The risks of delay?

Scott C. Kogan

Helen Diller Family Comprehensive Cancer Center, University of California San Francisco
Department of Laboratory Medicine, University of California San Francisco

Correspondence: S.C. Kogan
scott.kogan@ucsf.edu

Received: June 16, 2026.
Accepted: June 22, 2026.
Early view: July 2, 2026.

https://doi.org/10.3324/haematol.2026.301343

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

In the current issue of *Haematologica*, Cazzaniga, Shamsaei, Procter, John-Baptiste, Ford, and Greaves[1] provide new evidence that delayed exposure to organisms can promote leukemogenesis when exposure from birth does not.

Twenty-seven years ago Wiemels, Ford, Van Wering, Postma, and Greaves reported[2] that a pair of identical twins had developed B-cell acute lymphoblastic leukemia (B-ALL) 9 years apart, one at the age of 5 years and the other at the age of 14. They found that the leukemias in both twins contained an identical rearrangement of chromosomes 12 and 21 resulting in a *TEL-AML1* fusion (which is now denoted *ETV6::RUNX1*). On the basis of this finding and the fact that the bone marrow of the twin developing B-ALL at the age of 14 already had this fusion at the age of 5, the investigators suggested that, "consequent to a prenatal initiation of a leukemic clone, most probably by *TEL-AML* fusion itself, the latency of ALL can be both extremely variable and protracted. This, in turn, is likely to reflect the timing of critical secondary events." Prior and subsequent studies demonstrated that indeed the two most common genetic subtypes of pediatric B-ALL (*ETV6::RUNX1* and hyperdiploid) typically arise from cells carrying prenatally acquired genetic changes (reviewed by Greaves[3]). However, the rate of children born with *ETV6::RUNX1* fusions exceeds by 100- to 500-fold the number of children who develop *ETV6::RUNX1* B-ALL.[4,5] Hence, most children born with a common genetic marker of early childhood B-ALL never develop leukemia. Over the past 27 years there have been epidemiological, molecular, cellular, and organismal studies that have enhanced our knowledge of critical secondary events that promote leukemic transformation. Nevertheless, our current insight into why most children with prenatally acquired leukemia-associated genetic changes do not develop leukemia remains limited, as does our insight into reasons for the decades-long increase in the incidence of pediatric ALL.

The new report by Cazzaniga *et al.*[1] supports the long-standing "delayed infection" hypothesis: that the timing of exposure to particular microbes is one critical aspect of subsequent leukemia risk.[6] The investigators compared the development of B-ALL in groups of mice in which an *ETV6::RUNX1* transgene was expressed under the regulation of an IGH enhancer and β-globin promoter.[7] Other investigators had observed that mice expressing a Sca1-*ETV6::RUNX1* transgene did not develop leukemia when housed under specific pathogen-free (SPF) conditions but a subset (10 of 93, ~11%) did develop B-ALL when the mice were transferred at 4 to 5 months of age from an SPF to a common infectious environment.[8] Cazzaniga *et al*. followed four groups of IGH-*ETV6::RUNX1* transgenic animals. As in the study of Sca1-*ETV6::RUNX1* animals, no mice developed leukemia when housed in an SPF facility. However, when mice were transferred at 5 to 8 weeks of age to a common infectious environment (denoted SPF2 in the study by Cazzaniga *et al*.), 11% of animals (6 of 54) developed B-ALL, a remarkable concurrence of incidence given the different timing of transfer, different animal facilities, and different regulation of the transgene. A most significant finding was observed with a third group of mice: IGH-*ETV6::RUNX1* transgenic animals born into the common infectious environment (SPF2 facility). In contrast to animals moved into this facility at 5 to 8 weeks of age, none of 400 transgenic animals born in this facility developed leukemia! That is, mice exposed to infectious organisms at 5 to 8 weeks were at risk of leukemia whereas those exposed prior to or at birth were leukemia-free. Further supporting the investigators' interpretation that specific exposures at 5 to 8 weeks promoted leukemogenesis, a fourth group of 75 mice was transferred from the SPF facility to the common infectious environment (SPF2) after fumigation had eliminated several organisms and none of these mice developed leukemia. By comparing the organisms detected in their facilities with those detected in the facilities used by Rodríguez-Hernández *et al*. for their Sca1-*ETV6::RUNX1* studies, Cazzaniga *et al*. highlight norovirus as a candidate leukemogen. Altogether, this recent work with IGH-*ETV6::RUNX1* transgenic mice provides direct experimental evidence supporting the hypothesis that delayed infection promotes development of ALL in some individuals.

