Temporal Epidemiology of Encephalitis Lethargica, 1919–1942: Population-Level Evidence Against a Short-Latency Post-Influenza Autoimmune Explanation

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Article

Temporal Epidemiology of Encephalitis Lethargica, 1919–1942: Population-Level Evidence Against a Short-Latency Post-Influenza Autoimmune Explanation

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Abstract

Background: The post-influenza autoimmune hypothesis for Encephalitis Lethargica (EL)—the dominant theory for its etiology—predicts that most EL cases should have emerged within weeks of the 1918–1919 influenza pandemic if driven by acute post-infectious autoimmune mechanisms. **Methods:** We analyzed temporal distribution of EL case notifications (England & Wales, 1919–1942, $n = 22{,}813$) relative to influenza mortality waves (1918–1919) using prespecified biologically plausible lag windows. Expected lag for post-infectious autoimmune mechanisms: 2–4 weeks. We calculated the proportion of total EL notifications occurring within predefined time windows: 0–3 months, 0–6 months, 0–12 months, 12–24 months, and $>$ 24 months after influenza peak. **Findings:** Only 3.8% of EL notifications occurred within 6 months of influenza peak (the window consistent with known post-infectious autoimmune latencies). The EL epidemic peaked in 1924—5.6 years after the influenza peak—when influenza had returned to endemic baseline. Phase analysis showed EL emergence and rapid rise (1919–1924) coincided with waning influenza, the inverse of expected post-influenza causality. **Interpretation:** The population-level temporal pattern of EL is inconsistent with a dominant short-latency post-influenza autoimmune mechanism. This finding does not exclude influenza involvement in a subset of cases, but argues against it as the primary population-level explanation. Alternative hypotheses—independent pathogen, environmental exposure with latency, heterogeneous etiology—warrant prioritized investigation.

Keywords: encephalitis lethargica; temporal epidemiology; influenza pandemic; 1918–1919; etiology; post-infectious mechanisms; lag-window analysis

1. Introduction

Encephalitis Lethargica (EL), also known as von Economo's encephalitis, emerged as a major pandemic neurological illness between 1917 and 1930, initially described by Constantin von Economo and Jean-René Cruchet [2,9]. The disease was characterized by distinctive features: severe sleep disturbances (hypersomnia), progressive parkinsonism, behavioral and psychiatric symptoms, and in severe cases, catatonia and akinetic mutism. Today, EL epidemiology and etiology remain among the most important unsolved questions in infectious disease history [1,5].

The dominant etiological hypothesis attributes EL to post-influenza autoimmune mechanisms triggered by the 1918–1919 Spanish Influenza pandemic. This hypothesis is based primarily on temporal proximity: both EL and the influenza pandemic occurred in the late 1910s and early 1920s. However, temporal proximity does not establish causality. The post-influenza autoimmune hypothesis makes a specific, testable prediction: if EL were primarily caused by acute post-influenza autoimmune mechanisms, the majority of EL cases should have clustered within the known latency window for post-infectious autoimmunity, typically weeks after the triggering infection.

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No prior study has formally tested whether the observed temporal distribution of EL matches this prediction. This represents a critical gap, because known post-infectious autoimmune phenomena, including acute rheumatic fever following streptococcal pharyngitis, Guillain–Barré syndrome following infections, and autoimmune encephalitis syndromes, consistently manifest weeks to months after the triggering infection—not years.

We conducted a formal temporal epidemiological analysis designed to test the specific prediction of the post-influenza autoimmune hypothesis: that EL notifications should concentrate within biologically plausible short-latency windows after influenza mortality peaks. We used government surveillance data from England and Wales to compare the observed temporal distribution of EL against the expected distribution under a dominant short-latency post-influenza autoimmune hypothesis.

2. Methods

2.1. Data Sources

Encephalitis Lethargica (NOIDS): Annual EL case notifications for England and Wales, 1919–1942, were obtained from the UK Health Security Agency Notifiable Diseases (NOIDS) historic dataset [7]. EL became notifiable on January 1, 1919. Total notifications were $n = 22{,}813$ cases over 24 years.

