Repurposing N-Acetylcysteine for Novel Immunoresilience

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Abstract

N-acetylcysteine (NAC) has long been FDA-approved as both a mucolytic and an antidote to acetaminophen toxicity. The age-associated decline in immune function, known as immunosenescence, heightens infection susceptibility, diminishes vaccine responsiveness, and drives chronic inflammation. Amid increasing evidence demonstrating NAC's potential to support immunologic resilience, this article reviews historical and emerging insights into its immunomodulatory mechanisms. A landmark trial demonstrated that oral NAC prophylaxis fortified cell-mediated immunity and attenuated influenza-like symptoms, yielding a 54% reduced incidence of symptomatic illness. Through metabolic activation, NAC contributed to reduced systemic inflammation and hastened recovery by 3 days compared with placebo in viral respiratory disease. Pleiotropic antimicrobial effects are exemplified by the NAC-mediated upregulation of glutathione and vitamin D. Its coadministration with vitamin D further attenuates immunosenescence. Together with emerging reports of reduced mortality across the respiratory disease continuum, NAC may play a key role in supporting immunoresilience and preparedness against recurrent, evolving, and clinically relevant immunorespiratory threats.

Keywords: N-Acetylcysteine (NAC), combined metabolic activators (CMA), L-cysteine (LC), immunosenescence, immunoresilience, One Health framework.

Introduction

N-acetylcysteine (NAC), an acetylated form of the amino acid cysteine, is designated an essential medicine by the World Health Organization (WHO) and is approved by the U.S. Food and Drug Administration (FDA).[1] Initially FDA-approved in 1963 as a nebulized mucolytic for muco-obstructive airway disease,[2] NAC gained a second prescription indication in 1985 as an intravenous antidote for acetaminophen overdose.[3,4] Since then, its immunologic properties have

attracted increasing interest. NAC exemplifies a pleiotropic agent whose diverse mechanistic actions extend beyond its canonical indications. Such versatility underscores its repurposing potential, particularly for immunorespiratory resilience. Through deacetylation to cysteine, NAC provides the rate-limiting precursor for glutathione (GSH), the immune system's master antioxidant.[5] Immunosenescence, the age-related and progressive decline of immune function, impairs both innate and adaptive immunity.[6] It manifests as heightened infection susceptibility, diminished vaccine efficacy, and increased risk of chronic inflammatory conditions.[6] This decline is further compounded by the accumulation of senescent immune cells that secrete proinflammatory mediators, thereby driving systemic low-grade inflammation, termed "inflammaging," which accelerates age-related disease progression and impairs immune regulation.[6] A multicenter Italian trial conducted in 1997 found that only 25% of prophylactic NAC-treated adults developed symptomatic influenza, compared with 79% in the placebo group.[7] This 54% lower incidence is consistent with the NAC-mediated upregulation of both GSH and vitamin D, two key determinants of immunomodulation.[8] The coadministration of NAC alongside vitamin D concurrently attenuates immunosenescence, reflecting complementary antioxidant and anti-inflammatory synergy.[8] These findings collectively underscore NAC's expanding relevance as a prophylactic agent and as part of coadministration strategies that fortify immunorespiratory resilience, a premise substantiated by emerging clinical evidence.

A 2021 trial demonstrated that NAC coadministered with L-serine, L-carnitine, and nicotinamide riboside—collectively termed combined metabolic activators (CMA)—hastened recovery by 3 days in coronavirus disease 2019 (COVID-19).[9] In 2022, the FDA ruled that NAC's 1963 prescription designation excluded it from the definition of a dietary supplement, prompting its temporary removal from the U.S. market during the COVID-19 pandemic.[10,11]

