

LETTER TO THE EDITOR**COVID-19 and childhood acute lymphoblastic leukemia**

To the Editor:

Young children are not affected with life-threatening illnesses from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared to the adult population, despite having no immunity to this novel infectious agent. The coronavirus disease 2019 (COVID-19) pandemic may, however, impact the pediatric population in a different manner that may become more evident once it ends.

Acute lymphoblastic leukemia (ALL), the most common form of childhood cancer, has an overall incidence in the United States of 34 cases/ million individuals <20 years of age with the peak incidence of 75.2 cases/ million occurring in children between the ages of 1-4 years.¹ Hypotheses have been proposed, particularly by Dr Greaves, that account for the peak incidence in early childhood.² In Greaves' model, ALL arises by "two-hits"; the "first-hit" occurring prenatally with the generation of a preleukemia clone³ which may harbor a leukemia-associated genetic change (eg, ETV6-RUNX1 fusion translocation). A subsequent "second-hit" occurring postnatally in a population of "preleukemia" cells would initiate the final steps for leukemia to develop and manifest clinically. Interesting, the ETV6-RUNX1 fusion has been detected in up to 5% of healthy newborn blood samples, as an example of a relatively high proportion of children potentially harboring a "first-hit" preleukemia clone.⁴

Without a "second-hit," these children would not develop ALL. The "second-hit" is postulated to be exposure to a common infectious agent (eg, virus) in a susceptible child whose body harbors a population of preleukemia cells, although they have no immunity against the infection. This "perfect storm" may lead to an abnormal or overstimulated immune response leading to the proliferation of leukemia cells.

Measures have been implemented to control the spread of COVID-19, including social distancing with widespread closure of schools, businesses, and entertainment venues. Within a span of 2 months (March to April 2020), our respective children's hospitals (situated hundreds of miles apart in different states) have observed a marked reduction in the number of both emergency room visits and number of hospitalized children during the typical winter season when the various seasonal respiratory viruses including influenza and RSV circulate among the population.

Can the isolation of children at home lead to an avoidance of exposure to viruses and the leukemia-inducing "second-hit?" Will this result in a decreased number of childhood ALL cases in the near future? Conversely, can the infection of predisposed children by COVID-19 (even those who may be clinically asymptomatic) act as a

"second-hit," leading to an increased number of ALL cases following this pandemic? Interestingly, in 2003, a decreased number of pediatric ALL cases were diagnosed in Hong Kong following the severe acute respiratory syndrome (SARS) outbreak.⁵ The answers to these two potential scenarios may become evident in the near future with ongoing epidemiologic surveillance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

Jeffrey W. Taub  <https://orcid.org/0000-0003-2228-3235>

Ana C. Xavier  <https://orcid.org/0000-0002-3659-3798>

Jeffrey W. Taub¹ 

Yubin Ge²

Ana C. Xavier³ 

¹Division of Hematology/Oncology, Children's Hospital of Michigan, Detroit, Michigan

²Department of Oncology, Karmanos Cancer Institute, Detroit, Michigan

³Division of Hematology/Oncology, Children's of Alabama, Birmingham, Alabama

Correspondence

Jeffrey W. Taub, Children's Hospital of Michigan, 3901 Beaubien Blvd, Detroit, MI 48201.

Email: jtaub@med.wayne.edu

REFERENCES

1. Siegel DA, Henley SJ, Li J, Pollack LA, Van Dyne EA, White A. Rates and trends of pediatric acute lymphoblastic leukemia—United States, 2001-2014. *MMWR Morb Mortal Wkly Rep*. 2017;66:950-954.
2. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat Rev Cancer*. 2018;18:471-484.
3. Taub JW, Konrad MA, Ge Y, et al. High frequency of leukemic clones in newborn screening blood samples of children with B-precursor acute lymphoblastic leukemia. *Blood*. 2002;99:2992-2996.
4. Schäfer D, Olsen M, Lähnemann D, et al. Five percent of healthy newborns have an ETV6-RUNX1 fusion as revealed by DNA-based GIPFEL screening. *Blood*. 2018;131:821-826.
5. Li CK, Zee B, Lee J, Chik KW, Ha SY, Lee V. Impact of SARS on development of childhood acute lymphoblastic leukaemia. *Leukemia*. 2007;21:1353-1356.