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LETTER TO THE EDITOR

The impact of the COVID-19 pandemic on the future incidence of acute lymphoblastic leukaemia in children: Projections for Germany under a COVID-19 related scenario

Dear Editor,

1 | CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA AND SARS-CoV-2

There is convincing scientific evidence that the most frequent malignancy in childhood, acute lymphoblastic leukaemia (ALL) and in particular its major subtype B-precursor ALL (BCP-ALL), is related to patterns of exposure to infectious agents in early life.[1,2] Therefore, as already put forward by others,[3,4] it is likely that the current COVID-19 pandemic will impact on the risk of children of developing ALL and, consequently, on the ALL incidence on a population level. The underlying infections-related model acting on the two-hit hypothesis for ALL is the one developed by Greaves. According to this model, ALL results from two genetic hits, with the first occurring before birth, induced by prenatal exposures or random mutations. The second hit is induced by an abnormal reaction of the immune system to exposure to common infections, more commonly so in children with insufficient training of their immune system through lesser-than-required social contacts in their first 2 to 3 years of life.[2] For one particular genetic subtype of BCP-ALL, namely the ETV6/RUNX1 fusion type comprising about 25% of all BCP-ALL, it was shown that 5% of all healthy new-borns carry the first hit of which 0.2% later develop BCP-ALL.[5]

It is curious that when considering those infectious-related models of BCP-ALL risk in relation to the COVID-19 pandemic, both inflation and reduction in the ALL incidence are conceivable. On one hand, an infection with the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), very common in young children,[6] may directly act as trigger of the second hit. Single cases of BCP-ALL shortly after SARS-CoV-2 infection may support this scenario.[7] On the other hand, its possible impact could be that the social isolation of susceptible children during the COVID-19 pandemic would generally reduce the risk of experiencing a second, infectious hit.

Which of the two effects occur may soon become visible when incidence rates for the pandemic years are reported by cancer registries. Notably, cancer registration usually involves substantial delays with regard to data availability (due to delays in reporting, data cleaning and data preparation), so that reliable data will vastly only be available from 2022 onwards. For Germany, currently the only country for which a nationwide population-based assessment of the impact of the COVID-19 pandemic on childhood cancer incidence rates has been published, a remarkably increased incidence rate of childhood cancers, not specific to BCP-ALL, has been reported for 2020, but likely rather attributed to increased parental and possibly also doctor's awareness.[8]

2 | LOCKDOWN AND RISK OF ALL

The future impact of one of the factors of this immune system-related hypothesis can however be modelled,[1] namely the lack of immunological training due to the closure of nurseries and other childcare facilities during the pandemic and restrictions in how many children were limited or even deprived from social contacts. To model the resulting excess cases for this scenario, information on how many children would be affected and how their individual risk would change was needed (see also footnote of Table 1). For an estimate of the proportion of affected children, we obtained information from the Federal Statistical Office of Germany that 35% of 0 to 3-year olds attended childcare before the pandemic. For an estimate of change in risk, we used a systematic review of 14 individual studies on ALL risk in relation to early childcare, observing a 20% risk reduction in ALL in children who attended childcare at ages 0 to ≤2 years.[9] We use data of a large childhood population, the 11.3 million 0 to 14 year olds living in Germany, as well as high quality population-based data from the national German Childhood Cancer Registry.[8] As this model applies to ALL mainly occurring between ages 2 and 6 years, all projections relate to this age group only.

Table 1 shows the projections and the underlying statistical model, with the number of excess cases as the difference between the projected incidence rates following the model, compared to the expected incidence rate if no pandemic had occurred. The model suggests up to 99 additional ALL cases among 2 to 6 year old children in the period 2020 to 2024, so that 6.4% of the total of 1551 ALL cases might be attributable to the lockdown measures

Abbreviations: ALL, acute lymphoblastic leukaemia; BCP-ALL, B-cell precursor acute lymphoblastic leukaemia; SARS-CoV-1, severe acute respiratory syndrome coronavirus type 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2.

