

LEIDRAAD

Pre-operatieve diagnostiek naar COVID-19 bij asymptomatische kinderen ingepland voor chirurgie onder algehele anesthesie

Practice guideline

Pre-operative work-up for COVID-19 in asymptomatic children scheduled for surgery under general anesthesia

Leidraad

Pre-operatieve diagnostiek naar COVID-19 bij asymptomatische kinderen ingepland voor chirurgie onder algehele anesthesie

Disclaimer

This practice guideline is drafted to address the need for advice about pre-operative COVID-19 screening in children reporting no symptoms of COVID-19 after thorough history taking. The utility of COVID-19 screening in asymptomatic patients is highly dependent on the background prevalence of SARS-CoV-2 infection among the tested population and on the performance of screening tests. Due to the acute and dynamic nature of the pandemic and the lack of accurate estimates of COVID-19 prevalence among the Dutch population, it is difficult to generalize the possible effect of screening. Therefore, hospitals may deviate from this practice guideline based on a locally-formulated multidisciplinary statement when there are indications that the hospital is in an area of high COVID-19 infection prevalence.

Hospitals may choose to implement preoperative COVID-19 screening in pediatric patients in order to adhere to a uniform protocol where all perioperative patients groups are tested, as long as the guidelines for pre-operative screenings in adult and obstetric patients recommend testing.

Introduction

The SARS-CoV-2 pandemic has rapidly altered the practice of medicine globally and in the Netherlands. This current practice guideline was drafted by relevant medical specialists' associations under the auspices of the Dutch Association of Medical Specialists (FMS), and is a preliminary guide for how to perform a pre-operative COVID-19 workup for pediatric patients reporting no symptoms of COVID-19 who are awaiting elective or emergency surgery under general anesthesia.

The first filter in the diagnostic assessment of presence or absence of COVID-19 disease is **history taking**. This practice guideline specifically concerns pediatric patients who are considered asymptomatic based on a thorough history of current illness (coughing, cold, flu-like symptoms, anosmia, shortness of breath, muscle ache, fatigue, rhinorrhea, diarrhea) and without fever or hypoxia. History taking should also explicitly address whether pediatric patients have had recent contact with suspected COVID-19 cases. When pediatric **patients show any signs of infection or have been in contact with COVID-19 suspected or confirmed cases**, they should be considered as COVID-19 suspect and approached accordingly, thus **not using this guideline**.

The aim of this practice guideline is to provide advice for the pre-operative workup of pediatric patients reporting no symptoms of or exposure to COVID-19 (after thorough history taking) and awaiting surgery under general anesthesia with the best available current evidence-base, while acknowledging the limitations of this knowledge base.

Abbreviations and definitions

Asymptomatic patient	An asymptomatic patient who carries the SARS-CoV-2 virus but never experiences noticeable symptoms.
Children	0 – 18 years (including premature newborns)

COVID-19	Coronavirus disease 2019, caused by the virus SARS-CoV-2
Pre-symptomatic patient	An pre-symptomatic patient experiences no symptoms of COVID-19 at the time of evaluation, but will go on to subsequently develop COVID-19 symptoms in the future.
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2; virus causing COVID-19

Methods

A multidisciplinary working group was formed with representatives from pediatric surgery, radiology, anesthesiology, urology, ENT, pediatric infectious diseases, pulmonology and microbiology. The databases [Medline (via OVID), Embase (via Embase.com) and Google Scholar] were searched with relevant search terms until April 23, 2020. The detailed search strategies are depicted in Appendix 1.

Summary of the literature

The working group evaluated preprints and published literature to better characterize three possible risks relevant to the pre-operative pediatric population:

1. Do asymptomatic or pre-symptomatic SARS-CoV-2 positive children have an increased risk for adverse outcomes following elective or semi-elective surgery?
2. What is the transmission potential to health care workers from SARS-CoV-2 positive children who are asymptomatic at the time of pre-operative screening but undergo aerosol-generating procedures such as tracheal intubation?
3. What is the transmission potential to other hospitalized children from SARS-CoV-2 positive children who are asymptomatic at the time of screening?