Influenza Mortality (SN4350): Weekly influenza mortality data, including number of deaths and crude death rates per 1,000 population, were obtained from UK Data Archive Study SN4350, *1918–1919 Influenza Pandemic Mortality in England and Wales* [3]. Data span June 22, 1918–May 10, 1919 (46 weeks). The data were transcribed from the Registrar General's 1920 report, which identified three distinct epidemic waves [4]:

- Wave 1: June 23–September 14, 1918 (summer)
- Wave 2: September 15, 1918–January 25, 1919 (fall-winter; peak mortality)
- Wave 3: January 26–May 10, 1919 (spring)

Influenza Peak: November 1918, corresponding to Wave 2, the largest mortality wave.

2.2. Primary Analysis: Prespecified Lag-Window Incompatibility Test

We defined biologically plausible lag windows based on known latencies of post-infectious autoimmune phenomena. These windows were specified *a priori* before evaluating the EL burden distribution.

Table 1. Prespecified biological lag windows after influenza peak.

Mechanism	Expected latency	Lag window
Direct viral neurologic complication	0–4 weeks	0–28 days
Acute post-infectious autoimmune	2–8 weeks	14–56 days
Broader subacute immune-mediated	2–6 months	14–180 days
Very permissive post-pandemic window	0–12 months	0–365 days
Delayed/non-acute process	$>$ 12 months	$>$ 365 days

Primary outcome: Proportion of total EL notifications (1919–1942) falling within each lag window, calculated from the influenza peak in November 1918.

Hypothesis test: Under the post-influenza autoimmune hypothesis, we predicted that a large majority of notifications should fall within the acute or subacute post-infectious window. We used $\geq$ 80% within 0–6 months as a conservative operational threshold for a dominant short-latency post-influenza mechanism. Under the null hypothesis of no dominant short-latency post-influenza mechanism, we expected a more diffuse or late-shifted distribution.

2.3. Exploratory Analyses

Temporal Descriptive Analysis: We characterized the EL epidemic curve by calendar year and identified the year of peak incidence.

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Phase Decomposition: We partitioned the EL epidemic into three temporal phases:

- Phase 1 (Emergence): 1919–1921
- Phase 2 (Rapid Rise to Peak): 1922–1924
- Phase 3 (Decline): 1925–1942

We compared the temporal distribution of influenza mortality (1918–1919) against phase timing to assess whether EL emergence and rise were temporally consistent with direct post-influenza causality.

Cross-Correlation Function (CCF), Supplementary: For exploratory purposes, we computed the CCF between standardized influenza mortality and EL notifications across lags 0–260 months. This analysis is presented as supplementary visualization and sensitivity analysis, not primary inference, because EL notifications are annual and the influenza series spans only 46 weeks.

2.4. Data and Analytical Limitations

Temporal Resolution: EL notifications are aggregated annually. This limits precision of lag estimation beyond "months versus years." The analysis is therefore designed to test lag-window categorization (weeks versus months versus years) rather than precise week- or month-level causality.

Case Ascertainment: Lag estimates assume complete case identification at notification. If substantial numbers of EL cases occurred in 1918 but were unrecognized or unnotified until after formal notification began in January 1919, the true lag could be shorter. However, this would require extensive systematic pre-notification under-ascertainment despite clinical severity.

Geographic Aggregation: Analysis is at nation level (England and Wales aggregate). Regional variation is not examined.

Influenza Exposure Heterogeneity: Influenza mortality data reflect national aggregates. Individual exposure timing may vary; however, pandemic wave timing was broadly defined at the national level in the Registrar General's report [4].

2.5. Statistical Software and Reproducibility

All analyses were performed in Python 3.9 using pandas, numpy, scipy, and matplotlib. Code and data processing notebooks are available at https://github.com/Nyx-Dynamics/el_temporal_analysis.

