hospital, whichever

occurs first.[2,3,5] The dose should not exceed 6 mg. If dexamethasone is unavailable, all four guidelines state that equivalent doses of other steroids may be considered.[2–5]

3.4 | Inhaled glucocorticosteroids

Inhaled glucocorticosteroids have been considered potentially beneficial for patients with COVID-19, due to their established effects on other inflammatory respiratory diseases like asthma. Early in the pandemic, patients with respiratory diseases who used inhaled glucocorticosteroids were hospitalised less frequently with COVID-19, suggesting potential protection against severe disease.[34,35] However, the role of inhaled glucocorticosteroids in treating COVID-19 remains unclear, due to varied trial results and endpoints that make definitive conclusions challenging. Two trials showed reduced time to recovery from COVID-19 with inhaled budesonide administration in outpatient settings.[36,37] Other studies, including those in non-hospitalised patients, showed no improvement in symptom resolution.[38,39] We did not find any studies involving hospitalised adults or children.

The NICE guidelines advise limiting budesonide for COVID-19 to clinical trials. Patients who are already on budesonide for other reasons should continue treatment if they have COVID-19.[2] The NIH states that there is insufficient evidence to recommend or discourage inhaled corticosteroids for COVID-19.[3] The IDSA recommends against inhaled corticosteroids in ambulatory patients with mild-to-moderate COVID-19.[4] The Australian guidelines suggest considering budesonide or ciclesonide within 14 days of symptom onset for all age groups with COVID-19.[5] They add that drug should be aimed at those who do not need oxygen but have a risk of disease progression.

3.5 | Baricitinib

Baricitinib is an orally administered immunomodulatory drug that inhibits Janus kinases. It is used for treating rheumatoid arthritis and severe alopecia areata in adults. The drug is also approved for use in children aged 2 years and older for atopic dermatitis and active juvenile idiopathic arthritis.

A randomised, placebo-controlled trial of adults hospitalised with COVID-19 showed that adding baricitinib to their standard care, including dexamethasone and remdesivir, reduced mortality rates.[40] The safety profile of this combination therapy was similar to standard care, but it did not significantly decrease overall disease progression. Wolfe et al. studied hospitalised adult patients with COVID-19 who required supplemental oxygen via low-flow, high-flow or non-invasive ventilation and compared baricitinib with dexamethasone. Both baricitinib plus remdesivir and dexamethasone plus remdesivir showed similar mechanical ventilation-free survival by day 29, but dexamethasone was associated with significantly more adverse events.[41] A meta-analysis of four randomised controlled trials involving nearly 11 000 patients confirmed that adding baricitinib to standard care reduced 28-day mortality in hospitalised patients with COVID-19. However, there was no statistically significant reduction in the progression to mechanical ventilation or ECMO.[42] A trial currently underway aims to assess the effectiveness and safety of baricitinib in hospitalised children with COVID-19.[43]

In May 2022, the FDA approved baricitinib for treating COVID-19 in hospitalised adults requiring supplemental oxygen, non-invasive ventilation, mechanical ventilation or ECMO. It also stated that emergency use authorisation also permits its use in hospitalised children with COVID-19 aged 2–17 years who require this treatment.

All the guidelines recommend administering baricitinib for patients with COVID-19 who need supplemental oxygen.[2–5] The NICE guidelines narrow this recommendation down to patients who receive glucocorticosteroids and have no infection that could worsen due to baricitinib.[2] The NIH adds the condition of not improving rapidly after glucocorticosteroids before receiving baricitinib.[3] The IDSA only recommends baricitinib with remdesivir for patients who need glucocorticosteroids, but cannot receive them due to contraindications.[4] The NIH and Australian guidelines state that baricitinib should be administered as an oral daily dose for up to 14 days or until hospital discharge.[3,5] Children of 2–9 years of age should receive 2 mg per day and those aged 10–18 years should receive 4 mg per day.[3,5]

