

MEASURES FOR CHILDREN LESS THAN 3 YEARS OLD

RAG 30/06/2020

CONTEXT

Since the 4th of May, in a context of progressive lifting of lockdown measures and with the aim to identify and interrupt possible chains of transmission of SARS-CoV-2, a very wide case definition¹ is used for PCR testing of possible COVID-19 cases. This has led to a progressive increase in number of tests performed (see further), in general and more specifically in children, but with a very low and decreasing positivity rate (to less than 0.5% in the past week, e.g. 5 positive samples out of 1106 tests on 24/06, in children < 3 years old).

Since rhinitis in small children (which occurs very frequently, especially in children attending nurseries) is often associated with coughing (postnasal drip), this means that children with rhinitis are often complying to the case definition. This observation raises question on the need to keep such a wide definition for testing for small children. Both general practitioners and pediatricians report that the current testing strategy in young children is not sustainable.

In addition, the question is raised if the current classification of contacts, where all children belonging to the same section of a nursery are considered close contacts, and therefore tested/put in quarantine for 14 days, has to be kept or reevaluated.

RECOMMENDATIONS

- Testing in children under 3 years with clinical signs compatible with COVID-19 is only recommended if the child needs to be hospitalized or if the result will implicate that further measures such as quarantine or testing are needed to protect close contacts (e.g; family member at risk of a severe manifestation of COVID-19)..
- Children from the same household as a case of COVID-19 are considered as close contacts, with a high probability of infection. They remain in quarantine for 14 days without testing. If the child develops symptoms during quarantine, testing is not necessary neither, but the child is considered as a COVID-19 case. As a COVID-19 case, he/she can return to the nursery 7 days after the onset of the symptoms, if without fever for at least 3 days and if the symptoms significantly improved.
- For children living in a residential collectivity, the same measures need to be applied as in a household, for the children living in the same group/bubble.
- When a child in a nursery is confirmed COVID-19, the probability of transmission (to other children and the care-giver) is considered as low (low risk contact). No quarantine or testing is needed for

¹ Een mogelijk geval van COVID-19 is een persoon met

- minstens één van de volgende hoofdsymptomen die acuut ontstaan zijn, zonder andere duidelijke oorzaak : hoest; dyspnoe; thoracale pijn; acute anosmie of dysgeusie;

OF

- minstens twee van de volgende symptomen, zonder andere duidelijke oorzaak, koorts; spierpijn; vermoeidheid; rhinitis; keelpijn; hoofdpijn; anorexie; waterige diarree; acute verwardheid; plotse val;

OF

- verergering van chronische respiratoire symptomen (COPD, astma, chronische hoest...), zonder andere duidelijke oorzaak.

Bij kinderen is enkel koorts zonder duidelijke oorzaak voldoende om de diagnose van COVID-19 te overwegen tijdens deze epidemie.

these contacts, and the nursery (or section) is not closed, but parents of the other children are informed about the case.

- If one of the low risk contacts develops symptoms of possible COVID-19 within 14 days, he/she has to be tested. If the PCR result is positive, the whole bubble (section of a nursery or whole nursery) is closed and put 14 days in quarantine.
- If a care-giver has COVID-19 in a nursery, the children and colleagues working in the same bubble are considered as close contacts (14 days quarantine for all contacts and testing for the adults).
- Data on transmission in children overall, and children in nurseries more specifically, should be collected during the summer (K&G, ONE, summer camps, literature...), to allow an evaluation of the measures above by September.

RATIONALE

The following elements were taken into consideration:

- In the current epidemiological context, less than 0.5% of children below 3 years of age who are tested (presenting clinical symptoms of “possible” COVID-19 or asymptomatic) have a positive PCR result. To note also that a positive PCR result does not necessarily mean infectivity.
- Taking a nasopharyngeal swab in (small) children is painful.
- Following the rule “first do not harm”, the main principle is that a test should only be performed if the result leads to a change in behavior or action.
- Small children repeatedly present symptoms of possible COVID-19 (such as rhinitis with cough), leading to repeated testing.
- Repeated testing could lead to reluctance of parents to take the child to a doctor when ill, leading to delay in care.
- Based on the preliminary scientific evidence available, children have lower or equal susceptibility to SARS-CoV2 than adults, and lower risk of transmission to contacts.
- However, it is important to document further possible transmission between children in nurseries and increase knowledge. For this reason, testing is recommended for symptomatic children less than 3 years old if they are contacts of a confirmed COVID-19 case in a nursery.
- Modelling studies indicate that interventions aimed at children probably have a relatively small impact on reducing SARS-CoV-2 transmission.

