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Lactococcus lactis JCM5805 and Common Cold-Like Symptom Burden: Clinical Evidence Anchored to a Standardized Oral Lysate Platform

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Abstract: Background: Recurrent common cold-like and upper-respiratory symptoms create a substantial functional burden in healthy adults, athletes, children and healthcare-associated populations. *Lactococcus lactis* JCM5805 has been evaluated in multiple randomized trials using inactivated oral preparations, with symptom endpoints commonly linked to its pDC-interferon immunobiology. The present study integrates those clinical findings with a standardized JCM5805-derived lysate platform designed for reproducible oral formulation. Methods: A three-batch biphasic lysate process was characterized for phase-ratio reproducibility, soluble-fraction purification, reconstitution stability, viable-cell control, moisture and water activity. In parallel, randomized trials and meta-analytic evidence published through September 2026 were synthesized with emphasis on cough, feverishness, sore throat, nasal symptoms, upper respiratory illness, school absence and fatigue. Results: Fixed-ratio recombination reduced the coefficient of variation of the soluble:insoluble dry-matter ratio from 26.2% to 1.3% and lowered the 24 h sedimentation-volume ratio from 25.2±3.0% to 8.3±0.3%. Final powder water activity was 0.223±0.015. Clinical evidence shows a recurring pattern of reduced symptom-positive days in selected settings: a 2015 winter RCT in 213 adults reported fewer cough and feverishness days; a 2016 RCT in 396 healthy adults reported fewer sore-throat and cough days; a 2018 athlete trial reported fewer URTI-positive days (39 vs 56), sneezing/runny-nose days (36 vs 52) and fatigue-positive days (110 vs 128); and a 2022 Vietnamese schoolchild trial found lower early-period absence due to upper respiratory or gastrointestinal illness and fewer fever-positive days. A 2025 individual-participant meta-analysis of 555 participants found mean differences of -0.69 days/28 days for cough and -0.26 days/28 days for feverishness. More recent trials provide context on heterogeneity: in mild COVID-19 the composite symptom score was similar between groups, while viral load decreased earlier and smell/taste recovery showed a day-specific difference; in a 2026 healthcare-associated cohort, fever and fatigue days were lower with intake. Conclusion: Across diverse randomized studies, JCM5805 has shown a reproducible signal for selected cold-like and infection-related symptom endpoints, particularly cough, feverishness and upper-respiratory symptom days. A tightly standardized lysate platform can support future formulation-specific trials with prespecified symptom diaries, pDC biomarkers and exposure-response analysis.

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Keywords: *Lactococcus lactis*; common cold; upper respiratory symptoms; cough; feverishness; randomized trial; lysate; postbiotic.

1. Introduction

Common cold-like and upper respiratory symptoms are among the most frequent causes of short-term functional impairment in otherwise healthy populations. The burden is especially visible during winter, periods of high-intensity exercise, school attendance and healthcare exposure, where repeated episodes of cough, sore throat, rhinorrhea, feverishness and fatigue can accumulate into measurable losses of training, work or school participation. Because these syndromes are caused by multiple viruses and are influenced by host immune status, nutritional strategies that act on broad innate antiviral pathways rather than a single pathogen have attracted sustained interest.

JCM5805 is a food-associated *Lactococcus lactis* strain with a distinctive pDC-centered mechanism. In mechanistic studies, JCM5805 is taken up by pDCs and stimulates TLR9/MyD88-dependent production of type I and type III interferons [1–5]. Human trials have therefore often paired daily symptom diaries with immune endpoints such as pDC maturation markers, interferon responses and interferon-stimulated genes [6]. This design has generated an unusual body of evidence in which mechanistic and symptom-level observations can be compared across populations [7,9–20].

The standardized lysate platform evaluated here was designed to reduce batch-to-batch variability after cell disruption. Soluble and insoluble cell-derived fractions are treated independently and recombined at a controlled dry-matter ratio, followed by secondary heat treatment and spray drying. The resulting BALIMONT oral formulation framework provides a stable, non-culturable JCM5805-derived matrix that can be advanced into controlled symptom-focused studies without relying on live-cell viability as a product attribute.