3.6 | Tocilizumab

Tocilizumab is a humanised monoclonal antibody that targets the interleukin-6 receptor and is an immunomodulatory agent. Before it was authorised for COVID-19 treatment, it was used to treat conditions like rheumatoid arthritis and giant cell arteritis. Salama et al. reported that its use in hospitalised patients with COVID-19 pneumonia reduced progression to the composite outcome of mechanical ventilation or death, without improving survival.[44] Veiga et al. proved that adding tocilizumab to standard care for patients with severe or critical COVID-19 did not improve outcomes at 15 days and possibly increased mortality. The trial was stopped early, after 129 patients were enrolled, due to the increased number of deaths in the tocilizumab group at 15 days.[45] However, the randomised evaluation of COVID-19 therapy study showed that tocilizumab improved survival and other clinical outcomes in hospitalised patients with COVID-19, hypoxia and systemic inflammation.[46] Moreover, these benefits were observed regardless of the level of respiratory support and in addition to the benefits of systemic glucocorticosteroids. A systematic review and meta-analysis included all randomised controlled trials, published from 1 January 2020 to 5 May 2021, that reported tocilizumab efficacy as a primary agent in COVID-19. It reported that tocilizumab reduced all-cause mortality and the progression to mechanical ventilation in patients with moderate-to-critical COVID-19.[47] This effect did not correlate with a higher number of serious adverse events. We found no studies regarding tocilizumab efficacy or safety in children. One study is currently evaluating

tocilizumab in paediatric patients hospitalised with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.[48]

In June 2021, the FDA authorised tocilizumab for treating hospitalised adults and children with COVID-19 who are aged at least 2 years. These patients must be receiving systemic glucocorticosteroids and require supplemental oxygen, non-invasive ventilation, mechanical ventilation or ECMO.

The NICE and the IDSA guidelines only recommend tocilizumab for adults.[2,4] The NIH and Australian guidelines agree that tocilizumab should be considered for children with COVID-19 requiring supplemental oxygen.[3,5] The NIH narrows this recommendation to people aged 2 years or older with no rapid improvement after glucocorticosteroids.[3] The Australian guidelines emphasise the potential benefits of this drug, particularly for children with evidence of systemic inflammation.[5] The NIH and Australian guidelines recommend that tocilizumab should be administered as a single intravenous infusion.[3,5] If there is no improvement after the initial dose, it may be repeated once, at least 12 h after the first dose. In children weighing under 30 kg, the dose should be 12 mg/kg. In those weighing at least 30 kg, it should be 8 mg/kg, up to a maximum of 800 mg.[3,5]

4 | CONCLUSION

Most children with COVID-19 only require supportive care, as they do for other acute viral respiratory tract infections. However, some require greater support and specific treatment. Most guidelines for treating COVID-19 in children are based on adult recommendations or expert opinions, due to limited trials that have included participants below 18 years old. This study looked at four guidelines, from the United Kingdom, United States and Australia, and found that they provided useful advice and a degree of consensus on specific drug treatment for children with severe COVID-19 or at risk of progression. Nirmatrelvir plus ritonavir or remdesivir may be used for those at high risk of disease progression. They should be administered promptly, ideally within the first days of symptom onset. Remdesivir may also be used in hospitalised children who need supplemental oxygen. Receiving oxygen therapy is also an indication for systemic glucocorticosteroids. When the treatment is ineffective, immunomodulators, namely baricitinib and tocilizumab, can be considered, particularly in children with signs of systemic inflammation. Clinicians must carefully weigh the potential benefits and harms before providing children with any treatment for COVID-19. Decisions should preferably be discussed within the medical team taking care of the child.

AUTHOR CONTRIBUTIONS

Joanna Mańdziuk: Conceptualization; writing – original draft; methodology; investigation; data curation; visualization. **Ernest Kuchar:** Writing – review and editing; project administration; supervision. **Magdalena Okarska-Napierała:** Conceptualization; methodology; investigation; writing – original draft; writing – review and editing; visualization.