The following persons participated to this RAG advice:

Katrien Bonneux (OND), Karin Cormann (Deutschsprachigen Gemeinschaft), Laura Cornelissen (Sciesano), Herman Goossens (UA), Alice Hannecart (Sciensano), Tinne Lernout (Sciensano), Valeska Haisnez (AZG), Stefan Teughels (Wachtposten Vlaanderen), Anouk Vanlander (VWJ), Bart Van Overmeire (K&G – Opgroeien) and the Pediatric Task Force: Annick Covent, Ann De Guchtenaere, Marc Hainaut, Delphine Jacobs, Tyl Jonckheer, Marianne Michel, Petra Schelstraete, Koen Vanden Driessche, Dimitri Van Der Linden.

BELGIAN DATA IN CHILDREN LESS THAN 3 YEARS OLD

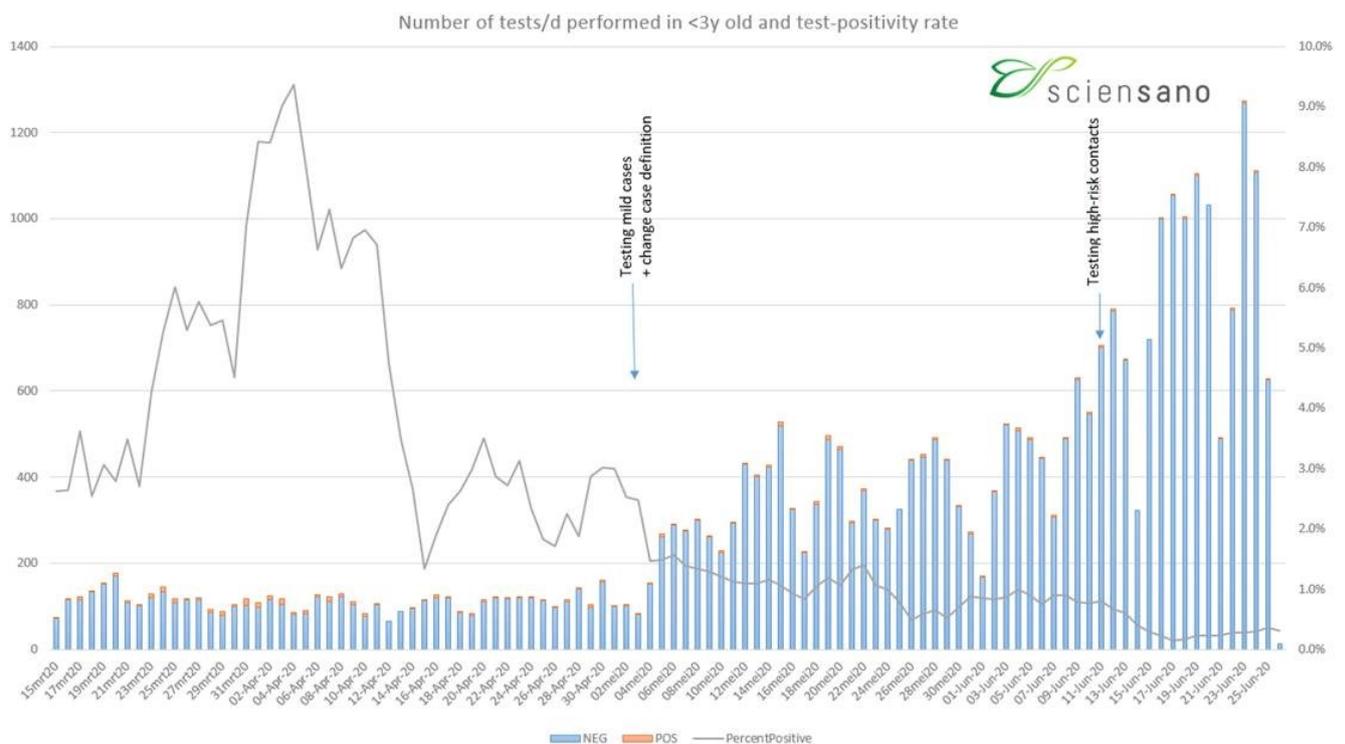
Little data is available on COVID-19 occurrence, transmission and symptoms in children less than 3 years old, in Belgium and elsewhere.

