

# Observed reduction in the diagnosis of acute lymphoblastic leukaemia in children during the COVID-19 pandemic

To contain the spread of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), the Norwegian government implemented lockdown restrictions from March 13, 2020: schools, day cares and after-school activities were closed, 2-week quarantine was required following international travel, physical distancing (2 m) was recommended, and groups were restricted to five people.<sup>1</sup> Simultaneously, there was great focus on personal hygiene recommendations. From the end of April, the restrictions were gradually scaled back with reopening of schools and day cares, physical distancing reduced to 1 m and groups up to 20 people allowed. The advice to stay home in case of respiratory symptoms or fever remained. New daily cases of SARS-CoV-2 infection fell nationally from maximum 297 in March 26, 2020, to 10-20 in June and July. In parallel, the number of diagnosed airway infections with other pathogens fell rapidly, probably reflecting the implemented lockdown measures. Acute respiratory infection is the most common illness in children.<sup>2</sup> We investigated the effect of the COVID-19 pandemic and lockdown on the diagnosis and follow-up of paediatric cancer patients at Oslo University Hospital (OUH).

All new cancer cases in patients <18 years in the south-eastern region of Norway (~2.6 million people) are admitted and diagnosed at OUH, and a clinical pathway for cancer in children is started. In this descriptive study, we retrospectively reviewed all clinical pathways for cancer in children resulting in a cancer diagnosis January 01, 2017–July 31, 2020, at OUH. We used the Poisson distribution, which gives the probability of a given number of events occurring in a fixed time interval, given a known event rate, to calculate the probability of the observed number of events during the COVID-19 pandemic lockdown, given the pre-lockdown event rate. We reviewed outpatient consultations and cancellations January 01–June 30, 2020, compared to January 01–June 30, 2019. Additionally, we examined airborne infectious pathogens (see supplementary data, Data S1) found by polymerase chain reaction (PCR) analysis of deep nasal swabs in children <18 years at OUH January 01, 2017–July 31, 2020, as an indirect measure of infectious disease in the community.

There were no hospitalised paediatric cancer patients diagnosed with COVID-19 the first 6 months of 2020. In 2017, 2018 and 2019, there were 82, 99 and 92 new paediatric cancer cases, respectively (mean 7.58 cases/month, 95% confidence interval (CI) 6.80–8.37,

median 7.5 cases/month, range 3–12). In the first 6 months of 2020, there were 35 new paediatric cancer cases (mean 5.83 cases/month, 95% CI 3.09–8.58, median 5.5 cases/month, range 1–11). The number of solid tumours both within and outside the central nervous system was stable; however, there was a marked reduction in acute lymphoblastic leukaemia (ALL) cases. In 2017, 2018 and 2019, there were 20, 31 and 22 new ALL cases, respectively (mean 2.03 cases/month, 95% CI 1.63–2.43, median two cases/month, range 0–4). In the first 6 months of 2020, there were three new ALL cases, and all were diagnosed before the lockdown (two in early March 2020) (Figure S1). In the first 4 months of the lockdown (13.03.2020–12.07.2020), not a single paediatric ALL was diagnosed. Based on the observed rate in 2017–2019, the probability of having no new ALL cases over 4 months is <0.001 (95% CI 0.00006–0.001). The probability of having ≤ 3 new ALL cases over 6 months is 0.002 (95% CI 0.0003–0.012). There were three new ALL cases in July 2020. Before 2020, the longest period with no observed ALL cases was 66 days and the lowest number of cases in a 4-month period was four, both occurring in 2017.

Numbers from the Department of Microbiology show an 82% and 76% decrease in airway pathogens found by PCR in children in April and May 2020 compared to the average for these months in 2017–2019 while the total number of tests was stable (Figure S1). In June and July, the reduction was 43% and 37%, respectively.

Cancellations of paediatric haematology and oncology outpatient clinic consultations at OUH increased by 50% in March 2020 compared to 2019, mainly due to patients/parents in quarantine or home isolation, fear of exposure to COVID-19 and flight traffic disruption. Telephone or video consultations were quickly implemented to avoid unnecessary delays. Eighteen per cent of outpatient consultations in March and 12% in April were over phone or video, reduced to 3% by June, compared to none in 2019.

Our review shows a marked reduction in paediatric ALL cases during the COVID-19 lockdown, though the absolute numbers are small. Similarly, the Children's Hospital of Philadelphia, USA, reported no new leukaemia cases from March 02, 2020–April 06, 2020, (35 days) compared to a 5-year average of one every 3 days,<sup>3</sup> and the first cases presenting in April required intensive care, indicating delayed diagnosis. The first cases of ALL at OUH in July 2020 did not show evidence of advanced disease.

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There have been reports of a reduction in paediatric solid tumours, both from Milano, Italy, and New York, USA.<sup>4,5</sup> New York but not Milano observed an increase in metastatic cases.

During the SARS-epidemic in Hong Kong in 2003, which also led to a lockdown of society, a decrease in new ALL cases in young children was seen.<sup>6</sup> This was hypothesised to be related to common infections playing a role in ALL development. Though we have seen a decrease in airway pathogens, we do not have a direct measure of common infections in society and we are limited by small numbers of ALL cases. The drop in ALL cases was observed from the beginning of the lockdown though one might have expected some latency; however, there had already been changes in behaviour in society before the lockdown was implemented. In addition to infection, there may have been reduced contact with other environmental factors potentially involved in leukaemogenesis during the lockdown. The role of infectious disease in ALL development is not clear, but the social experiment of the COVID-19 lockdown might give an indication when different experiences around the world are compared, for example in a large multicentre study including regions with and without lockdown.

#### CONFLICT OF INTEREST

None.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.