COVID-19 characteristics in children

The understanding of COVID-19 disease in pediatric populations is rapidly evolving. In general, children appear to experience milder symptoms than adults (Dong, 2020; Hua, 2020; Lu, 2020; de Souza, 2020; Qiu, 2020; Wang, 2020, CDC 2020). A large Chinese case series reported the characteristics of 728 PCR-confirmed pediatric cases. More than 95% were classified as asymptomatic, mild, or moderate. 2.9% were classified as “severe” or “critical”, which is lower than the reported rate in parallel series of adults in China (15.7%) (Dong, 2020, Guan, 2020). Young children, and particularly infants appear to be at a higher risk for “severe” or “critical” COVID-19 disease. Children can have a severe disease course with pediatric intensive care admissions, but often with a lower (4.2%) mortality rate than adults (Shekerdemian, 2020). The proportions of severe and critical cases reported in China were 8.2%, 2.2%, 0.6%, 1.1%, and 5.1% for the age groups <1, 1 to 5, 6 to 10, 11 to 15, and ≥16 years, respectively (Dong, 2020). A parallel retrospective analysis of 2,572 pediatric cases in the United States confirmed these findings: PCR-confirmed pediatric patients were less often symptomatic than adults (7% vs 27%) and smaller percentages of children were hospitalized as compared to adults (5.7% vs 10% respectively). However, these percentages may be affected by the practiced testing policy. Children aged <1 year accounted for the highest percentage (15%–62%) of hospitalization among pediatric patients with COVID-19 (Bialek, 2020). Children with hospitalization and severe COVID-19 outcomes have more frequent underlying medical conditions (Shekerdemian, 2020; CDC, 2020). Currently, only a few children with COVID-19 have died (Shekerdemian, 2020; de Souza, 2020; CDC, 2020). One infant is reported to have died after intussusception surgery, but no details on the case have become available.

Post-operative outcomes of children who undergo surgery while reporting no symptoms indicative for COVID-19

It is unknown whether children who are PCR-positive for SARS-CoV-2 and undergo surgery have worse outcomes than children without the disease. Three retrospective chart reviews have reported adverse post-operative outcomes in adults who were unintentionally scheduled for surgery while being in the

incubation period of COVID-19 or having asymptomatic COVID-19 (Arminian, 2020; Lei, 2020; Li Y, 2020). These studies suggested that adult patients may be at significant risk for adverse post-operative outcomes such as ICU admission or increased mortality. To date, there have been no similar studies reporting post-operative outcomes in children who underwent surgery while being asymptomatic or in the presymptomatic phase of COVID-19.

COVID-19 transmission potential in children

Much uncertainty remains about children's SARS-CoV-2 transmission potential. There is concern that the lower case rates reported amongst children reflect selective testing of only the most unwell. However, in population-wide studies, children appear to be less frequently infected than adults (Ludvigsson, 2020; Gudbjartsson, 2020). A large study from Iceland that screened 6% of the general population for SARS-CoV-2 PCR positivity, showed there was a lower incidence of SARS-CoV-2 infection in children compared to older persons. None of 848 children under the age of 10 years tested positive, whereas 100 of 12232 persons (0.8%; 95% CI, 0.7 to 1.0) 10 years of age or older tested positive (Gudbjartsson, 2020). Another study investigated the infection rate among different age groups in Gangel, Germany. That study reported a non-significantly lower infection rate among those aged between 5 and 14 compared to those aged between 15 and 79, and a quite similar infection rate in persons aged 80 years and older. However, these results may be influenced by the representation of these age groups in the carnival festivities that turned out to be a major driver of the infection rate (Streeck, 2020). Data from contact tracing research of the Dutch Public Health Service (GGD) and data from 40 general practices revealed only few infected children (RIVM, 2020). All European studies were conducted during a period of total or partial lockdown in which children were not exposed to other children. In contrast, a large contact-tracing study in China showed that children were as likely as adults to be infected with no differences in infection rates of children and the general population (Bi, 2020). Reported differences in incidence by age could be due to two reasons:

1. There could be age-varying susceptibility to infection by SARS-CoV-2, where children may be less susceptible to becoming infected on contact with an infectious person.
2. Children may be as susceptible to SARS-CoV-2 infection as other individuals, but may more frequently experience shorter, milder or no symptoms (Davies, 2020).

The relative transmissibility of subclinical infections in children in the community remains unknown, however data during a (partial) lock-down situation suggest this is likely to be smaller than in adults (RIVM, 2020). In adults, increasing literature reports that asymptomatic or pre-symptomatic patients may infect others (Arons, 2020; Kimball, 2020; Rothe, 2020; Wei, 2020; Xia, 2020) and that these transmissions may contribute to a considerable proportion of the total infections (Ferretti, 2020; Ganyani, 2020; He, 2020).