Some data are available from K&G and ONE, but these are far from being exhaustive.

From mid-May until mid-June, 25 “confirmed cases” of COVID-19 were reported by nurseries to K&G, of whom 8 were adults and 17 were children, aged < 4 years. There is no information on clinical symptoms. The total capacity of children in nurseries is about 90 000, but not all children attended a nursery during that period. Also, not all cases might have been reported.

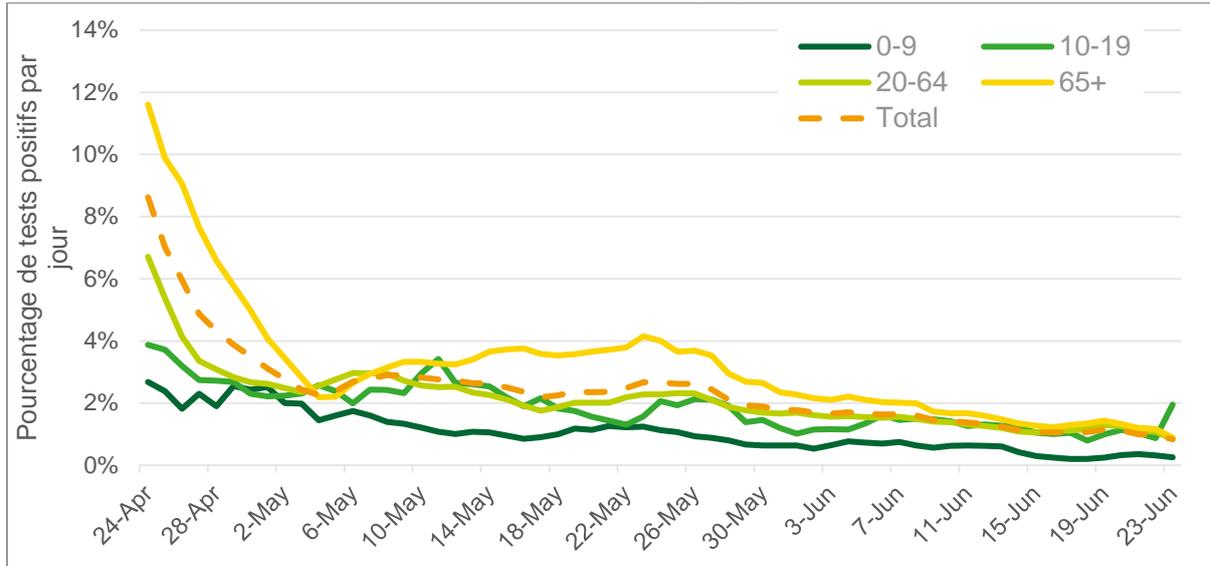
Since the beginning of the outbreak, 108 confirmed cases (and almost 70 of them from the end of April) were reported to ONE, by nurseries without a medical doctor and needing assistance for investigation and control measures. From May until now, 25 cases were reported in children, 12 in adult staff, 22 in parents, and 6 in other household contacts. To note that the attendance rate of nurseries was rather low during the epidemic and gradually resumed in June, and that a lot of “possible cases” are not tested.

The figure below presents the number of PCR tests performed in children < 3 years between 15/03 and 25/06, and the positivity rate. Starting from 04/05, the number of tests performed increased progressively. However, the number of positive results (orange bars) did not increase. No information is available on the setting of the testing (symptomatic child, pre-op screening, contacts).



The test positivity rate has consistently been lower in children (0-9) than in older age groups (Figure below).

Test positivity rate by age group



LITERATURE

Severity of disease in young children (<1 year old)

COVID-19 is generally a mild disease in children, including infants. However, a small proportion develop severe disease requiring ICU admission and prolonged ventilation, although fatal outcome is overall rare (1). Being younger than 1 month is a significant risk factor for requiring ICU admission.

A systemic review of 18 papers, covering 160 infants (0-1 year old), showed that infants and neonates are a particularly vulnerable group, because more likely to suffer critical illness, but morbidity and mortality are low (2). To note that critical illness was considered as requiring hospitalization, but this does not necessarily mean severe disease. Only 7% of infants required ICU and 16% of hospitalized infants were asymptomatic.

