

CLL-1256 Evolution of Infection-Associated Mortality Among Decedents With Chronic Lymphocytic Leukemia: A 22-Year National Multiple-Cause-of-Death Analysis, 2003–2024

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INTRODUCTION

- Severe infections represent a primary cause of morbidity and fatal complications in chronic lymphocytic leukemia (CLL) due to disease-related immune dysfunction and hypogammaglobulinemia.
- Over the past two decades, therapeutic paradigms transitioned from cytotoxic chemoimmunotherapy (e.g., FCR/BR) toward targeted small-molecule inhibitors (BTK and BCL-2 inhibitors), fundamentally altering immunosuppressive profiles and survivorship.
- Population-level evaluation of nationwide Multiple Cause of Death records clarifies long-term infectious vulnerability across therapeutic eras.

AIM

- Primary Aim:** Quantify 22-year national trends (2003–2024) in fatal infectious co-mention among CLL-associated decedents.
- Secondary Aim:** Assess subtype-specific shifts (pneumonia, sepsis, fungal infections) and evaluate trajectory inflection points associated with the 2013/2014 introduction of targeted pathway inhibitors.

METHOD

Data Source: CDC WONDER / NCHS Multiple Cause of Death files (2003–2024) evaluating decedents with CLL (ICD-10 code C91.1) in underlying or contributing fields.

Infectious Endpoints: Pneumonia (J18.x), sepsis (A40.x/A41.x), and fungal infections (B35–B49).

Statistical Analysis: Binomial logistic regression across the full study period and piecewise modeling with an inflection knot in 2013 comparing pre-targeted (2003–2013) vs. modern targeted (2014–2024) eras.

CONCLUSIONS

- Infectious mortality among CLL decedents declined over the past two decades, driven almost entirely by reductions in fatal pneumonia, whereas sepsis rates remained stagnant.
- The attenuation of decline after 2013 indicates persistent immune vulnerability in the targeted therapy era, underscoring the ongoing necessity of antimicrobial prophylaxis, immunoglobulin monitoring, and prompt sepsis management in routine clinical practice.

RESULTS

National Cohort (N=156,400): Evaluated 74,131 decedents in the pre-targeted era and 82,269 in the post-targeted era.

Overall Infectious Trajectory: Infectious co-mention decreased from **23.4%** in 2003 to **15.7%** in 2024 (21.6% pre-2014 vs. 18.7% modern era; OR **0.985**/yr, 95% CI 0.983–0.987, $p < 0.001$).

Post-2013 Inflection: Piecewise modeling revealed that the rapid pre-2014 decline attenuated significantly in the modern targeted era (slope-change OR **1.024**, 95% CI 1.016–1.032, $p < 0.001$).

Subtype-Specific Divergence:

Pneumonia: Declined from **14.4% to 8.1%**.

Sepsis: Remained largely unchanged (**10.4% in 2003 vs. 9.9% in 2024**; era means: 10.8% vs. 10.5%).

Fungal Infections: Remained rare across both eras (**0.70% to 0.49%**).