An observational study analyzing literature descriptions of children and household transmission clusters of SARS-CoV-2 in China, Singapore, South Korea, Japan, and Iran found that of the 31 household transmission clusters that were identified, 9.7% (3/31) were identified as having a pediatric index case (Zhu, 2020). Another study suggested that a symptomatic child with numerous interactions at three different schools did probably not transmit the virus, despite proven contact with 169 other children who were all followed for two weeks (Danis, 2020). Household configurations differ significantly by country and are difficult to generalize. However, preliminary data on contact tracing among 54 households in the Netherlands during lock-down suggests that none had an index case who was younger than 12 years old (RIVM, 2020).

The relative transmissibility of SARS-CoV-2 asymptomatic or pre-symptomatic children in healthcare settings has not been described, however there is a high likelihood that there is meaningful transmission potential among SARS-CoV-2 positive children who undergo aerosolizing procedures. Despite being asymptomatic or mildly symptomatic, children can have very high nasopharyngeal

SARS-CoV-2 viral loads and viral loads in children do not vary significantly from viral loads in adults (Jones, 2020; Kam, 2020). Tracheal intubation - which can generate aerosols - has consistently been associated with a high increased risk of transmission of viruses such as SARS and MERS to health care workers (Tran, 2012; Loeb 2004; Fowler 2004; Liu, 2009). Intubation in children is more frequently complicated with a high rate of critical severe events during the anesthesia management, which may increase risks of intra-operative aerosolization through difficult intubation/re-intubation, suction before and after intubation, manipulation of oxygen masks, etc (Habre, 2017; Tran 2012).

Diagnostic testing for COVID-19

Nasopharyngeal swabs for SARS-CoV2 in symptomatic patients are prone to sampling error and have demonstrated suboptimal sensitivity in adults (Kim, 2020). It is likely that PCR sensitivity is higher in earlier stages of disease when shedding peaks and that patients with severe disease have higher viral loads than those with asymptomatic/mild disease (Liu Y, 2020; Wolfel R, 2020). Viral loads detected in asymptomatic and pre-symptomatic patients do not appear to be less in than in symptomatic patients (Arons 2020; Zou L NEJM2020) To the best of our knowledge, there are no studies investigating the diagnostic accuracy of PCR specifically in pediatric populations.

CT has been frequently used as a screening tool for pre-operative asymptomatic SARS-CoV-2 in adults but the [recommendation](#) has been adjusted after preliminary data on the SCOUT-1 trial became available, showing a low sensitivity and specificity of CT as screening tool to identify asymptomatic SARS-CoV-2 positive patients. In a systematic review of 27 studies including 184 children with PCR confirmed COVID-19, 63% showed chest CT abnormalities (de Souza, 2020). In children with little or no respiratory symptoms the sensitivity of CT may even be lower (Merkus, 2020).

Conclusions

The literature suggests that the vast majority of children infected by SARS-CoV-2 experience mild or moderate illness, or no symptoms at all. Some children may also be severely affected, particularly in very young age groups and children with co-morbidities.

The literature suggests that children may have a lower incidence of SARS-CoV-2 disease as compared to adults - either through a lower susceptibility to infection or a shorter more mild illness course or study bias due to decreased testing and bias due to studies done in times of lock-down.

There is currently no literature that reports post-operative outcomes in children who have undergone surgery while being in the incubation period of COVID-19 or while having COVID-19 without symptoms, however children may have a lower risk of a severe disease course.

Children, especially under the age of 12 years, may have a lower transmission potential in the community than adults, although evidence is limited and assembled during times of lock-down.

Despite lack of direct supporting evidence, there is a realistic risk that asymptomatic or pre-symptomatic SARS-CoV-2 children can transmit SARS-CoV-2 to HCW during aerosol-generating procedures in hospital settings.

Chest CT seems to have a poor sensitivity in children with little or no respiratory symptoms.

Clinical considerations

The committee's primary aim is to increase patient safety and diminish risks for health care workers inadvertently exposed to SARS-CoV-2 during operative aerosolizing procedures. As stated, children more generally experience asymptomatic, mild or moderate COVID-19 disease. Children also appear to have a lower severe disease incidence than adults. It is unknown whether this is because they

have a shorter, more asymptomatic and mild disease course or if they have a lower susceptibility to infection. Children may have lower transmission risk in the community and general hospital setting. Children pose a realistic transmission risk to HCW in the hospital during aerosol-generating procedures due to having high viral loads despite lack of symptomatology, and higher rates of critical severe events during anesthesia management than adults (Habre, 2020). The committee acknowledges these risks during aerosol-generating procedures (Tran, 2020; Weissman, 2020) and recognizes the importance of providing adequate protection of health care workers during these risk-bearing events (Livingston, 2020; Hanson, 2020). This needs to be balanced with the yield of testing. From a patient perspective, this may be limited because children experience less COVID-19 related problems. Furthermore, testing all pediatric surgical patients has a high impact on daily practice (commitment of hospital staff, utilization of screening materials etc.)