A Chinese retrospective study of a case series of 2143 pediatric patients with suspected (65.9%) and confirmed (34.1%) COVID-19 infection, shows severity of illness by age-group. The proportion of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1% and 3.0% for the age group of <1, 1-5, 6-10, 11-15 and >15 years, respectively. Of note, the group of suspected cases had more severe and critical cases which could be caused by other respiratory infections (3). The mechanisms of difference in clinical manifestations remain to be determined.

The Sciensano report on hospitalized children (n=249) also found a higher proportion of all child COVID-19-related hospitalizations in the youngest ages (0-1 year old), and notably those younger than three months (4). In this age group, 116 (46.6%) hospitalizations were recorded.

The fact that newborns with a fever are more rapidly tested (and thus have a higher probability to be confirmed) and the fact that infection in a newborn leads to more concern (and thus more hospitalizations), can probably explain their overrepresentation.

SARS-CoV-2 viral loads and viral isolation in children

Possible transmission of SARS-CoV-2 from children, even neonates, is plausible as shown by successful viral cultures of SARS-CoV-2 from approximately half of twenty-three RT-PCR positive symptomatic children. Samples were collected at a median of 2 days (IQR 1-3) after symptom onset (5).

In addition, a large study by the group of Christian Drosten in Germany, reported on viral loads (estimated by real-time RT-PCR threshold cycle values) of 3,712 COVID-19 patients. Their results indicated that viral loads in the very young may not differ significantly from those of adults (6). Neither timing of testing and clinical presentation (asymptomatic versus symptomatic) were reported in this

study and the manuscript was largely criticized by scientists around the world (7). The German group replied with a revised version of the manuscript with more detailed analyses, showing a possibility of lower viral infectivity in children : viral loads of at least 250,000 copies, a threshold previously established for the isolation of infectious virus in cell culture at more than 5% probability, were observed in 29.0% of kindergarten-aged patients 0-6 years old (n=38), versus 37.3% of those aged 0-19 (n=150), and 51.4% of those aged 20 and above (n=3153) (8). However, according to the authors, the differences might be related to differences in test utilization, and the number of persons is small for the younger age groups.

Transmission in nurseries

No data on transmission of SARS-CoV-2 in nurseries specifically nor in the age group 0 to 3 years old has been found.

The data below concern children in general, and can be used as reference.

Transmission in children

Data on transmission of SARS-CoV in children is currently limited.

Zhu et al (preprint article) identified through a literature review 31 household transmission clusters that involved children (in China, Singapore, the USA, Vietnam and South Korea). A child was the index case in only three (9.7%) households. The authors compared this with household transmissions during the H5N1 influenza virus, where a child was the index case in 54% of households (9). In one of these studies, a household cohort study in China among 392 household contacts, the secondary attack rate to children was 4% compared with 17.1% for adults (10).

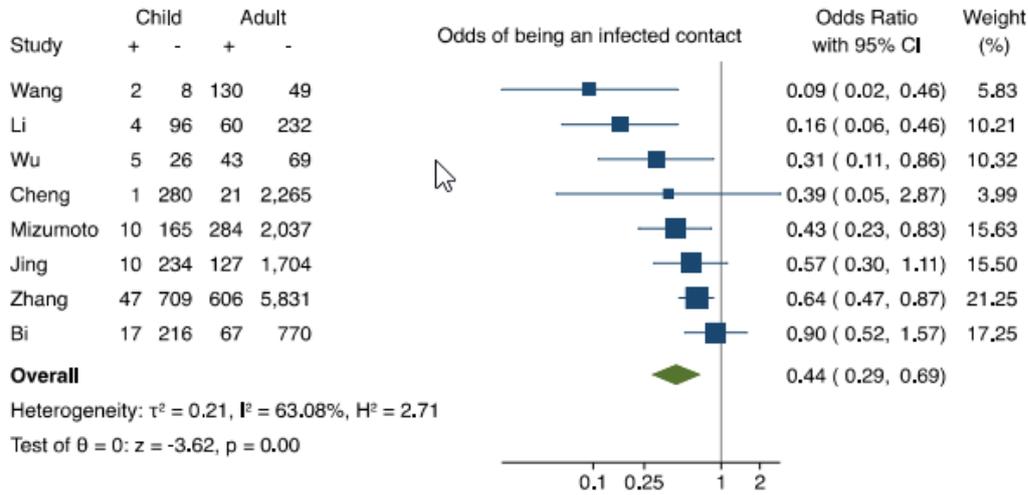
Some reports or studies are available on clusters in schools. In Ireland three pediatric cases (children > 10 years of age) and three adult cases of COVID-19 with a history of school attendance were identified via the national infectious disease surveillance system, prior to the closure of schools (11). These cases had not been infected within the school setting. A total of 1,155 contacts of these six cases were identified (exposure at school in the classroom, during sports lessons, music lessons, religious ceremony). 1,025 contacts were followed-up for at least 14-days after last exposure, and no onward child-to-child or child-to-adult transmission was identified. Transmission was only observed outside the school environment, between two of the adult cases and a further adult. Of note, only symptomatic contacts were tested with PCR, so hypothetical asymptomatic secondary cases were not captured.