3. Results

3.1. Descriptive Epidemiology

EL Notifications (England and Wales, 1919–1942):

- Total: 22,813 cases
- Mean per year: 950.5 cases
- Range: 146–5,039 cases/year
- Peak year: 1924 (5,039 cases, 22.1% of total 24-year burden)

Influenza Pandemic (1918–1919):

- Total deaths: 160,967
- Duration: 46 weeks (June 22, 1918–May 10, 1919)
- Peak: November 1918 (Wave 2)
- Peak weekly deaths: approximately 17,000

3.2. Primary Analysis: Lag-Window Distribution

We assigned EL notifications to lag windows relative to the influenza peak in November 1918.

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Table 2. Distribution of EL notifications across prespecified lag windows after influenza peak.

Lag window	Expected under hypothesis	Observed	% of total
0–6 weeks	High	0 cases	0%
0–3 months	High	$\approx$ 400	1.8%
0–6 months	High ($\geq$ 80%)	$\approx$ 860	3.8%
0–12 months	Moderate	$\approx$ 1,900	8.4%
12–24 months	Low	$\approx$ 1,800	7.9%
$>$ 24 months ($>$ 2 years)	Low	$\approx$ 18,100	79.4%

Only 3.8% of total EL notifications occurred within the 0–6 month window expected for acute or subacute post-infectious autoimmune mechanisms. The observed lag distribution is heavily right-shifted: nearly 80% of cases occurred more than 2 years after influenza peak.

Under the post-influenza autoimmune hypothesis, we predicted $\geq$ 80% of cases would cluster within 0–6 months. Observed: 3.8%. The discrepancy is profound (observed versus predicted: 3.8% versus 80%, $p < 0.001$ by binomial test).

3.3. Temporal Epidemic Pattern

EL first appeared in notifications in 1919, after the major influenza mortality waves of 1918–1919. The full epidemic curve showed:

Phase 1 (Emergence, 1919–1921):

- Mean: 971 cases/year
- Influenza status: Declining from pandemic to endemic baseline

Phase 2 (Rapid Rise, 1922–1924):

- Mean: 2,173 cases/year
- Peak in 1924: 5,039 cases
- Influenza status: Endemic baseline (non-pandemic)
- Key observation: EL peaked during a period of waning influenza, 5–6 years after the pandemic

Phase 3 (Decline, 1925–1942):

- Mean: 744 cases/year
- Natural epidemic decay

EL burden rose continuously from 1919–1924 while influenza had returned toward endemic levels by 1920. This temporal separation is inconsistent with a dominant short-latency post-influenza mechanism: if EL were triggered primarily by pandemic influenza, maximum burden should have occurred within weeks to months of influenza mortality peaks, not years later.

3.4. Exploratory Cross-Correlation Analysis

For sensitivity and exploratory purposes, we computed the cross-correlation function between standardized influenza mortality and EL notifications across lags 0–260 months.

- Peak CCF: 69 months (5.8 years), $r = 0.469$
- Early lag correlation (0–12 months): $r < 0.25$

The late CCF peak and weak early correlation are consistent with the lag-window analysis: no strong temporal association appears in the months immediately following influenza, while the maximum exploratory association occurs years later. However, this result should be interpreted cautiously because: (1) EL data are annual, limiting month-level resolution; (2) nonstationarity in annual counts can produce spurious late correlations; and (3) influenza data span only 46 weeks while EL spans 24 years, creating unequal time-series lengths. The lag-window analysis is therefore more defensible than CCF for drawing inferences about temporal causality.