After weighing the above-mentioned arguments, the committee strongly recommends following the PBM leidraad, i.e. at minimum the use of II/IIR surgical mask, gloves and face shields or protective glasses for all aerosol-generating procedures in asymptomatic patients. The committee agrees that strict adherence to this protocol is the most effective protection of the health care worker. Pre-operative PCR screening with a moderate sensitivity in a situation of a low prevalence has little added value and may even lead to a false safety assumption and to less strict adherence to the PBM protocol. Therefore, the committee does not recommend performing diagnostic testing in asymptomatic pediatric patients prior to a surgical procedure under general anesthesia for COVID-19 infection. The committee advises protection for all attending health care workers during all aerosol-generating procedures according to the [leidraad Medische procedures die een infectieuze aerosol genereren \(IAGP\) met SARS-CoV-2](#) en [leidraad Persoonlijke Bescherming in de \(poli\)klinische setting vanwege SARS-CoV-2](#). The latter implies the use of surgical mask type II or IIR combined with goggles or face-shield. Since not specifically mentioned in these documents, ventilating children via an uncuffed tube should be considered as an aerosol-generating procedure.

The fact that this guideline deviates from the screening guideline for adult patients and obstetric patients may lead to logistic and health care provider compliance problems. Therefore, hospitals may choose to adhere to pre-operative PCR screening until more evidence becomes available or should the adult and obstetric guidelines alter testing recommendations.

Legitimacy of the practice guideline

In formulating these recommendations, the committee recognizes that the evidence base is poor and there is an urgent need for more information about the utility of PCR in pre-operative screening in pediatric populations. A multi-center coordinated study is currently ongoing to evaluate the utility of preoperative PCR testing asymptomatic pediatric patients and this data will be used to further evaluate the current guideline.

Recommendations/Aanbevelingen

The committee recommends adequate PPE protection against SARS-CoV-2 infection for all operations of pediatric patients under general anesthesia according to the leidraad [Persoonlijke beschermingsmiddelen in de \(poli\)klinische setting vanwege SARS-CoV-2](#)

When strictly adhering to the PBM leidraad, the committee recommends against the use of pre-operative diagnostic testing for SARS-CoV-2 asymptomatic pediatric patients who are scheduled to undergo an aerosol-generating procedure e.g. tracheal intubation.

De commissie adviseert adequate bescherming tegen SARS-CoV-2 infectie bij alle operaties bij kinderen onder algehele anesthesie volgens de leidraad [Persoonlijke beschermingsmiddelen in de \(poli\)klinische setting vanwege SARS-CoV-2](#)

Indien de leidraad PBM goed gevolgd wordt, adviseert de commissie bij kinderen zonder voor COVID-19 verdachte klachten die een operatie onder algehele anesthesie ondergaan geen preoperatief diagnostisch PCR onderzoek te verrichten naar de mogelijke aanwezigheid van een SARS-CoV-2 infectie.

Disclaimer 1

Hospitals may deviate from this practice guideline based on a locally-formulated multidisciplinary statement when there are indications that the hospital is in an area of high active COVID infection prevalence.

Hospitals may choose to implement preoperative COVID-19 screening in pediatric patients in order to adhere to a uniform protocol where all perioperative patients groups are tested, as long as guidelines for pre-operative screenings in adult and obstetric patients recommend testing.

Disclaimer 2

All associations involved have taken the greatest possible care in formulating the content of this Practice Guideline. Nevertheless, they accept no liability for any inaccuracies in this document, for any damages or for other consequences arising from or related to the use of this Practice Guideline.

Working group

Dr. R. Bakx, pediatric surgeon at Amsterdam UMC, location AMC and chairman of the guideline committee of the Dutch Surgical Association, on behalf of the Dutch Surgical Association

Prof. dr. W. Feitz, pediatric urologist at Radboudumc, on behalf of the Dutch Association of Urology

Dr. W. Klein, pediatric radiologist at Radboudumc on behalf of the Dutch Radiological Society

Dr. P. Merkus, pediatric pulmonologist at Radboudumc, on behalf of the Dutch Paediatric Society

Dr. A. Riezebos-Brilman, consultant clinical microbiologist at UMC Utrecht, on behalf of the Dutch Society for Medical Microbiology

J. van Schuppen MSc, pediatric radiologist at Amsterdam UMC, location AMC, on behalf of the Dutch Radiological Society

dr. M. Stevens, pediatric anesthesiologist at Amsterdam UMC, location AMC, on behalf of the Dutch Association of Anesthesiology