In a report by the National Centre for Immunisation Research and Surveillance of New South Wales, Australia, a total of 18 COVID-19 cases (9 students and 9 staff) were identified in 15 schools (10 high schools and 5 primary schools) (12). The public health staff identified 863 close contacts. Of these, only two students have been identified as possible secondary cases (one child from a primary school as based on PCR, and one child from a high school based on development of antibodies). No teacher or staff member contracted COVID-19 from any of the initial school cases. In this investigation, cases developing symptoms within 14 days follow-up were tested with PCR on nasal swabs, but also a non-specified portion of non-symptomatic contacts were tested between day 5 and 10 with PCR and, at a later time, point serology. Overall, 1/3rd of contacts were tested with PCR.

Risk of children becoming infectious contacts after exposure

It has been suggested that children are less susceptible to become infected with the virus. It might be due to differences in expression of ACE-2, which functions as receptor for SARS-CoV-2. Expression of ACE-2 in the nasal epithelium is lower in the lower age groups, research shows (13). A meta-analysis of contact tracing studies (n=9), shows lower susceptibility to SARS-CoV-2 in children and young people (<20 years). The pooled OR estimate for being an infected contact in children compared with adults was 0.44 (0.29, 0.69) with substantial heterogeneity (63%) (14). See Figure below.

Figure 2. Pooled estimate of odds of being an infected contact in children compared adults for all contact tracing studies



A single study, by Bi et al, reported contrary results. This study, assessing 391 cases and 1286 close contacts in Shenzhen, reported an overall household secondary attack rate of 11.2% (95% CI 9.1–13.8), and children were as likely to be infected as adults (infection rate 7.4% (11/148) in children <10 years vs population average of 6.6%) (15). Results are shown in the following figure.