Citizen petitions and stakeholder lawsuits finally compelled updated FDA guidance permitting NAC sale under enforcement discretion, thereby preserving public availability.[12] In addition to evidence of reduced mortality in hospitalized patients with COVID-19,[13,14] preclinical studies have demonstrated NAC's antiviral activity against both swine-origin (H1N1) and avian-origin (H5N1) influenza A viruses,[15-17] mobilizing further clinical investigations.[18] Surveillance data highlight the dynamic viral mutations that contribute to sustained pandemic potential of H5N1 and related clades.[19] Genetic plasticity has enabled unprecedented animal-to-human H5N1 spillover, with a single mutation sufficient to shift receptor specificity from avian to human.[20] Amid rising mammal-to-mammal transmission and the attendant risk of mutations enabling sustained mammalian spread, emerging avian influenza infections across multiple mammalian species remain highly concerning.[21] The emergence of avian H5N1 influenza in U.S. dairy cattle and domestic pets raises critical public health concerns, underscoring the need for heightened surveillance and enhanced biosecurity measures to mitigate continual mammalian transmission.[22]

In response to longstanding and emerging infectious disease threats, the U.S. government adopted the One Health approach to unify the compartmentalized efforts of multiple federal agencies. In early 2025, the Centers for Disease Control and Prevention (CDC) confirmed 66 H5N1 cases and reported its first U.S. fatality.[23] This galvanized the Department of the Interior (DOI), the U.S. Department of Agriculture (USDA), and the CDC to issue the National One Health Framework to Address Zoonotic Diseases and Advance Public Health Preparedness. The framework is designed to strengthen coordination, collaboration, and communication among transdisciplinary, multisector entities.[24] As public health experts warn against H5N1 influenza complacency in the wake of COVID-19,[22] this platform offers a unified framework for proactive interagency collaboration during public health emergencies. One Health's Objective 2.5

emphasizes supporting and expanding initiatives that preserve and restore ecosystem health by addressing the underlying drivers of complex zoonotic disease emergence, reemergence, spillover, and spillback, thereby strengthening resilience in people and the ecosystems sustaining them.[25] As a glutathione precursor that mediates cytoprotection and mitigates oxidative stress,[26] NAC is positioned as a pragmatic therapeutic candidate directly aligned with this objective.[25] In light of evidence showing NAC reduced the incidence of clinically apparent H1N1 illness by 54%,[7] renewed attention is warranted given that H5N1 case fatality rates consistently exceed 50%.[27] If the H1N1 reduction proves even partly generalizable to avian H5N1 influenza, NAC would remain directly aligned with Objective 2.5's emphasis on resilience. Repurposing NAC for novel immunoresilience is grounded in emerging evidence demonstrating its capacity to prevent, treat, and reduce immunorespiratory disease mortality.[28-31] The historical oscillation between regulatory restriction and therapeutic resurgence emphasizes the imperative to critically reassess NAC's pleiotropic clinical potential, as well as misaligned policy barriers that may preclude future access to this potentially life-saving intervention. Elucidating NAC's resilience-fortifying mechanisms provides the foundation for rigorously evaluating its clinical utility.

N-Acetylcysteine: Immunorespiratory Mechanisms and Clinical Evidence

NAC's in vivo antioxidant activity is threefold: free radical scavenging and direct neutralization of oxidant species, indirect reinforcement of GSH through cysteine provision that sustains GSH's antioxidant activity and enzymatic substrate role, and disulfide bond cleavage that repletes thiol pools to preserve redox balance.[32] NAC's thiol-driven activity also cleaves disulfide bonds in mucin glycoproteins, thereby reducing the viscosity of bronchial secretions and enhancing mucociliary clearance.[32] In concert with free radical neutralization and GSH upregulation, these dual disulfide mechanisms uniquely reinforce immunorespiratory resilience.