This paper evaluates the second major functional axis associated with the JCM5805 evidence base: reduction in common cold-like and upper respiratory symptom burden. The analysis combines formulation standardization data with randomized human evidence, emphasizing symptom-positive days and functional outcomes while retaining the mechanistic pDC–interferon pathway as the biological context.

2. Materials and Methods

2.1 Standardized lysate formulation

The JCM5805-equivalent *Lactococcus lactis* culture was thermally pre-inactivated, cooled and homogenized twice at 190 MPa. Following centrifugal separation, the soluble phase was processed by sequential 100 kDa permeation and 10 kDa retention with concentration/diafiltration, while the insoluble fraction was washed and micronized. The two fractions were recombined at 2.95:1–3.05:1 on a dry-matter basis, subjected to a second 75°C/15 min heat treatment, combined with maltodextrin/gum arabic carrier and spray dried. Three independent batches were characterized for inter-batch consistency and powder performance.

2.2 Clinical evidence strategy

Randomized and controlled human studies were identified through a structured search of PubMed-indexed literature and publisher databases through September 2026. Eligible studies examined oral JCM5805/LC-Plasma preparations and reported at least one infection-related symptom or functional endpoint. Priority outcomes were cough, feverishness, sore throat, rhinorrhea/sneezing, cumulative upper respiratory illness days, fatigue, school absence, viral-load kinetics and symptom composite scores. Where available, effect estimates and p values were extracted directly from trial reports or meta-analysis. Trials in different populations were interpreted in relation to their specific intervention duration, exposure setting and outcome definition.

3. Results

3.1 Formulation consistency relevant to symptom trials

Before quantitative adjustment, the soluble:insoluble dry-matter ratio varied from 1.82:1 to 3.11:1 across batches. Fixed-ratio recombination produced $3.00\pm0.04:1$ with a coefficient of variation of 1.3%, compared with 26.2% before adjustment. The 24 h sedimentation-volume ratio of a 5% aqueous dispersion decreased from $25.2\pm3.0\%$ for natural-ratio recombination to $8.3\pm0.3\%$ after fixed-ratio control. The final powder met a non-culturable specification (<10 CFU/g with negative enrichment), moisture averaged $3.83\pm0.25\%$, and water activity was 0.223 ± 0.015 . These attributes provide the formulation consistency required for symptom trials in which day-to-day exposure should remain stable across participants and batches.

Table 1. Quality Attributes and Standardization Results of the Active Material for Future Human Studies

Quality attribute	Observed result	Relevance to future human studies
Soluble:insoluble ratio after standardization	$3.00\pm0.04:1$; CV 1.3%	Controls relative exposure to soluble and particulate cell-derived material
24 h sedimentation-volume ratio	$8.3\pm0.3\%$	Supports consistent reconstitution and dose delivery
Final moisture	$3.83\pm0.25\%$	Supports powder storage stability
Water activity (25°C)	0.223 ± 0.015	Low-aw state supports physical stability
Culturable <i>L. lactis</i>	<10 CFU/g; enrichment negative	Confirms an inanimate formulation state

3.2 Randomized evidence for common cold-like and upper respiratory outcomes

In a 2015 randomized double-blind trial of 213 adults during winter, daily JCM5805-containing yogurt for 10 weeks reduced cumulative days with cough and feverishness relative to placebo, while ex vivo influenza stimulation showed a stronger interferon-related response [7]. A larger 2016 randomized trial enrolled healthy adults and included 396 completers; 12 weeks of heat-killed JCM5805 was associated with fewer sore-throat days ($p<0.05$) and cough days ($p<0.001$), together with higher pDC HLA-DR and antiviral-gene responses [9].

In 2018, 51 male athletes undergoing consecutive high-intensity training received either heat-killed JCM5805 or placebo for 13 days. The JCM5805 group accumulated fewer URTI-positive days (39 vs 56; $p=0.028$), fewer sneezing/runny-nose days (36 vs 52; $p=0.032$), and fewer fatigue-positive days (110 vs 128; $p=0.032$) [11]. A later 14-day athlete trial in 37 participants again found higher pDC CD86 and fewer cumulative fatigue days, with favorable changes in an autonomic fatigue index [16].