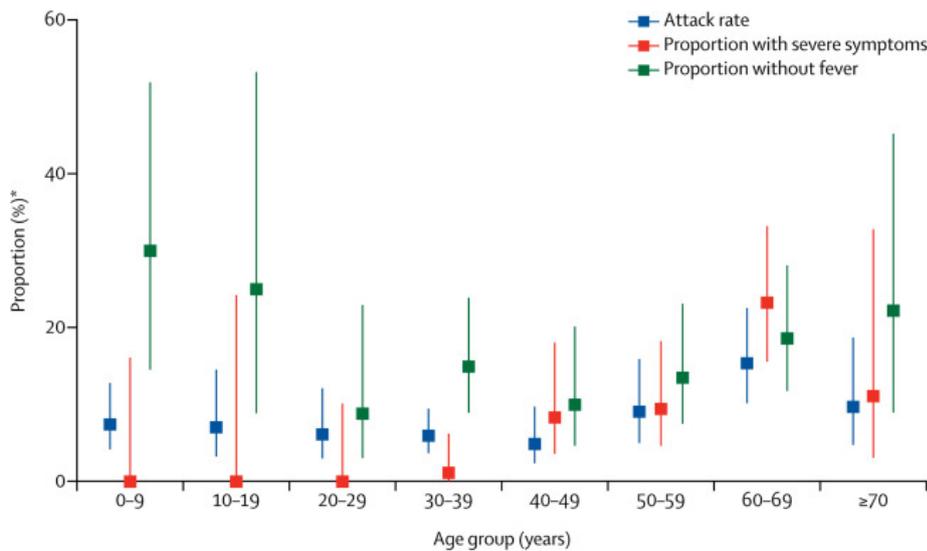
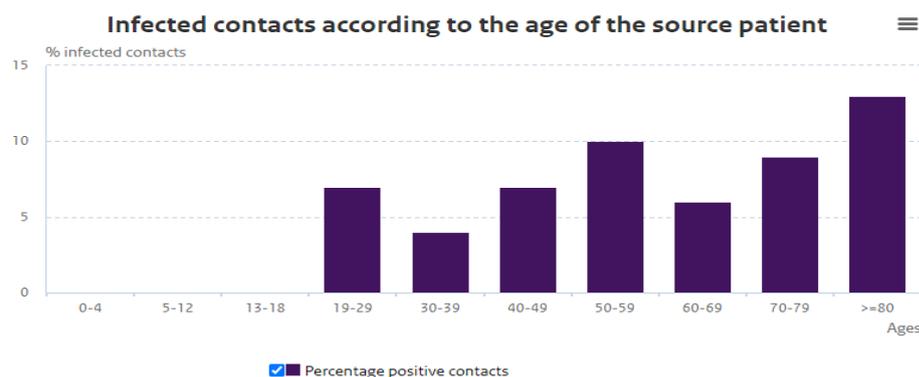
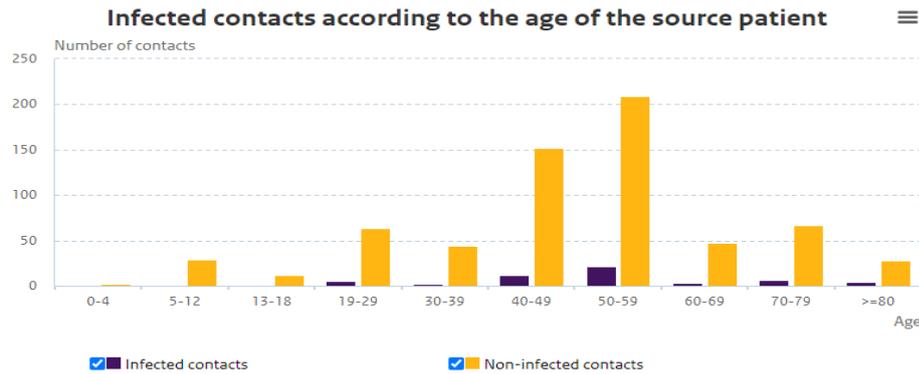


Figure 3 Attack rate among close contacts, baseline severity, and proportion of cases without fever at initial assessment by age group

RIVM research on the reported cases shows that COVID-19 is primarily spread between persons of approximately the same age (16,17). This is based only on data from patients with symptoms. Most of these people are between the ages of 40 and 80 years. Patients under 20 years seem to play a much smaller role in the spread than adults and the elderly. When transmission occurs, it is mainly in the home situation.

According to a study among 54 households with children (n= 227), children aged 1 to 11 were less likely to have a positive PCR and serological test result than older children and adults, in families of a confirmed COVID-19 patient (16). In contrast, unpublished data from 8 weekly serosurveys in Geneva showed similar rates of antibodies in children as in adults (18).



Finally, an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada and South Korea estimates that susceptibility to infection in children (<20yo) is approximately half that of adults (>20yo) and that clinical symptoms manifest in 21% (95% credible interval: 12–31%) of infections in 10- to 19-year-olds, rising to 69% (57–82%) of infections in people aged over 70 years (19). Accordingly, interventions aimed at children might have a relatively small impact on reducing SARS-CoV-2 transmission, particularly if the transmissibility of subclinical infections is low.

Likewise, in their Risk Assessment published on 23th of April, ECDC reviewed the child-to-other transmission and concluded that it appeared to be uncommon (20). Although data on the role of children in transmitting the disease remain limited, they suggest that when deciding which measures can be lifted first, those measures should be chosen that target specific age groups (< 10 years of age) where evidence shows continued limited disease transmission is less likely to result in major public health impact.