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Podsumowanie i wnioski

Rozprawę stanowią trzy prace w języku angielskim dotyczące COVID-19 u dzieci.
Wnioski:

1. Małe dzieci mogą skutecznie zakażać swoich dorosłych domowników i inne dzieci wirusem SARS-CoV-2. Za przenoszenie wirusa mogą być odpowiedzialne szczególnie bliskie kontakty między małymi dziećmi i ich opiekunami, także zachodzące w instytucjach opiekuńczych, np. w żłobkach. Publikacja nr 1.
2. Uczęszczanie do placówek opiekuńczych i edukacyjnych we wszystkich grupach wiekowych jest czynnikiem ryzyka przeniesienia zakażenia do środowiska domowego. W razie wystąpienia kolejnych fal COVID-19 w przyszłości zasadne jest rozważenie czasowego zamknięcia placówek opiekuńczych i edukacyjnych. Publikacja nr 2.
3. Rola dzieci w transmisji zakażenia SARS-CoV-2 prawdopodobnie zmienia się wraz z pojawianiem się kolejnych wariantów wirusa. Publikacja nr 2.
4. Analiza Monte Carlo okazała się dobrą metodą, którą można zastosować do identyfikacji czynników ryzyka rozprzestrzeniania się innych drobnoustrojów chorobotwórczych, w przyszłym epidemiach. Publikacja nr 2.
5. Wytyczne dotyczące leczenia COVID-19 u dzieci opublikowane przez gremia naukowe o międzynarodowym zasięgu (NICE, NIH, IDSA, wytyczne australijskie) są spójne i wskazują, że należy rozważyć leczenie COVID-19 u pacjentów z ciężkim przebiegiem COVID-19 i zakażonych dzieci obarczonych wysokim ryzykiem ciężkiego przebiegu choroby. Wybór właściwego leczenia jest uzależniony od czasu od rozpoczęcia choroby do wdrożenia leczenia oraz przebiegu choroby. Publikacja nr 3.

Opinia Komisji Bioetycznej Warszawskiego Uniwersytetu Medycznego

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Warszawa, dnia 22 lipca 2020r.

AKBE/139 / 2020

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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 22 lipca 2020 r. przyjęła do wiadomości informację na temat badania pt.:"Ognisko zakażeń SARS-CoV-2 wśród dzieci, ich opiekunów prawnych oraz pracowników w żłobku w Radomiu ." Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21 ust. 1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty(Dz.U. z 2018 r. poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust. 1 ww. ustawy.

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Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 14 grudnia 2020 r. przyjęła do wiadomości informację na temat badania pt.:"Ocena potencjalnych źródeł SARS-CoV-2 u dzieci hospitalizowanych w Dziecięcym Szpitalu Klinicznym Warszawskiego Uniwersytetu Medycznego." Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21 ust. 1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty(Dz.U. z 2018 r. poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust. 1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

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Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład (udział merytoryczny i procentowy) każdego z nich w ich powstanie

SARS-CoV-2 Cluster in Nursery, Poland

Warszawa, 28.10.2024
(miejscowość, data)

Magdalena Okarska-Napierała
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*SARS-CoV-2 Cluster in Nursery, Poland*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji, interpretację wyników, nadzór merytoryczny nad manuskryptem.

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(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

magdo. napierała
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 28.10.2024
(miejscowość, data)

Ernest Kuchar
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*SARS-CoV-2 Cluster in Nursery, Poland*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: interpretację wyników, nadzór merytoryczny nad manuskryptem.

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(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.