Dr. H. Verschuur, otorhinolaryngologist/head and surgeon at Haaglanden Medisch Centrum, on behalf of Dutch Society of Ear, Nose and Throat Surgery

Dr. T. Wolfs, ID- pediatrician at Wilhelmina Kinder Ziekenhuis, on behalf of the Dutch Paediatric Society

With support of:

Dr. J. Buddeke, advisor Knowledge Institute of Medical Specialists

Dr. V. Harris, internist-infectious disease specialist at Amsterdam UMC, location AMC

Dr. M. den Ouden-Vierwind, advisor Knowledge Institute of Medical Specialists

References

- Aminian, A., Safari, S., Razeghian-Jahromi, A., Ghorbari, M., Delaney, C.P. (2020) COVID-19 Outbreak and Surgical Practice: Unexpected Fatality in Perioperative Period. *Annals of Surgery*
- Bi, Q., Wu, Y., Mei, S., Ye, C., Zou, X., Zhang, Z., Liu, X., Wei, L., Truelove, S., Zhang, T., Gao, W., Cheng, C., Tang, X., Wu, X., Wu, Y., Sun, B., Huang, S., Sun, Y., Zhang, J., Ma, T., Lessler, J., Feng, T. (2020). Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study *The Lancet Infectious Diseases* [https://dx.doi.org/10.1016/s1473-3099\(20\)30287-5](https://dx.doi.org/10.1016/s1473-3099(20)30287-5)
- Bialek, S., Gierke, R., Hughes, M., ... & Skoff, T. (2020). Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020. *Morbidity and Mortality Weekly Report*, 69(14), 422.
- Cai, J., Xu, J., Lin, D., Xu, L., Qu, Z., Zhang, Y., ... & Xia, A. (2020). A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clinical Infectious Diseases*.
- CDC website. Consulted at April 28. <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html>
- Danis, K., Epaulard, O., Bénet, T., Gaymard, A., Campoy, S., Bothelo-Nevers, E., ... & Boudalaa, Z. (2020). Cluster of coronavirus disease 2019 (Covid-19) in the French Alps, 2020. *Clinical Infectious Diseases*.
- Davies, N. G., Klepac, P., Liu, Y., Prem, K., Jit, M., Eggo, R. M., & CMMID COVID-19 working group. (2020). Age-dependent effects in the transmission and control of COVID-19 epidemics. *medRxiv*.
- Dong, Y., Mo, X., Hu, Y., Qi, X., Jiang, F., Jiang, Z., & Tong, S. (2020). Epidemiology of COVID-19 among children in China. *Pediatrics*.
- Ferretti, L., Wymant, C., Kendall, M., Zhao, L., Nurtay, A., Abeler-Dörner, L., ... & Fraser, C. (2020). Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. *Science*.
- Fowler RA, Guest CB, Lapinsky SE, Sibbald WJ, Louie M, Tang P, et al. Transmission of severe acute respiratory syndrome during intubation and mechanical ventilation. *Am J Respir Crit Care Med* 2004;169(11):1198–202.
- Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... & Du, B. (2020). Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*.
- Gudbjartsson, D. F., Helgason, A., Jonsson, H., Magnusson, O. T., Melsted, P., Norddahl, G. L., ... & Eiríksdóttir, B. (2020). Spread of SARS-CoV-2 in the Icelandic Population. *New England Journal of Medicine*.
- Habre, W., Disma, N., Virag, K., Becke, K., Hansen, T. G., Jöhr, M., ... & Boda, K. (2017). Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *The Lancet Respiratory Medicine*, 5(5), 412-425.
- Hanson K. , Caliendo, J. A.M., Arias C. A., Englund J.A., Lee M.J., Loeb M., ...&Mustafa R.A (2020). Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19. Published by IDSA, 5/6/2020
- Hu, Z., Song, C., Xu, C., Jin, G., Chen, Y., Xu, X., ... & Wang, J. (2020). Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Science China Life Sciences*, 1-6.
- Hua, C. Z., Miao, Z. P., Zheng, J. S., Huang, Q., Sun, Q. F., Lu, H. P., ... & Ji, L. D. (2020). What We Should Know About SARS-CoV-2 Infection in Children.
- Jones T, et al, An analysis of SARS-CoV-2 viral load by patient age. PREPRINT https://zoonosen.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/Weitere_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age.pdf
- Kam KQ, Yung CF, Cui L, et al. A Well Infant with Coronavirus Disease 2019 (COVID-19) with High Viral Load [published online ahead of print, 2020 Feb 28]. *Clin Infect Dis*. 2020;ciao201. doi:10.1093/cid/ciao201

Kimball, A. (2020). Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility—King County, Washington, March 2020. *MMWR. Morbidity and Mortality Weekly Report*, 69.