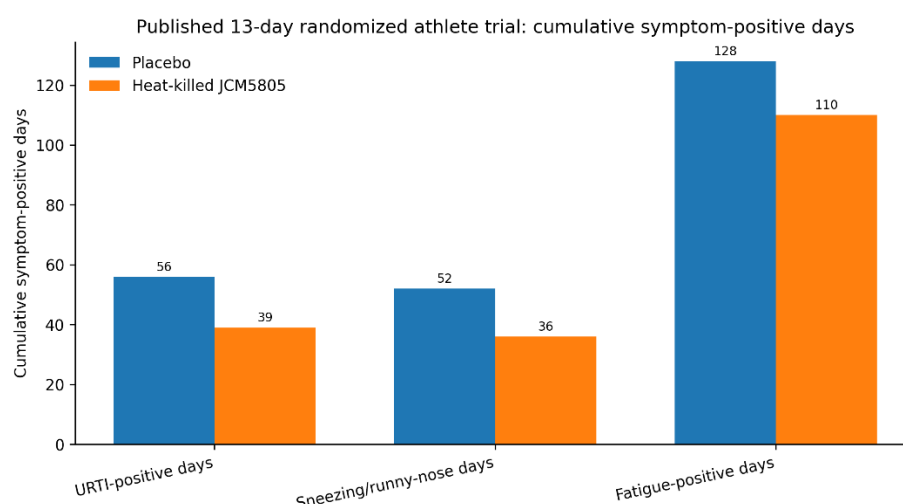


Figure 1. Published cumulative symptom-positive days in the 13-day randomized athlete trial of heat-killed JCM5805 [11].

The evidence extends beyond adult winter studies. In Malaysia, an eight-week randomized trial of 320 healthy volunteers found fewer cumulative days of several dengue-fever-like symptoms, including fever, muscle pain, joint pain and retro-orbital pain, although DENV exposure and the overall symptomatic ratio were similar between groups [14]. In northern Vietnam, 892 schoolchildren were included in the final analysis of an eight-week randomized trial. During the first four weeks, absence due to upper respiratory or gastrointestinal illness was lower in the JCM5805 group (OR 0.57, $p=0.004$), absence due to upper respiratory disease alone was also lower (OR 0.56, $p=0.005$), and fever-positive days were reduced (OR 0.58, $p=0.001$) [15].

The 2025 individual-participant meta-analysis provides the most quantitative summary of cold-like symptom endpoints. Using data from 555 participants, daily JCM5805 intake reduced cumulative cough by a mean of 0.69 days per 28 days (95% CI -1.24 to -0.14) and feverishness by 0.26 days per 28 days (95% CI -0.52 to -0.0038) compared with control [18]. Other symptoms showed greater heterogeneity, suggesting that cough and feverishness represent the most reproducible symptom-level signals across the integrated healthy-adult datasets.

Recent disease-specific trials add clinically useful context. In the 2025 PLATEAU study of 100 patients with mild COVID-19, the prespecified composite symptom endpoint was similar between groups. However, the JCM5805 group showed an earlier reduction in SARS-CoV-2 viral load on day 4, a higher pDC measure on day 8, and a higher proportion without smell/taste disturbance on day 13 [19]. In 2026, a randomized double-blind study among healthcare-associated Vietnamese participants analyzed 101 completers and reported fewer cumulative days of fever and fatigue after four weeks, alongside increased expression of the interferon-stimulated gene MxA [20].

Table 2. Summary of Clinical Studies on the Effects of Heat-Killed *Lactiplantibacillus plantarum* JCM5805 on Respiratory and Infection-Related Symptoms

Study	Population / duration	Primary symptom or functional signal	Context
Sugimura et al., 2015 [7]	213 adults; 10 wk	Fewer cough and feverishness days	Winter influenza-like illness setting
Shibata et al., 2016 [9]	396 completers; 12 wk	Fewer sore-throat ($p<0.05$) and cough days ($p<0.001$)	Healthy adults; heat-killed JCM5805

