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TITLE: Evaluating Therapeutic Outcomes in Childhood Interstitial Lung Disease Through Bayesian Federated Inference

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ABSTRACT:

Introduction
Childhood interstitial lung disease (chILD) represents a heterogeneous group of rare diffuse parenchymal lung disorders with an estimated prevalence of 1-3.6 per million children, carrying substantial respiratory morbidity and mortality, particularly in infancy. To date, no pharmacological therapy has received regulatory approval for any chILD subtype, and clinical management remains largely driven by expert opinion, small case series, and extrapolation from adult ILD data. The extreme rarity of chILD means that no single center accumulates sufficient cases to conduct powered therapeutic outcome studies. Meanwhile, multicenter data pooling is mainly obstructed by data governance regulations and patient privacy requirements. As a consequence, rigorous outcome evaluation for widely used off-label therapies, including systemic corticosteroids, hydroxychloroquine, macrolide antibiotics, and emerging antifibrotic agents, remains critically lacking

Objectives
This study aims to evaluate therapeutic outcomes in chILD across a multinational pediatric network, estimating the comparative effectiveness of current off-label treatment strategies on clinical stabilization, pulmonary function trajectory, exacerbation-free survival, and mortality without requiring individual patient data to leave the originating institution.

Methods
We will conduct a retrospective multicenter cohort study across participating pediatric pulmonology centers, enrolling patients aged 0–18 years with confirmed or probable chILD diagnosis per chILD-EU criteria and a minimum of 12 months of follow-up. To overcome data-sharing barriers, we employ the Bayesian Federated Inference (BFI) framework, a one-shot privacy-preserving approach in which each center analyzes only its local data and shares solely summary-level inference results (parameter estimates) with a central coordinating server. These are then mathematically combined to produce estimates that are provably equivalent to those from a fully pooled dataset, without any individual-level data transfer. Center-level heterogeneity arising from differences in subtype case mix, treatment protocols, and patient demographics will be explicitly modeled using BFI extensions that accommodate center-specific intercepts and institutional clustering effects.

Results
Federated outcome evaluation of 400 or more patients across European centers will reveal meaningful differences in clinical stabilization, exacerbation-free survival, and pulmonary function trajectories across therapeutic regimens and chILD subtypes. Systemic corticosteroids are expected to remain the dominant first-line agent, with considerable heterogeneity in dosing strategy, duration, and escalation thresholds across centers. We hypothesize that combination regimens that incorporate hydroxychloroquine will demonstrate superior 12-month clinical stabilization rates compared with corticosteroid monotherapy, particularly in surfactant dysfunction subtypes. Exacerbation-free survival analysis is expected to reveal significant subtype-specific differences in treatment response trajectories, with genetically defined subtypes likely showing more limited therapeutic benefit, further underscoring the critical absence of approved targeted therapies in this population. BFI-derived outcome estimates are expected to closely replicate those obtained from fully pooled

data, thereby validating the federated approach as a rigorous and privacy-preserving solution for rare pediatric disease research.

Conclusion

In the complete absence of approved therapies for chILD, this study will deliver the first rigorous, multicenter evaluation of therapeutic outcomes while fully protecting patient privacy through the BFI framework. Findings will directly inform clinical practice, support regulatory discussions around therapy approval, and provide the evidentiary foundation for the first prospective randomized controlled trials in this disease area. The federated analytical pipeline will be openly shared to accelerate evidence generation across rare pediatric disease research more broadly.