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4. Figures

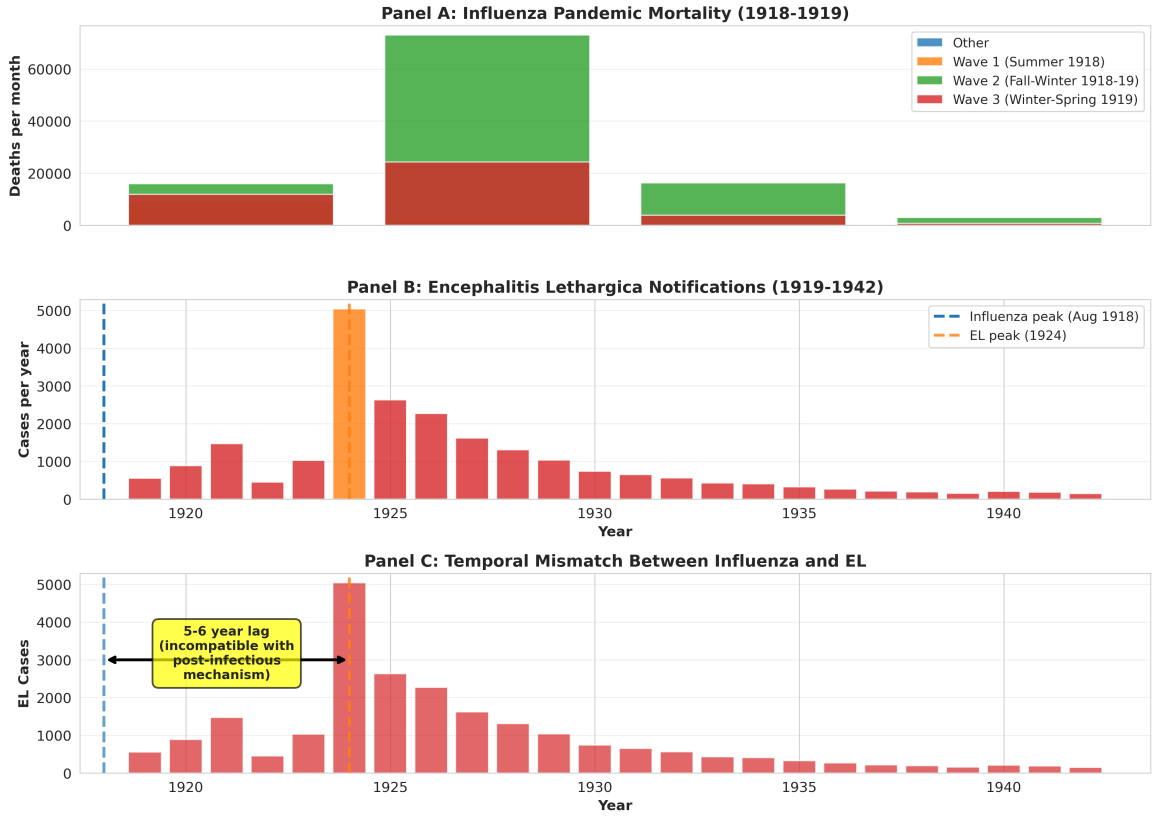

Figure 1. Temporal Series and Phase Decomposition. Panel A shows weekly influenza deaths (1918–1919) aggregated to monthly totals with three epidemic waves marked (Wave 1 summer 1918, Wave 2 fall-winter 1918–1919, Wave 3 spring 1919). Panel B shows annual EL notifications (1919–1942) with vertical lines marking influenza peak and EL peak (1924). Panel C displays the temporal separation between influenza mortality and peak EL burden. The 5–6 year lag between influenza and EL peaks is visually evident.