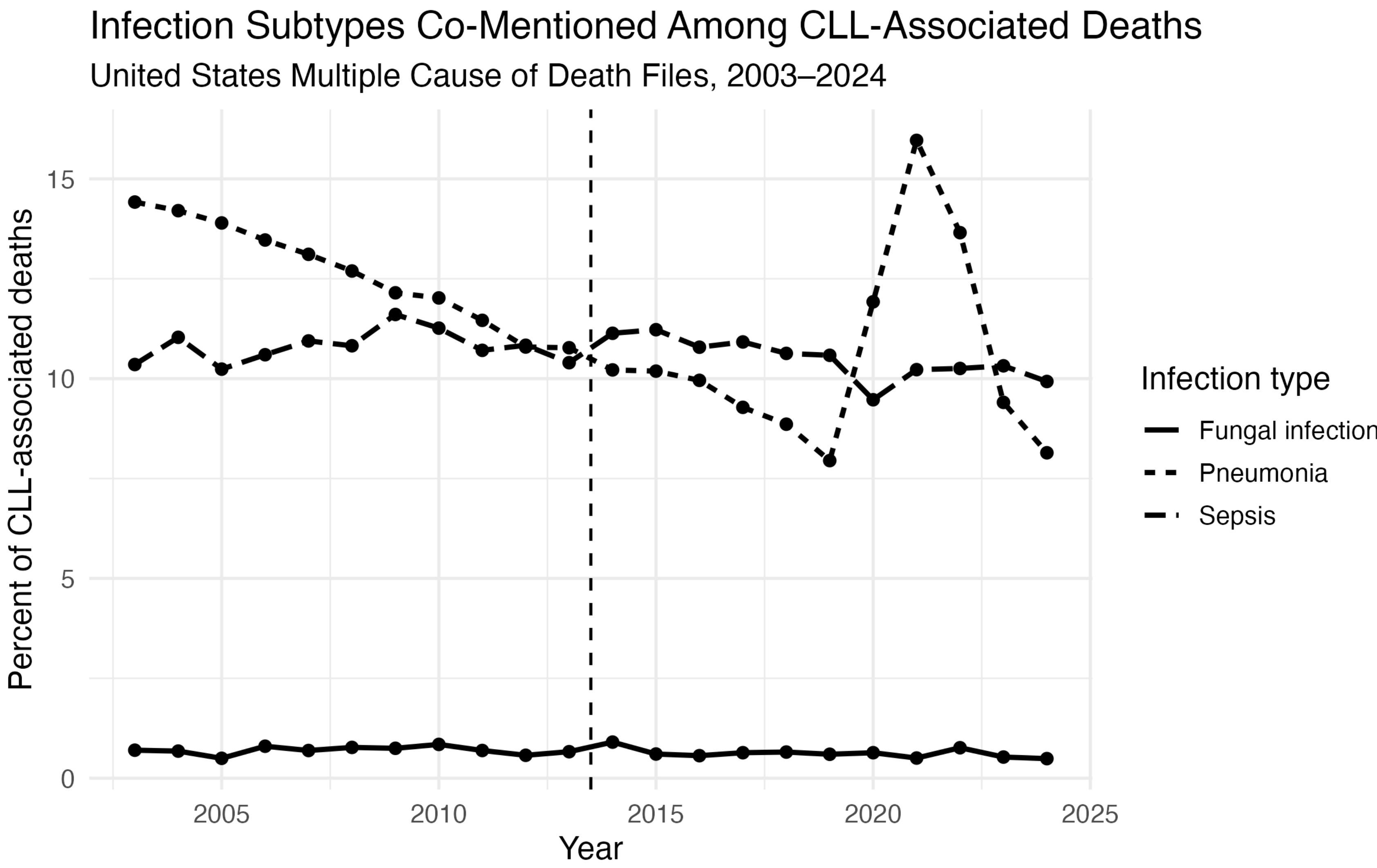
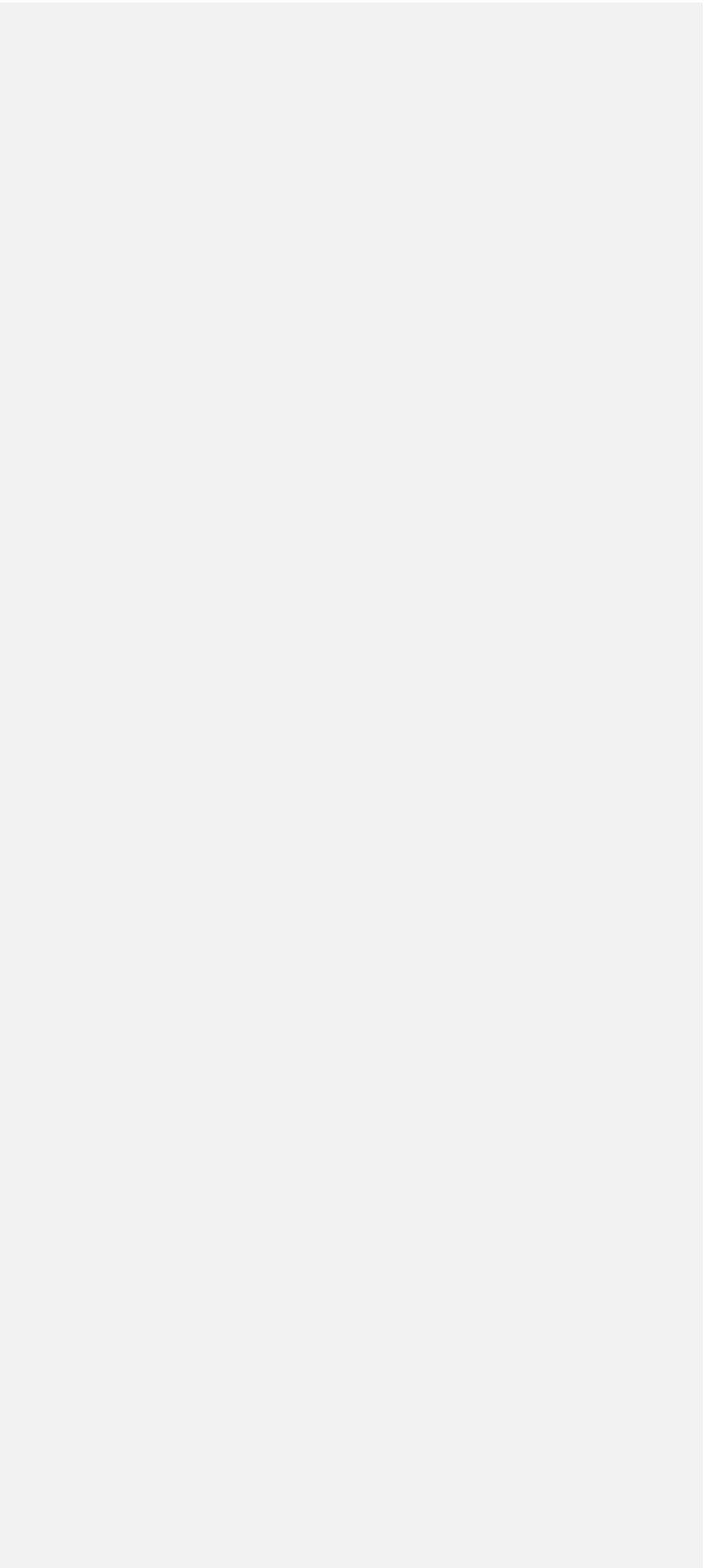


Figure 1. 22-Year Trajectories of Terminal Infectious Subtypes Among CLL Decedents (2003–2024). Annual proportion of nationwide CLL-associated deaths co-mentioning pneumonia, sepsis, and opportunistic fungal infections. The dashed vertical line denotes the 2013 inflection knot (FDA approval of ibrutinib). While pneumonia mortality declined substantially, sepsis mortality remained persistent, and approximately 1 in 6 CLL decedents in 2024 continued to have terminal infectious complications.

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