The deacetylation of NAC releases L-cysteine (LC), an enantiomer functionally equivalent to the semiessential amino acid derived from methionine. Coadministration of LC alongside vitamin D upregulates glutathione synthesis, vitamin D–metabolizing genes, vitamin D–binding protein (VDBP), and vitamin D receptor (VDR) expression.[33] Vitamin D deficiency affects nearly 45% of the U.S. population and an estimated one billion individuals worldwide.[33] This widespread deficiency is not a benign finding, as it correlates with elevated all-cause mortality, [34] most acutely reflected in respiratory deaths.[35] A cross-sectional study of 31,466 U.S. adults corroborated these mortality patterns by demonstrating that serum 25-hydroxyvitamin D concentrations below 30 nmol/L were linked to sharply higher risks of respiratory infection, including head or chest colds, influenza, pneumonia, and otitis.[36] With nearly half of Americans vitamin D deficient, these findings emphasize LC's relevance as a supplement supporting respiratory health and infectious disease resilience. One Health's Objective 3.7 advances the understanding, development, and adoption of nature-based solutions to strengthen community and environmental resilience against zoonotic disease and related environmental disruptions.[25] LC supplementation mirrors its endogenous enantiomer and directly advances this objective by providing a natural pathway for enhancing immunoresilience. Through conversion into GSH's metabolomic intermediary LC and through direct antioxidant pleiotropy, NAC underscores how resilience-fortifying mechanisms culminate in measurable clinical outcomes.

Early landmark research demonstrated that oral NAC (600 mg twice daily for 6 months) reduced clinically apparent H1N1 illness by 54%, with only 25% of treated adults developing symptomatic influenza compared with 79% receiving placebo.[7] In lethal influenza mice models, NAC coadministered with ribavirin increased survival to 92%,[15] and with oseltamivir to 100%,[16] prompting an ongoing randomized trial (NCT03900988) of intravenous NAC plus oseltamivir in

adults hospitalized with pneumonia-complicated influenza.[18] Severe COVID-19 clinical reports further highlight NAC's translational potential. Nebulized NAC (10–15 g daily for 11 days) facilitated weaning from mechanical ventilation, while continuous high-dose IV NAC infusion (75 mg/kg loading, followed by down-titration) facilitated multi-organ dysfunction resolution.[17] In a 10-patient ventilator-dependent cohort, IV NAC markedly reduced inflammatory markers, improved oxygenation, and achieved an 80% survival rate, thereby exceeding precedent survival benchmarks for COVID-19 critical illness.[17] The Memorial Sloan Kettering Cancer Center in New York is actively evaluating NAC therapy for severe or critically ill COVID-19 patients in a Phase 2 clinical trial (NCT04374461) set to complete in 2026,[37] underscoring its expanding relevance across respiratory infections in alignment with One Health preparedness.

The antiviral spectrum of NAC encompasses H1N1 and H5N1 influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), and human immunodeficiency virus (HIV).[17] These RNA viruses rely on the NF-κB pathway which is inhibited by NAC for replication, and molecular modeling further implicates NAC in binding the cysteine-145 active site of the SARS-CoV-2 main protease (Mpro), thereby interrupting viral propagation through a complementary biochemical mechanism.[17] Recent evidence corroborates this mechanistic plausibility, showing that oral bismuth coadministered with NAC inactivated cysteine proteases including Mpro, curtailed viral replication and ameliorated lung pathology in vivo.[38] Bismuth, long employed in combination therapy for *Helicobacter pylori* eradication, now reemerges as a broad-spectrum anti-coronavirus agent when coadministered with NAC.[38] Together with COVID-19 studies showing that oral NAC (1200 mg daily) attenuates neutrophil oxidative burst while preserving phagocytic function and host antimicrobial defense,[17] NAC remains uniquely positioned to fortify immunoresilience against evolving zoonotic threats.

NAC as a Pleiotropic Adjunct for One Health Preparedness

A single glutamine-to-leucine mutation in the H5N1 hemagglutinin protein can shift receptor tropism from avian to human,[20] underscoring persistent expert admonitions against complacency in One Health preparedness.[22] Highly pathogenic avian influenza (HPAI) H5N1 introduced into pulmonary epithelium demonstrated that NAC treatment inhibited viral replication while sharply reducing cytopathic effects, apoptosis, and inflammatory cytokine release.[17] Such protective pleiotropy extends beyond H5N1, as mucus hypersecretion and virulence drive severity across respiratory infections and COPD exacerbations, where NAC consistently reduces the frequency and intensity of these exacerbations.[39] The mucin-transcribing gene MUC5AC is pathophysiologically overexpressed in asthma, COPD, and microbial illness.[39] While NF-κB activation underlies dysregulation across pulmonary tissues, NAC inhibits NF-κB hyperactivity, mitigates oxidative stress, and downregulates MUC5AC overexpression in pulmonary epithelium infected with influenza A, influenza B, and RSV.[39] In light of NAC's illuminated pleiotropism newly clarifying its capacity to transcriptionally regulate aberrant gene expression and curtail mucin hypersecretion, these findings command further elucidation of NAC's pleiotropic qualities aligned with One Health preparedness and immunoresilience frameworks that support the amelioration of post-infectious systemic sequelae.