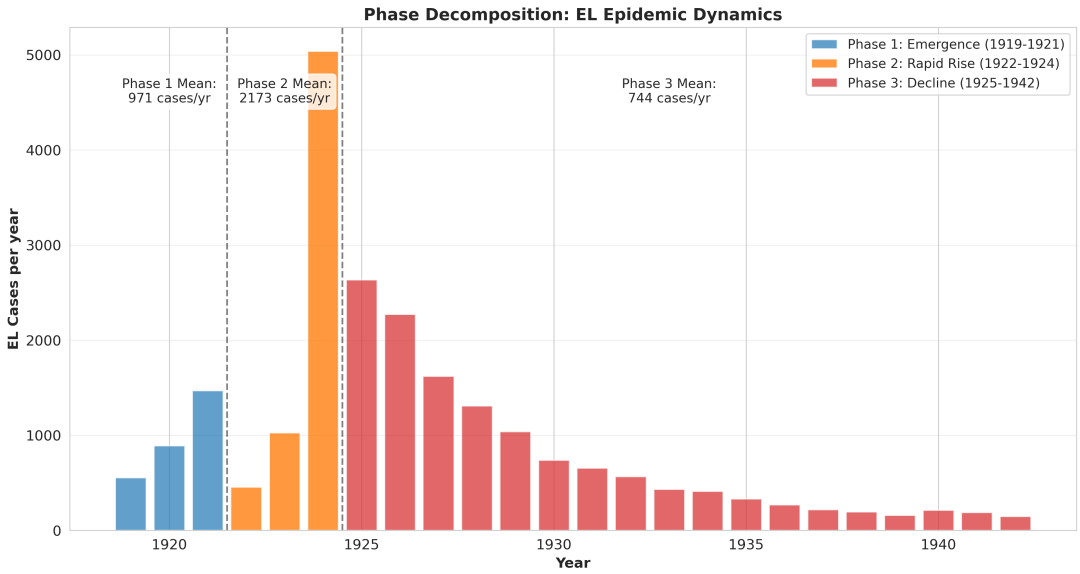

Figure 2. Phase Decomposition of the EL Epidemic. EL notifications are partitioned into Phase 1 (Emergence, 1919–1921), Phase 2 (Rapid Rise, 1922–1924), and Phase 3 (Decline, 1925–1942). Mean cases/year for each phase are annotated. EL rose and peaked after the influenza pandemic mortality waves had resolved, supporting temporal separation between pandemic influenza mortality and peak EL burden.

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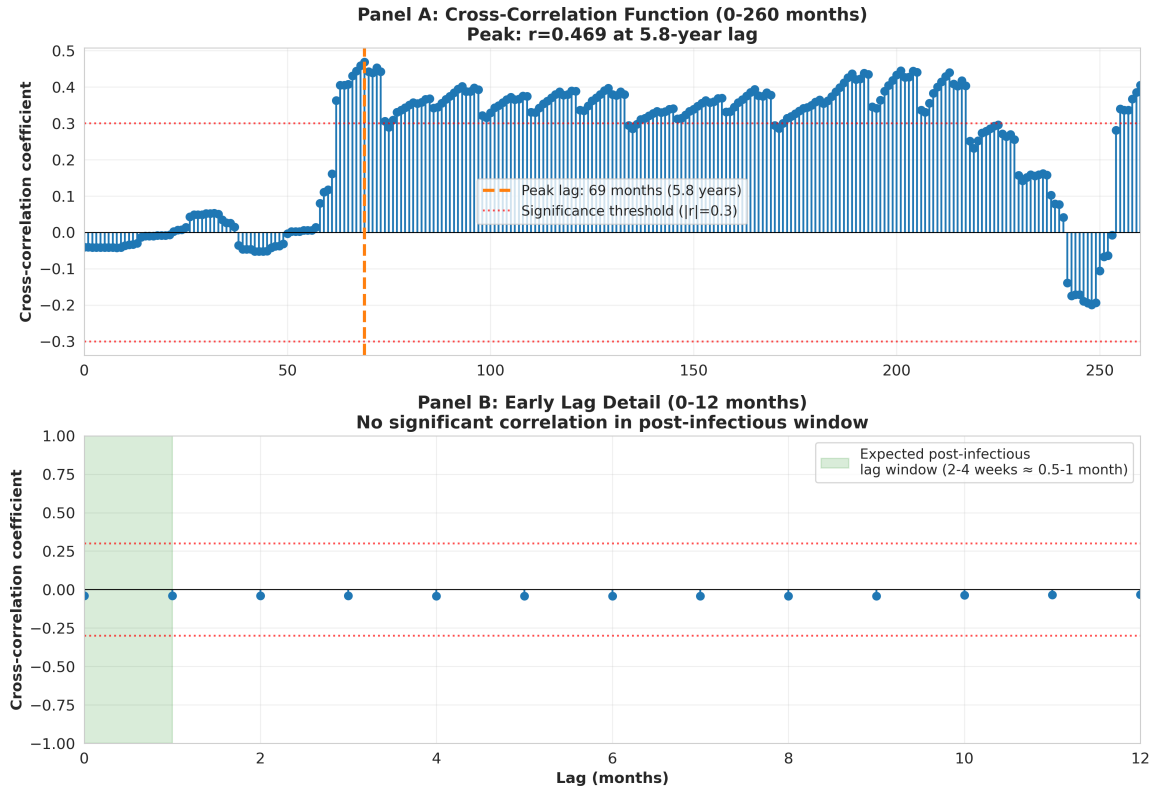