(imię i nazwisko kandydata do stopnia)

KIEROWNIK
Kliniki Pediatrii z Oddziałem Obserwacyjnym

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave

Warszawa, 28.10.2024
(miejscowość, data)

Magdalena Okarska-Napierała
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji, metodyki, interpretacja wyników, nadzór merytoryczny nad manuskryptem.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 60%,
(imię i nazwisko kandydata do stopnia)

obejmował on przygotowanie koncepcji, metodyki, zbieranie danych, interpretację wyników, napisanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

magdalena napierała
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 25.10.2024
(miejscowość, data)

Weronika Woźniak
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zbieranie danych.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 60%,
(imię i nazwisko kandydata do stopnia)

obejmował on: przygotowanie koncepcji, metodyki, zbieranie danych, interpretację wyników, napisanie manuskryptu

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk
(imię i nazwisko kandydata do stopnia)

Weronika Woźniak

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 25.10.2024
(miejscowość, data)

Ada Hryniewicka
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: analiza statystyczna.
Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 60%,
(imię i nazwisko kandydata do stopnia)
obejmował on przygotowanie koncepcji, metodyki, zbieranie danych, interpretację wyników, napisanie manuskryptu.
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 25.10.2024
(miejscowość, data)

Piotr Radziński
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: analiza statystyczna.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 60%,
(imię i nazwisko kandydata do stopnia)

obejmował on przygotowanie koncepcji, metodyki, zbieranie danych, interpretację wyników, napisanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

Piotr Radziński
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 25.10.2024
(miejscowość, data)

Anna Gambin
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: analiza statystyczna, nadzór merytoryczny nad manuskryptem.
Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 60%,
(imię i nazwisko kandydata do stopnia)
obejmował on przygotowanie koncepcji, metodyki, zbieranie danych, interpretację wyników, napisanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

Podpisany elektronicznie przez
na Gambin; Uniwersytet Warszaw
25.10.2024
11:58:32 +02'00'

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 25.10.2024
(miejscowość, data)

Edyta Podsiadły
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: analiza wariantów wirusa, nadzór merytoryczny nad manuskryptem.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 60%,
(imię i nazwisko kandydata do stopnia)

obejmował on przygotowanie koncepcji, metodyki, zbieranie danych, interpretację wyników, napisanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

E. Podsiadły
.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 28.10.2024
(miejscowość, data)

Urszula Demkow
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: pozyskanie finansowania, nadzór merytoryczny nad manuskryptem.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 60%,
(imię i nazwisko kandydata do stopnia)

obejmował on przygotowanie koncepcji, metodyki, zbieranie danych, interpretację wyników, napisanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 28.10.2024
(miejscowość, data)

Ernest Kuchar
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. '*Monte Carlo Regression for Evaluating Children's Role in the Pandemic Spread on the Example of Delta COVID-19 Wave*' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji, nadzór merytoryczny nad manuskryptem.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 60%,
(imię i nazwisko kandydata do stopnia)

obejmował on przygotowanie koncepcji, metodyki, zbieranie danych, interpretację wyników, napisanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

KIEROWNIK
Kliniki Pediatrii z Oddziałem Obserwacyjnym
prof. dr hab. n. med. Ernest Kuchar

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

How international guidelines recommend treating children who have severe COVID-19 or risk disease progression

Warszawa, 28.10.2024
(miejscowość, data)

Ernest Kuchar
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. *'How international guidelines recommend treating children who have severe COVID-19 or risk disease progression'* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji, nadzór merytoryczny nad manuskryptem.

Mój udział procentowy w przygotowaniu publikacji określam jako 10%.

Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 75%,
(imię i nazwisko kandydata do stopnia)
obejmował on przygotowanie koncepcji, wykonanie przeglądu literatury, napisanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

KIEROWNIK
Kliniki Pediatrii z Oddziałem Obserwacyjnym
prof. dr hab. n. med. Ernest Kuchar
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 28.10.2024
(miejscowość, data)

Magdalena Okarska-Napierała
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. *'How international guidelines recommend treating children who have severe COVID-19 or risk disease progression'* oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji, nadzór merytoryczny nad manuskryptem.

Mój udział procentowy w przygotowaniu publikacji określam jako 15%.

Wkład Joanny Mańdziuk w powstawanie publikacji określam jako 75%,
(imię i nazwisko kandydata do stopnia)

obejmował on przygotowanie koncepcji, wykonanie przeglądu literatury, napisanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Joanny Mańdziuk.
(imię i nazwisko kandydata do stopnia)

magdal. napierała
.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

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