Lei, S., Jiang, F., Su, W., Chen, C., Chen, J., Mei, W., ... & Xia, Z. Y. (2020). Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine*, 100331.

Liao, J., Fan, S., Chen, J., Wu, J., Xu, S., Guo, Y., ... & Song, C. (2020). Epidemiological and clinical characteristics of COVID-19 in adolescents and young adults. *medRxiv*.

Li, Y. K., Peng, S., Li, L. Q., Wang, Q., Ping, W., Zhang, N., & Fu, X. N. (2020). Clinical and Transmission Characteristics of Covid-19—A Retrospective Study of 25 Cases from a Single Thoracic Surgery Department. *Current Medical Science*, 1.

Livingston, E. H. (2020). Surgery in a Time of Uncertainty: A Need for Universal Respiratory Precautions in the Operating Room. *JAMA*.

Liu W, Tang F, Fang LQ, De Vlas SJ, Ma HJ, Zhou JP, et al. Risk factors for SARS infection among hospital healthcare workers in Beijing: a case control study. *Trop Med Int Health*. 2009;14(Suppl 1):52–9.

Lin, J., Duan, J., Tan, T., Fu, Z., & Dai, J. (2020). The isolation period should be longer: Lesson from a child infected with SARS-CoV-2 in Chongqing, China. *Pediatric Pulmonology*.

Loeb M, McGeer A, Henry B, Ofner M, Rose D, Hlywka T, et al. SARS among critical care nurses, Toronto. *Emerg Infect Dis*. 2004 Feb;10(2):251–5.

Lu, X., Zhang, L., Du, H., Zhang, J., Li, Y. Y., Qu, J., ... & Wu, C. (2020). SARS-CoV-2 infection in children. *New England Journal of Medicine*.

Ludvigsson, J. F. (2020). Systematic review of COVID-19 in children show milder cases and a better prognosis than adults. *Acta Paediatrica*.

Merkus, P. J., & Klein, W. M. (2020). Value of Chest CT as COVID 19 screening tool in children. *European Respiratory Journal*.

Qiu, L., Zhang, C., Wu, J., Xiong, J., Chai, J., Luo, M., ... & Gong, L. (2020). A Retrospective Study of 186 Patients Reveals the Strongest Immunity in the Early Two Years of Life Against Coronavirus Disease 2019.

RIVM website. Consulted at May 11th. <https://www.rivm.nl/coronavirus-covid-19/vragen-antwoorden/kinderen-covid-19>

Rothe, C., Schunk, M., Sothmann, P., Bretzel, G., Froeschl, G., Wallrauch, C., ... & Seilmaier, M. (2020). Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *New England Journal of Medicine*.

Shekerdemian, L., Mahmood, N., Wolfe, K., Riggs, B., Ross, C., McKiernan, C., Heidemann, S., Kleinman, L., Sen, A., Hall, M., Priestley, M., McGuire, J., Boukas, K., Sharron, M., Burns, J. (2020). Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units *JAMA Pediatrics* 174(9)<https://dx.doi.org/10.1001/jamapediatrics.2020.1948>

de Souza, T. H., Nadal, J. A., Nogueira, R. J. N., Pereira, R. M., & Brandao, M. B. (2020). Clinical Manifestations of Children with COVID-19: a Systematic Review. *medRxiv*.

Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*

Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. *MMWR Morb Mortal Wkly Rep.* ePub: 1 April 2020.
DOI: [http://dx.doi.org/10.15585/mmwr.mm6914e1external icon](http://dx.doi.org/10.15585/mmwr.mm6914e1external%20icon)

Xia, W., Liao, J., Li, C., Li, Y., Qian, X., Sun, X., ... & Liu, J. (2020). Transmission of corona virus disease 2019 during the incubation period may lead to a quarantine loophole. *medRxiv*.

Xia, W., Shao, J., Guo, Y., Peng, X., Li, Z., & Hu, D. (2020). Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatric pulmonology*.

Zhang, X., Chen, W., Hu, C., Huang, L., Hu, Z., Zeng, Y., ... & Yi, Y. (2020). Characterization of a big family cluster infection associated with SARS-Cov-2 in Nanjing district.

Zhu, Y., Bloxham, C. J., Hulme, K. D., Sinclair, J. E., Tong, Z. W. M., Steele, L. E., ... & Gilks, C. (2020). Children are unlikely to have been the primary source of household SARS-CoV-2 infections.