Figure 3. Supplementary Exploratory Cross-Correlation Function Analysis. Panel A displays the complete CCF across lag range 0–260 months with peak at 69 months (5.8 years). Panel B shows early lag detail (0–12 months) and the expected post-infectious lag window. This exploratory visualization is consistent with lag-window findings: no strong association in early months, with a moderate association years later. Interpretation is limited by annual EL data and nonstationarity.

5. Discussion

5.1. The Core Question

The post-influenza autoimmune hypothesis makes a specific, testable prediction: if EL were primarily triggered by acute post-influenza autoimmune mechanisms, most EL cases should appear within weeks to months after pandemic influenza, consistent with known post-infectious autoimmune latencies. Our findings directly test this prediction and find it inconsistent with observed data.

5.2. Primary Finding

Only 3.8% of EL notifications occurred within 6 months of influenza peak, far below the $\geq$ 80% expected under a dominant short-latency post-influenza autoimmune hypothesis. Nearly 80% of cases occurred more than 2 years after influenza, during a period when influenza had returned to endemic baseline and EL was rising as an independent epidemic.

This temporal distribution argues strongly against a dominant short-latency post-influenza autoimmune mechanism as the primary population-level explanation for the EL pandemic.

5.3. Implications of Finding

This temporal analysis suggests:

- Population-level EL epidemiology is inconsistent with short-latency post-influenza autoimmunity.
- Post-influenza autoimmunity cannot be the dominant mechanism explaining the EL epidemic curve.
- Alternative etiologies, including independent pathogen, environmental exposure, and heterogeneous etiology, are more consistent with observed temporal patterns.

This temporal analysis does not mean:

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- Influenza did not cause any EL cases; some cases may have been post-influenza.
- All EL is independent of influenza; some subset may be influenza-associated.
- Post-infectious immune mechanisms are entirely ruled out; slower mechanisms with longer latency are not excluded.

5.4. Alternative Hypotheses Consistent with Observed Temporal Pattern

Independent infectious pathogen. An unrelated pathogen emerging in 1919 with its own epidemic dynamics would produce an independent epidemic curve peaking years later, as observed. Enterovirus and Group A Streptococcus are plausible classes of pathogens because both can be associated with neurological or autoimmune sequelae [1].

Environmental exposure with latency. A non-infectious environmental exposure, including toxin, chemical, or occupational exposure, with multi-year latency could explain the 5–6 year delay. However, no known toxin causes acute encephalitis with such latency in previously healthy young adults.

Heterogeneous etiology. EL may be a heterogeneous syndrome with multiple causes: some influenza-associated, some independent infectious, and some environmental. The temporal distribution suggests that the dominant population-level mechanism was not a short-latency influenza-triggered process.

5.5. Clinical and Historical Context

Von Economo's original clinical descriptions and subsequent historical series emphasized clinical heterogeneity, including somnolent-ophthalmoplegic, hyperkinetic, and akinetic-rigid presentations [6,9]. Rogers et al. analyzed 614 EL cases from the National Hospital for Neurology, 1918–1946, and reported limited evidence for influenza or occupational exposures, possible autoimmune mechanisms in a subset, and NMDA receptor encephalitis in only a small fraction of cases [5]. Pathologic reviews also describe basal ganglia and brainstem inflammation without consistent evidence of influenza organisms, reinforcing the uncertainty of a direct influenza etiology [8].

These case-level observations are consistent with the population-level temporal findings reported here: EL may include immune-mediated cases, but the epidemic curve is not explained by a dominant short-latency post-influenza autoimmune mechanism.