References

1. Götzinger F, Santiago-Garcia B, Noguera-Julian A, Lanaspá M, Lancella L, Calo Carducci FI et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health* 2020. Published Online June 25 2020. DOI:[https://doi.org/10.1016/S2352-4642\(20\)30177-2](https://doi.org/10.1016/S2352-4642(20)30177-2)
2. Raba AA, Abobaker A, Elgenaidi IS, Daoud A. Novel Coronavirus Infection (COVID-19) in Children Younger Than One Year: A Systematic Review of Symptoms, Management and Outcomes. *Acta Paediatr.* review article.2020 Jun 17. Doi:10.1111/apa.15422.
3. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. *Pediatrics* June 2020, 145 (6) e20200702; DOI: <https://doi.org/10.1542/peds.2020-0702>.

- 4 Litzroth A, Cornelissen L, Wyndham-Thomas C, Montourcy M, De Rouck M, Van Beckhoven D. Surveillance of hospitalized children and adolescents with confirmed COVID-19 infection. Report for hospitals – 08/06/2020.
- 5 L'Huillier AG, Torriani G, Pigny F, Kaiser L, Eckerle I. Shedding of infectious SARS-CoV-2 in symptomatic neonates, children and adolescents [Internet]. *Infectious Diseases (except HIV/AIDS)*; 2020 May [cited 2020 Jun 5]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2020.04.27.20076778>
- 6 Jones TC, Mühlemann B, veith T, Zuchowski M, Hofmann J, Stein A et al. An analysis of SARS-CoV-2 viral load by patient age. 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
- 7 Science Media Centre. <https://www.sciencemediacentre.org/expert-reaction-to-a-preprint-looking-at-the-amount-of-virus-from-those-with-covid-19-in-different-age-groups/>
- 8 Jones TC, Mühleman B, Veith T, Biele G, Zuchowski M, Hofmann J et al. An analysis of SARS-CoV-2 viral load by patient age. Preprint. https://virologie-ccm.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/Weitere_Dateien/Charite_SARS-CoV-2_viral_load_2020-06-02.pdf.
- 9 Zhu Y, Bloxham CJ, Hulme KD, Sinclair JE, Tong ZWM, Steele LE, et al. Children are unlikely to have been the primary source of household SARS-CoV-2 infections. *medRxiv*. 2020 Mar 30;2020.03.26.20044826.
- 10 Li W, Zhang B, Lu J, Liu S, Chang Z, Cao P, et al. The characteristics of household transmission of COVID-19. *Clinical Infectious Diseases*. 2020.
- 11 Heavey L, Casey G, Kelly C, Kelly D, McDarby G. No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020. *Eurosurveillance*. 2020 May 28;25(21):2000903.
- 12 Report: COVID-19 in schools – the experience in NSW | NCIRS [Internet]. [cited 2020 Jun 2]. Available from: <http://ncirs.org.au/covid-19-in-schools>
- 13 Bunyavanich S, Do A, Vicencio A. Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults. *JAMA* [Internet]. 2020 May 20 [cited 2020 May 29]; Available from: <https://jamanetwork.com/journals/jama/fullarticle/2766524>
- 14 Viner RM, Mytton OT, Bonelle C, Melendez-Torres GJ, Ward JL, Hudson L et al. Susceptibility to and transmission of COVID-19 amongst children and adolescents compared with adults: a systematic review and meta-analysis | medRxiv [Internet]. [cited 2020 Jun 2]. Available from: <https://www.medrxiv.org/content/10.1101/2020.05.20.20108126v1>.
- 15 Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. *Lancet Infect Dis*. 2020 Apr 27.
- 16 van der Hoek W, Backer JA, Bodewes R, Friesema I, Meijer A, Pijnacker R et al. De rol van kinderen in de transmissie van SARS-CoV-2. <https://www.ntvg.nl/artikelen/de-rol-van-kinderen-de-transmissie-van-sars-cov-2/volledig>.
- 17 RIVM. Children and COVID-19. <https://www.rivm.nl/en/novel-coronavirus-covid-19/children-and-covid-19>
- 18 Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, et al. Repeated seroprevalence of anti-SARS-CoV-2 IgG antibodies in a population-based sample from Geneva, Switzerland. *medRxiv*. 2020 May 6;2020.05.02.20088898.
- 19 Davies NG, Klepac P, Liu Y, Prem K, Jit M, CMMID COVID-19 working group. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nature Medicine* (2020).
- 20 ECDC. Rapid Risk Assessment: Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK– ninth update. April 23th 2020.