Greaves and colleagues have previously reviewed the

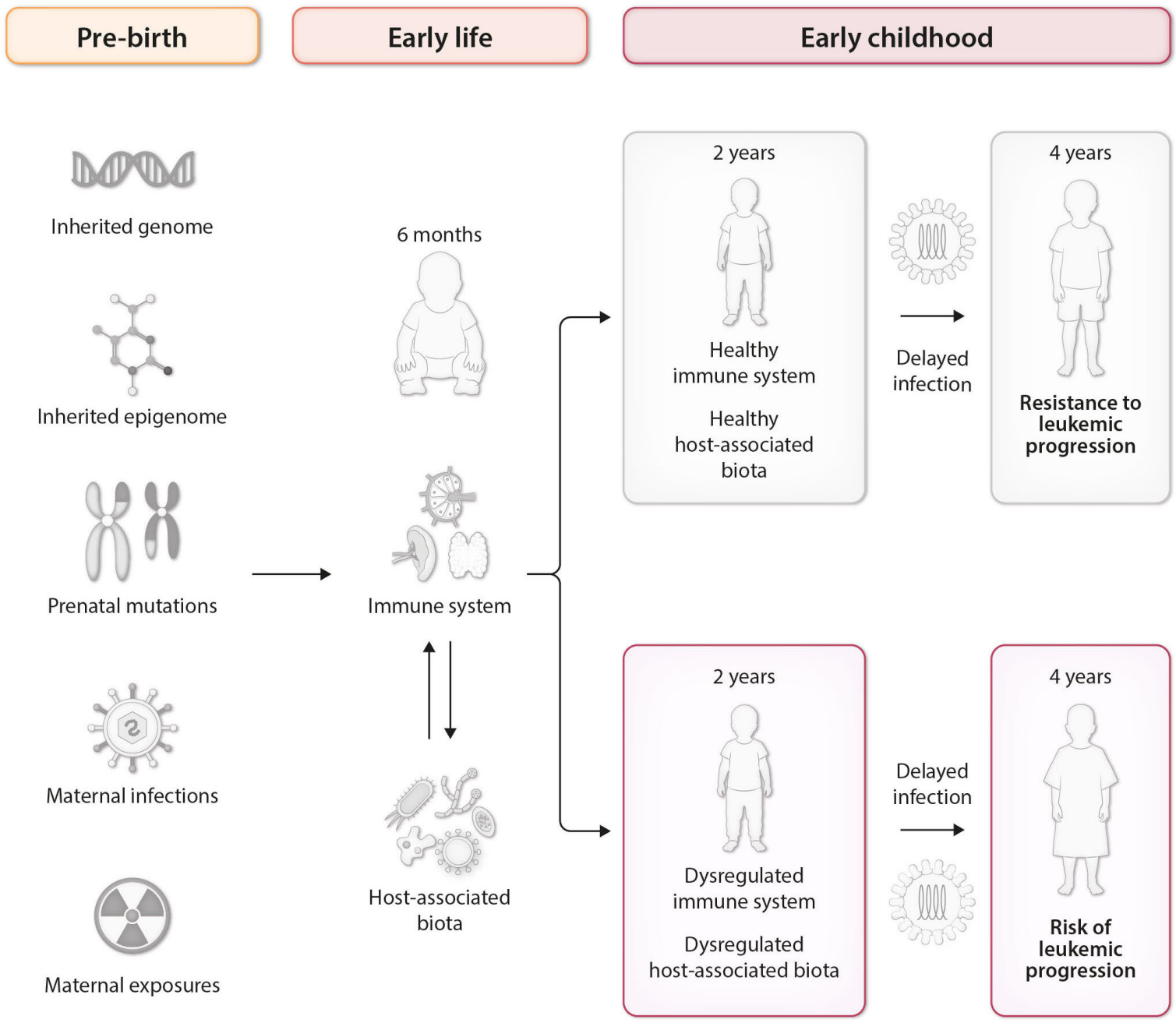


Figure 1. A view of the risk of childhood leukemia. Multiple factors influence risk prior to birth. Early life experiences contribute to the development of the immune system, development of host-associated biota, and their interactions. Early exposures can foster healthy development. Among children born at increased risk of leukemia, a healthy immune system (including a healthy interaction with host-associated biota) can protect a child from subsequent challenges. When exposures are delayed, some infectious agents have the capacity to promote progression to leukemia in children with dysregulation of their immune system and their biota.

etiology of ALL, have discussed the complexity of epidemiological and experimental data, and have speculated on what would be needed to intervene as public policy to reduce ALL risk.[3,9] The hypothesis that delayed infection increases ALL risk has been placed in the context of the broader hypothesis that exposures/experiences that may modulate leukemia risk (including birth route, breast feeding, social contacts, diet, and antibiotics) do so through changes in immune system development in concert with changes in the infant microbiome. Indeed, Cazzaniga *et al.* present their preliminary findings on the microbiomes present in the varied groups of mice they studied, laying the groundwork for further investigations that could link particular delayed infection leukemogens to microbiome-mediated causal mechanisms. It is an appealing idea to envision reducing the risk of ALL, type 1 diabetes, and allergies through early interventions that promote a health-supporting microbiome.[10,11] The appeal of promoting healthy children through microbiome manipulation makes it all the more important that those of us within the scientific community publish our work as "our present understanding," highlight limitations, and avoid language that promotes interventions before there is a preponderance of evidence that an intervention does more good than harm. The new functional abilities of large language models to scour peer-reviewed work and present "conclusions" to anyone with access to the internet mandates that our scientific discourse be more measured in the future than in the past.