TABLE 1 Numbers of incident diagnoses of acute lymphoblastic leukaemia (ALL) in 2-6-year-old children in Germany in 2006, 2019 and 2020-2024, by scenario

		Absolute number of cases (crude rates by 1 000 000 children)						
Scenario	Description[a]	2006	2019	2020	2021	2022	2023	2024
No COVID-19	Expected situation if no pandemic lockdown had occurred	278 (75.3)	271 (70.1)	284 (71.9)	288 (71.8)	293 (71.7)	294 (71.6)	293 (71.6)
COVID-19	Closure of childcare facilities during the pandemic (pE = 1 and RR = 1.25)	278 (75.3)	271 (70.1)	302	308	313	314	314
	Excess numbers of cases between no COVID-19 and COVID-19 scenarios	–	–	18	20	20	20	21

Note: Absolute numbers and rates for 2006 and 2019 are based on data from the German Childhood Cancer Registry, for the years 2020 to 2024 projections are presented.

[a]We modelled ALL incidence rates based on a Poisson regression model that changes the at-risk population size. First, we defined by E, a binary exposure variable that takes the value 0 for children who do attend day-care (hereinafter referred to as the "nonexposed" group) and 1 for those who do not (the "exposed" group), and defined the corresponding proportion of children, pE, not in day-care centres and/or families. Then, we assumed that the observed number of cases can be decomposed into the sum of two Poisson-distributed random variables: one for each of the two exposure groups. We finally used the following constrained model, $D_i \sim$ Poisson (μ_i = lambda [PY_{0i} + RR * PY_{1i}]), where D_i denotes the observed number of cases, *i* the calendar year (from 2006 to 2019), lambda the incidence rate, RR the relative risk, and PY_{0i} and PY_{1i} are person-years (PYs) among nonexposed and exposed, respectively. RR is the relative risk defined by the risk of cancer in the exposed group compared to the nonexposed group (using the inverse of the effect from reference #9), which is estimated by the ratio of incidence rates. While the total person-years (PY_i), at time *i*, is decomposed into: $PY_i = (1 - pE_i) * PY_i + pE_i * PY_i = PY_{0i} + PY_{1i}$, the expected number of cases, μ_i, is equal to: lambda * ((1 − pE_i) + pE_i * RR) * PY_i. We obtained an estimate of the parameter lambda with a maximum likelihood procedure. Predicted numbers of cases due to the closure of childcare facilities during the pandemic (COVID-19 scenario) were computed using this model and assuming a prevalence pE equal to 1. For comparison, expected incidence rates if no pandemic had occurred (no COVID-19 scenario) were also calculated using a (period-) Poisson regression model.

preventing the child's immune system to be adequately trained. This projection is based on our assumptions and may be an overestimate as the childcare facilities were not permanently closed during the pandemic. On the other hand, social interactions with other children were in general reduced among all children, so if this contact reduction was sufficient to pose a risk, our projection may underestimate the real effect.

3 | CONCLUSIONS

Taken together, significant changes in the incidence of childhood BCP-ALL in Germany and other countries are expected in the next years. The careful comparison between countries where the percentage of SARS-CoV-2 infected children differs significantly, will hopefully provide us with new and compelling ideas how to prevent BCP-ALL[10]—for at least some children a still deadly disease. Should the incidence only marginally change due to the pandemic, then immune stimulation by behavioural interventions alone would hardly offer major prevention avenues, as they would unlikely be more comprehensive than the pandemic.

Decisions about lockdown measures in the youngest children need to consider the possible increase in ALL risk, which need to be balanced against possible benefits for the children.

In any case, we support the suggestion by Greaves[3] that it would be very informative to know how many newly-diagnosed BCP-ALL cases experienced unrecognised, asymptomatic SARS-CoV-2 infection. This could be easily achieved by routine checking of SARS-CoV-2 nucleocapsid antibodies during diagnostic work-up.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. Conceptualisation, Joachim Schüz, Arndt Borkhardt, Friederike Erdmann; methodology, Liacine Bouaoun, Joachim Schüz, Arndt Borkhardt, Friederike Erdmann; formal analysis,

Liacine Bouaoun; data curation, Friederike Erdmann; writing—original draft preparation, Joachim Schüz; writing—review and editing, Joachim Schüz, Arndt Borkhardt, Liacine Bouaoun, Friederike Erdmann; project administration, Friederike Erdmann, Joachim Schüz; visualisation, Liacine Bouaoun. All authors approved the final manuscript as submitted, agreed to be accountable for all aspects of the work and had the final responsibility for the decision to submit for publication.

DATA AVAILABILITY STATEMENT

Access to aggregated data may be made available upon reasonable request.

ETHICS STATEMENT

No ethics approval or consent was required for this study, as no active participation of patients was required. This research was carried out in compliance with the requirements of the General Data Protection Regulation (GDPR) and in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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