Zhu Y et al, Children are unlikely to have been the primary source of household SARS-CoV-2 infections
PREPRINT <https://www.medrxiv.org/content/10.1101/2020.03.26.20044826v1.full.pdf>

Zou, L., Ruan, F., Huang, M., Liang, L., Huang, H., Hong, Z., ... & Guo, Q. (2020). SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *New England Journal of Medicine*, 382(12), 1177-1179.

Appendix

Search	Query
#9	Search #3 AND #8 AND #6
#8	Search ("COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR ("Coronavirus"[MeSH Terms] OR "Coronavirus Infections"[Mesh:NoExp] OR pneumonia virus*[tiab] OR cov[tiab]) AND (outbreak[tiab] OR wuhan[tiab] OR novel[all] OR 19[tiab] OR 2019[tiab] OR epidem*[tiab] OR epidemic[all] OR epidemic*[all] OR pandem*[all] OR new[tiab])) OR coronavirus*[tiab] OR corona virus*[tiab] OR ncov[tiab] OR 2019ncov[tiab] OR covid19[tiab] OR "covid 19"[tiab] OR "sars cov 2"[tiab] OR sars2[tiab] OR "ncov 2019"[tiab] OR "sars coronavirus 2"[tiab] OR "sars corona virus 2"[tiab] OR "severe acute respiratory syndrome cov 2"[tiab] OR "severe acute respiratory syndrome cov2"[tiab] OR severe acute respiratory syndrome cov*[tiab] OR cov2[tiab]) AND ("2019/12"[Date - Entrez] : "3000"[Date - Entrez]) Sort by: Best Match
#7	Search #4 AND #6
#6	Search #2 OR #5
#5	Search "Aerosols"[Mesh] OR "Disease Transmission, Infectious"[Mesh] OR "Cross Infection"[Mesh] OR "Safety"[Mesh] OR nosocomial infection*[tiab] OR cross infection*[tiab] OR hospital infection*[tiab] OR disease transmission[tiab] OR infection transfer[tiab] OR "infection transmission"[tiab] OR "infectious transmission"[tiab] OR "transmission of infection"[tiab] OR "transmission of infections"[tiab] OR "transmission of infectious disease"[tiab] OR "transmission of infectious diseases"[tiab] OR contamination*[tiab] OR infection risk*[tiab] OR occupational hazar*[tiab] OR virus transmission[tiab] OR viral transmission[tiab] OR infection risk*[tiab] OR safe*[tiab] OR shed*[tiab] OR aerogenic transmission[tiab] OR aerosol*[tiab]
#4	Search ("Severe Acute Respiratory Syndrome"[Mesh] OR "SARS Virus"[Mesh] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR ("Coronavirus"[MeSH Terms] OR "Coronavirus Infections"[Mesh:NoExp] OR pneumonia virus*[tiab] OR cov[tiab]) AND (outbreak[tiab] OR wuhan[tiab] OR novel[all] OR 19[tiab] OR 2019[tiab] OR epidem*[tiab] OR epidemic[all] OR

Search	Query
	epidemic*[all] OR pandem*[all] OR new[tiab])) OR coronavirus*[tiab] OR corona virus*[tiab] AND ("2019/12"[Date - Entrez] : "3000"[Date - Entrez]) OR (ncov[tiab] OR 2019ncov[tiab] OR covid19[tiab] OR "covid 19"[tiab] OR sars*[tiab] OR severe acute respiratory syndrome[tiab] OR sudden acute respiratory syndrome[tiab] OR mers[tiab] OR middle east respiratory syndrome[tiab])
#2	Search "Asymptomatic Diseases"[Mesh] OR asymptomatic[tiab] OR pre-symptomatic*[tiab] OR presymptomatic[tiab] OR mild*[tiab] OR no sign[tiab] OR no signs[tiab]