Disclosures

No conflicts of interest to disclose.

References

1. Cazzaniga V, Shamsaei E, Procter J, John-Baptiste P, Ford AM, Greaves M. Timing of microbial exposure and risk of infection-promoted acute lymphoblastic leukaemia. Haematologica. 2026;111(10):3525-3529.
2. Wiemels JL, Ford AM, Van Wering ER, Postma A, Greaves M. Protracted and variable latency of acute lymphoblastic leukemia after TEL-AML1 gene fusion in utero. Blood. 1999;94(3):1057-1062.
3. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. Nat Rev Cancer. 2018;18(8):471-484.
4. Mori H, Colman SM, Xiao Z, et al. Chromosome translocations and covert leukemic clones are generated during normal fetal development. Proc Natl Acad Sci U S A. 2002;99(12):8242-8247.
5. Schafer D, Olsen M, Lahnemann D, et al. Five percent of healthy newborns have an ETV6-RUNX1 fusion as revealed by DNA-based GIPFEL screening. Blood. 2018;131(7):821-826.
6. Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukemia. Leukemia. 1988;2(2):120-125.
7. Ford AM, Palmi C, Bueno C, et al. The TEL-AML1 leukemia fusion gene dysregulates the TGF-beta pathway in early B lineage progenitor cells. J Clin Invest. 2009;119(4):826-836.
8. Rodriguez-Hernandez G, Hauer J, Martin-Lorenzo A, et al. Infection exposure promotes ETV6-RUNX1 precursor B-cell leukemia via impaired H3K4 demethylases. Cancer Res. 2017;77(16):4365-4377.
9. Greaves M, Cazzaniga V, Ford A. Can we prevent childhood leukaemia? Leukemia. 2021;35(5):1258-1264.
10. Peppas I, Ford AM, Furness CL, Greaves MF. Gut microbiome immaturity and childhood acute lymphoblastic leukaemia. Nat Rev Cancer. 2023;23(8):565-576.
11. Gallant R, Reza S, Wiemels JL, Greaves M. Microbiome and pediatric leukemia, diabetes, and allergies: systematic review and meta-analysis. PLoS One. 2025;20(5):e0324167.