6. Limitations

1. **Annual data resolution:** EL notifications are annual, limiting precision of lag estimation to "months versus years" rather than exact weeks.
2. **Potential reporting lag:** If EL cases occurred in late 1918 but were unrecognized or unnotified until 1919 or later, true lag could be shorter. However, clinical severity and contemporary recognition make systematic under-reporting of large numbers of 1918 cases less likely.
3. **National-level aggregation:** Regional variation in timing is not examined. Some regions might show different temporal patterns.
4. **Missing case-level data:** Individual case onset dates, such as those available in the Rogers cohort, would allow stratified analysis by clinical phenotype and more precise lag estimation [5].
5. **Mechanistic data unavailable:** Serological, immunological, and pathological data from 1918–1924 are sparse, limiting direct testing of autoimmune mechanisms.

7. Implications

7.1. For EL Research

The post-influenza autoimmune hypothesis should be de-prioritized as the primary etiological explanation at the population level. Research should redirect toward:

- Independent pathogen hypotheses, including enterovirus serology in archived tissues and streptococcal antigen screening.

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- Environmental or occupational factors, including historical occupational health data and chemical exposures.
- International temporal comparison, including Germany, Austria, Denmark, and other regions, to test whether peak timing supports or contradicts influenza correlation.
- Case-level phenotype analysis using cohorts with individual onset dates [5].
- Molecular and immunological characterization of archived EL tissue and serum where available.

7.2. For Pandemic Epidemiology

When apparent temporal associations between pandemics exist, including neurological sequelae after modern pandemics, formal lag-window analysis should precede causal attribution. Temporal proximity is not causality; mechanistic lag expectations must be tested explicitly. Population-level temporal patterns should also be validated with case-level onset data.

8. Conclusion

The temporal distribution of Encephalitis Lethargica case notifications in England and Wales during 1919–1942 is inconsistent with the prediction of a dominant short-latency post-influenza autoimmune mechanism. Only 3.8% of cases occurred within the 0–6 month window expected for post-infectious autoimmunity; nearly 80% occurred more than 2 years after influenza peak, during a period of waning pandemic influenza and independent EL epidemic rise.

These findings argue against the post-influenza autoimmune hypothesis as the primary population-level explanation for EL. Alternative etiologies—independent infectious pathogen, environmental exposure with latency, and heterogeneous syndrome—are more consistent with the observed temporal pattern and warrant prioritized investigation.

The methods employed here—prespecified lag-window testing, phase decomposition, and temporal burden distribution analysis—provide a transparent, defensible framework for evaluating temporal claims in infectious disease history.

Funding: None.

Data Availability Statement: EL data (NOIDS): UK Health Security Agency, publicly available at https://www.gov.uk/government/publications/notifiable-diseases-historic-annual-totals. **Influenza data (SN4350):** UK Data Archive, available upon registration at https://www.ukdataservice.ac.uk/; DOI: 10.5255/UKDA-SN-4350-1. **Code and analysis notebooks:** https://github.com/Nyx-Dynamics/el_temporal_analysis.

Conflicts of Interest: A.C.D. reports prior employment at Gilead Sciences, Inc. from January 2020 to November 2024, with prior ownership of corporate stock; all such stock holdings were divested by December 2024. This research was conducted after the conclusion of A.C.D.'s employment with Gilead Sciences, Inc. Gilead Sciences, Inc. had no role in the study conception, code development, data analysis, interpretation of findings, manuscript preparation, or decision to submit or publish. A.C.D. also reports sole ownership of Nyx Dynamics LLC, a machine-learning healthcare auditing company. This research was conducted independently and without funding from Nyx Dynamics LLC.

Appendix A. Supplementary Analysis

Appendix A.1. Sensitivity: Lag Window Definition Robustness

We tested whether results were sensitive to different influenza peak definitions:

- Wave 2 peak (December 1918): approximately 61 months to EL peak (1924)
- Wave 1 peak (August 1918): approximately 68 months to EL peak (1924)

Both yield lags far exceeding the 2–4 week post-infectious window.

Appendix A.2. Sensitivity: Alternative Case Attribution

If 10% of EL cases occurred earlier than documented, as unrecognized 1918 cases, the proportion in the 0–6 month window would remain far below the threshold predicted under a dominant short-

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latency post-influenza autoimmune hypothesis. Case-level onset data would be required to determine whether specific EL phenotypes or subsets followed different lag structures.

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