Study	Population / duration	Primary symptom or functional signal	Context
Komano et al., 2018 [11]	51 male athletes; 13 d	URTI 39 vs 56 days; sneeze/runny nose 36 vs 52	High-intensity training
Khor et al., 2021 [14]	320 healthy Malaysians; 8 wk	Fewer fever, myalgia, arthralgia and retro-orbital pain days	Dengue-like symptom setting
Thu et al., 2022 [15]	892 analyzed children; 8 wk	URID/GID absence OR 0.57; URID absence OR 0.56; fever OR 0.58	Vietnamese elementary schoolchildren
Komano et al., 2023 [16]	37 athletes; 14 d	Fewer cumulative fatigue days; higher pDC CD86	High training load
Kato et al., 2025 [18]	555 participants in symptom meta-analysis	Cough MD -0.69 d/28 d; feverishness MD -0.26 d/28 d	Integrated randomized adult evidence
Yamamoto et al., 2025 [19]	100 mild COVID-19 patients; 14 d	Composite symptoms similar; earlier viral-load decline; day-13 smell/taste signal	Disease-specific RCT
Low et al., 2026 [20]	101 analyzed healthcare-associated adults; 4 wk	Fewer fever and fatigue days	Healthcare exposure setting

4. Discussion

Across the JCM5805 trial portfolio, the most recurrent symptom signals involve cough, feverishness, upper-respiratory symptom days and fatigue. The consistency is not absolute, nor would it be expected across populations exposed to different viruses, seasonal patterns and outcome definitions. Instead, the evidence shows a repeated direction of effect under several conditions in which innate antiviral demand is increased: winter circulation of respiratory viruses, intense athletic training, school exposure and healthcare-related exposure. The 2025 meta-analysis strengthens this interpretation by identifying cough and feverishness as the endpoints that remain statistically distinguishable after participant-level integration of randomized trials [18].

The symptom evidence is biologically coherent with the pDC–interferon findings. JCM5805 has been linked to pDC maturation, IFN- α responses and antiviral genes such as ISG15, VIPERIN and MxA [4,5,9,17,20]. This is relevant because symptom burden reflects both pathogen replication and host inflammatory responses; a nutritional intervention that alters early innate antiviral readiness may therefore influence the duration or accumulation of selected symptoms even when it does not change every clinical endpoint. The PLATEAU trial illustrates this point: the overall symptom composite was similar, but viral-load kinetics, pDC measures and a specific smell/taste endpoint changed at defined time points [19].

The current lysate standardization data contribute an important formulation dimension. Symptom trials are sensitive to exposure consistency, particularly when effects are modest and outcomes are counted daily. Reducing phase-ratio CV from 26.2% to 1.3% and stabilizing reconstitution behavior limits one source of uncontrolled between-batch variability. In practical terms, a fixed-ratio lysate allows future studies to define dose using total lysate dry matter while maintaining a consistent balance between soluble and particulate cell-derived material.

The clinical literature also helps refine trial design. Cough and feverishness are strong candidates for prespecified primary or key secondary endpoints, while nasal symptoms, fatigue, school/work absence and validated global measures such as WURSS can provide complementary information. pDC CD86/HLA-DR, IFN- α , MxA and related ISGs can be incorporated as mechanistic endpoints. Stratification by baseline immune status, training load, age and infection exposure may further clarify contexts in which the response is greatest.

4.1 Current Scope and Future Directions

The present analysis emphasizes symptom endpoints that have already shown the strongest reproducibility in randomized JCM5805 studies. A next-stage trial of the complete lysate formulation can build on this evidence by using a fixed daily dry-matter dose, predefined cough and feverishness metrics, validated respiratory-symptom scoring, pDC biomarkers and prospective adherence monitoring. Longer observation across a respiratory-virus season would further characterize durability, while parallel virologic testing would help separate infection frequency, viral kinetics and symptom expression. This design would extend the existing strain-level evidence into a formulation-specific clinical framework.

5. Conclusion

Randomized clinical studies of inactivated *Lactococcus lactis* JCM5805 show a recurring reduction in selected common cold-like and infection-related symptom endpoints, with cough, feverishness, upper-respiratory illness days and fatigue emerging most consistently. The 2025 individual-participant meta-analysis supports this pattern quantitatively, while later trials demonstrate that responses can vary by disease context and endpoint. The standardized biphasic lysate described here provides a reproducible oral platform with tightly controlled fraction ratio, low water activity and non-culturable status. Together, the formulation data and published human evidence define a clear pathway for future controlled studies of respiratory symptom burden using integrated clinical and pDC–interferon endpoints.

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