Meta-analytic evidence in more than 4 million COVID-19 survivors found 27.8% with memory disorders, 27.1% with cognitive impairment, and 23.8% with attention impairment.[40] A randomized, double-blind, Phase 2 trial demonstrated a 29% neurocognitive improvement in patients with Alzheimer's disease treated with NAC plus CMA coadministration, underscoring its pleiotropy in potentially mitigating postviral neurocognitive sequelae.[41] At 12 months postinfection, COVID-19 survivors have approximately 50% higher ischemic stroke risk (HR

1.50) and more than 100% higher hemorrhagic stroke risk (HR 2.19).[42] In addition to its thiol-mediated mucolysis, NAC's pleiotropy mimics von Willebrand factor (VWF) proteolysis via disulfide bond reduction, mediating thrombolysis by destabilizing platelet cross-links and dissolving arterial thrombi in a dose-dependent fashion without prolonging bleeding time.[43,44] Amid widespread COVID-19–related dyscognition and stroke burden, NAC within CMA therapy offers pleiotropic potential to mitigate neurocognitive decline, and as monotherapy it counteracts hypercoagulable states that drive arterial thrombosis without impairing hemostasis. These findings support a role for NAC in infectious sequelae.

Conclusion

Repurposing NAC for novel immunoresilience illuminates how a well-tolerated, inexpensive agent may transcend its canonical roles to address ongoing, recurrent, and emerging health threats. Across the viral continuum, NAC exhibits pleiotropy ranging from glutathione replenishment and vitamin D synergy to mucolytic and thrombolytic disulfide cleavage and viral replication blockade. Emerging evidence supports a potential key role in reducing symptomatic burden, mortality, and neurocognitive decline, while preclinical models extend its relevance to thrombolysis and vascular protection. Within the One Health framework, NAC epitomizes a biochemical bridge toward public health preparedness for emerging zoonotic infections. Harnessing its far-reaching grasp unlocks new pragmatic yet profound opportunities: to attenuate immunosenescence, mitigate postinfectious sequelae, and translate pleiotropic insight into clinically aligned actions capable of overcoming the pressing issues of global health insecurity. From humble origins, NAC advances a renaissance of resilience, One Health alignment, and translational clinical practice.

Key Points

- N-acetylcysteine (NAC) has demonstrated both mucolytic and immunomodulatory benefits in respiratory infections, including H1N1, H5N1, RSV, and SARS-CoV-2, with emerging evidence supporting its dual prophylactic and therapeutic potential.
- A pivotal yet under-recognized landmark study elucidated how oral NAC prophylaxis significantly reduced the incidence of symptomatic influenza, compelling modern trials with adequate statistical power to validate reproducibility of the legacy trial implications.
- In response to longstanding and emerging infectious health threats, the U.S. government adopted the One Health approach to unify agency compartmentalization. The National One Health Framework to Address Zoonotic Diseases and Advance Public Health Preparedness was launched in early 2025 to facilitate coordination, collaboration, and communication across various federal government agencies.
- Repurposing accessible, affordable, well-studied, and well-tolerated biochemicals such as NAC offers allied healthcare a pragmatic One Health–aligned intervention grounded in emerging evidence implicating its key pleiotropic role in supporting immunoresilience.
- Emerging evidence supports NAC as a safe, adjunctive option in treating respiratory infections by multifaceted mechanisms including, but not limited to, curtailing incidence of influenza-like symptomatology, fortifying cell-mediated immunity, blocking viral replication, dampening mucin gene overexpression, mitigating immunosenescence, and enabling vitamin D and glutathione upregulation, thereby supporting resilience.

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