Search	Query
#23	Search #22 AND #17
#22	Search ((coronavirus*[tiab] OR corona virus*[tiab] OR pneumonia virus*[tiab] OR cov[tiab] OR ncov[tiab]) AND (outbreak[tiab] OR wuhan[tiab])) OR covid19[tiab] OR "covid 19"[tiab] OR ((coronavirus*[tiab] OR corona virus*[tiab]) AND 2019[tiab]) OR "sars cov 2"[tiab] OR sars2[tiab] OR new coronavirus*[tiab] OR new corona virus*[tiab] OR "ncov 2019"[tiab] OR "sars coronavirus 2"[tiab] OR "sars corona virus 2"[tiab] OR "severe acute respiratory syndrome cov 2"[tiab] OR "severe acute respiratory syndrome cov2"[tiab] Filters: Publication date from 2019/12/01
#21	Search ((coronavirus*[tiab] OR corona virus*[tiab] OR pneumonia virus*[tiab] OR cov[tiab] OR ncov[tiab]) AND (outbreak[tiab] OR wuhan[tiab])) OR covid19[tiab] OR "covid 19"[tiab] OR ((coronavirus*[tiab] OR corona virus*[tiab]) AND 2019[tiab]) OR "sars cov 2"[tiab] OR sars2[tiab] OR new coronavirus*[tiab] OR new corona virus*[tiab] OR "ncov 2019"[tiab] OR "sars coronavirus 2"[tiab] OR "sars corona virus 2"[tiab] OR "severe acute respiratory syndrome cov 2"[tiab] OR "severe acute respiratory syndrome cov2"[tiab]
#20	Search #18 AND #19
#19	Search "Sensitivity and Specificity"[MeSH] OR specificit*[tw] OR screening[tw] OR accura*[tw] OR reference value*[tw] OR false positive[tw] OR false negative[tw] OR predictive value*[tw] OR roc[tw] OR likelihood*[tw] OR likelihood*[tw]
#18	Search #1 AND #17
#17	Search #10 OR #12 OR #11 OR #16
#16	Search "Polymerase Chain Reaction"[Mesh] OR polymerase chain reaction[tiab] OR pcr[tiab]
#12	Search ("Tomography, X-Ray Computed"[Mesh] OR computed tomograph*[tiab] OR ct[tiab] OR cts[tiab] OR cat scan*[tiab] OR computer assisted tomograph*[tiab] OR computerized tomograph*[tiab] OR computerised tomograph*[tiab] OR computed x ray tomograph*[tiab] OR computed xray tomograph*[tiab]) AND ("Thorax"[Mesh] OR thorax[tiab] OR thorac*[tiab] OR chest[tiab])
#11	Search (Ultrasonography"[Mesh] OR "diagnostic imaging"[Subheading] OR ultraso*[tiab] OR sonograph*[tiab] OR echograph*[tiab] OR echocardiograph*[tiab] OR echotomograph*[tiab]) AND ("Thorax"[Mesh] OR thorax[tiab] OR thorac*[tiab] OR chest[tiab])
#10	Search "Radiography, Thoracic"[Mesh] OR "X-thorax"[tiab] OR thoracic radiograph*[tiab]
#1	Search "Severe Acute Respiratory Syndrome"[Mesh] OR "SARS Virus"[Mesh] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR 2019ncov[tiab] OR 2019 ncov[tiab] OR novel coronavirus*[tiab] OR novel corona virus*[tiab] OR ((coronavirus*[tiab] OR corona virus*[tiab] OR pneumonia virus*[tiab] OR cov[tiab] OR ncov[tiab]) AND (outbreak[tiab] OR wuhan[tiab]))

Search	Query
	<p>OR covid19[tiab] OR covid 19[tiab] OR ((coronavirus*[tiab] OR corona virus*[tiab]) AND 2019[tiab]) OR sars*[tiab] OR new coronavirus*[tiab] OR new corona virus*[tiab] OR ncov 2019[tiab] OR “sars corona virus”[tiab] OR “sars-like cov”[tiab] OR “sars-like coronavirus”[tiab] OR sars-related cov[tiab] OR sars-related coronavirus[tiab] OR sarsr-cov[tiab] OR “severe acute respiratory syndrome-like coronavirus”[tiab] OR “severe acute respiratory syndrome-related coronavirus[tiab] OR hcov-sars[tiab] OR human sars coronavirus[tiab] OR sars cov[tiab] OR sars associated coronavirus”[tiab] OR sars coronavirus[tiab] OR sars virus[tiab] OR sars-cov[tiab] OR sars-associated coronavirus[tiab] OR severe acute respiratory syndrome coronavirus[tiab] OR severe acute respiratory syndrome virus[tiab] OR mers coronavir*[tiab] OR mers vir*[tiab] OR mers-cov[tiab] OR middle east respiratory syndrome coronavir*[tiab] OR severe acute respiratory infection*[tiab]</p>

In addition to abovementioned search specific strategy, on a daily basis all pre-prints are screened with the relevant terms for COVID-19 (covid19|"covid 19"|2019ncov|"2019 ncov|cov|coronavirus"|"2019 novel|new coronavirus|cov"| "wuhan coronavirus|cov|ncov|outbreak"|"wuhan*coronavirus|cov|ncov|outbreak"|"wuhan**coronavirus|cov|ncov|outbreak"|"coronavirus|cov|ncov*wuhan")