frontiers in Virology

TYPE Perspective
PUBLISHED 27 March 2026
DOI 10.3389/fviro.2026.1801380

OPEN ACCESS

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RECEIVED 01 February 2026
REVISED 10 March 2026
ACCEPTED 13 March 2026
PUBLISHED 27 March 2026

CITATION
de Bernardis E, Lugoboni F, Busà L, Petronio Petronio G and Di Marco R (2026) Re-opening the question of lower SARS-CoV-2 attack rates in active smokers: a perspective on viral interference and Tobacco Mosaic Virus. *Front. Virol.* 6:1801380. doi: 10.3389/fviro.2026.1801380

Re-opening the question of lower SARS-CoV-2 attack rates in active smokers: a perspective on viral interference and Tobacco Mosaic Virus

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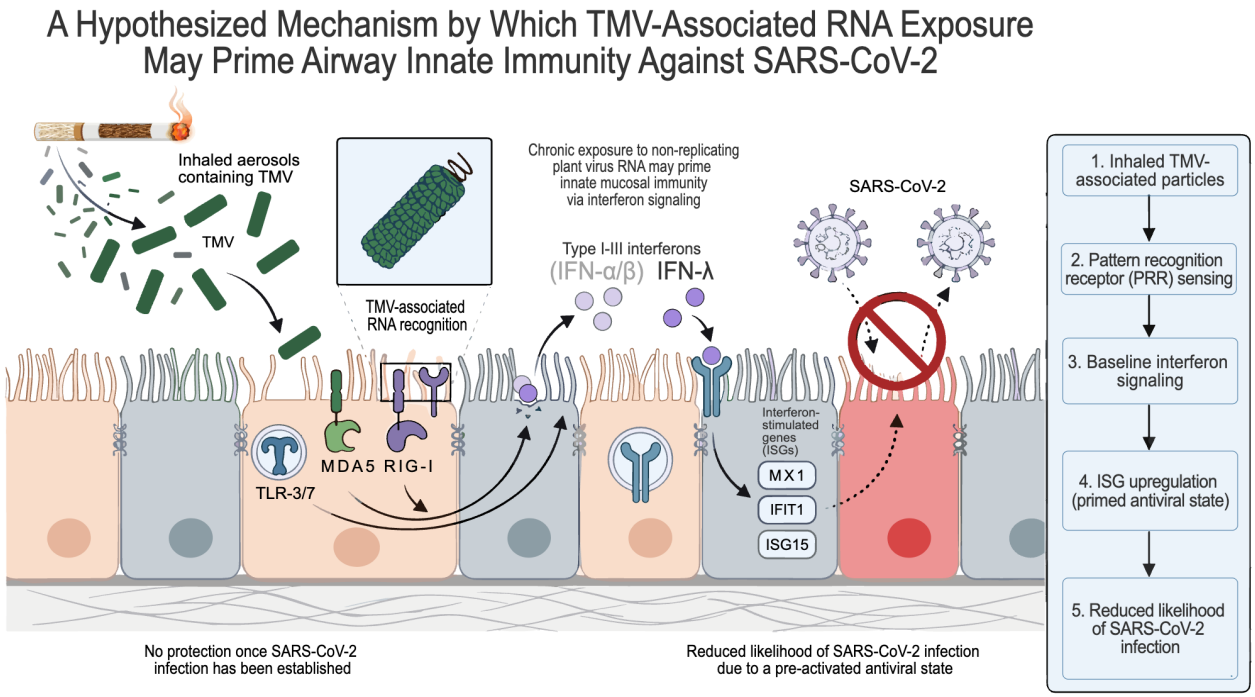
During the COVID-19 pandemic, multiple observational studies reported a counterintuitive epidemiological observation: active smokers appeared less frequently infected or seropositive for SARS-CoV-2 compared with never-smokers, despite smoking being a risk factor for severe COVID-19 once infection occurs. This apparent paradox was rapidly marginalized due to public health concerns, leaving an informative biological observation largely unexplored. This Perspective proposes a mechanistic hypothesis to explain this paradox. We argue that much of this tension arises from a conceptual conflation between two distinct phases of the disease process: susceptibility to infection and progression to severe illness after infection has been established. Recent advances in virology and mucosal immunology make this question biologically plausible and experimentally tractable. These include: (i) evidence that plant viruses, including Tobacco Mosaic Virus (TMV), have been reported to be immunogenic in humans and capable of eliciting innate immune responses; (ii) direct documentation of mucosal exposure to TMV in smokers; and (iii) an improved understanding of viral interference, replication-independent RNA sensing, and interferon-lambda–mediated epithelial protection against SARS-CoV-2. This Perspective does not advocate smoking. Rather, it contends that if a specific biological component embedded within a harmful exposure were to modulate susceptibility to viral infection, scientific and ethical responsibility would require identifying that component, disentangling it from harm, rendering it safe, and evaluating its translational potential. We synthesize experimental evidence to propose interferon-mediated priming of innate mucosal immunity associated with Tobacco Mosaic Virus exposure as a testable mechanism underlying reduced SARS-CoV-2 attack rates in active smokers.

KEYWORDS
innate mucosal immunity, interferon lambda, One Health, SARS-CoV-2 susceptibility, smoking paradox, Tobacco Mosaic Virus, viral interference



GRAPHICAL ABSTRACT
Hypothetical model of TMV-associated epithelial interferon priming and potential modulation of viral susceptibility. Repeated inhalation of aerosols containing Tobacco Mosaic Virus (TMV)–associated particles could, hypothetically, under certain exposure conditions, result in contact of the airway epithelium with non-replicating plant virus RNA. Following cellular uptake, TMV-associated RNA may be detected by epithelial pattern recognition receptors (PRRs). Endosomal sensors (e.g., TLR3/7) can recognize internalized viral RNA, whereas cytosolic sensors (RIG-I and MDA5) would require access of RNA to the cytoplasm. Engagement of these pathways may induce low-level baseline interferon signaling, with a prominent role for epithelial type III interferons (interferon-λ, IFN-λ). This signaling could promote upregulation of interferon-stimulated genes (ISGs), including antiviral effectors such as myxovirus resistance protein 1 (MX1), interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), and interferon-stimulated gene 15 (ISG15), thereby establishing a transient, exposure-dependent antiviral state at the mucosal surface. In such a pre-activated state, the threshold for successful SARS-CoV-2 infection at the stage of viral entry or early replication may be increased. Importantly, this proposed mechanism is hypothesized to operate prior to viral establishment and does not imply protection once SARS-CoV-2 infection has occurred. The model illustrates a potential form of innate mucosal priming rather than durable adaptive immunity.

1 Introduction

The COVID-19 pandemic produced many apparent contradictions, but one persistent and underexplored observation concerns the relationship between cigarette smoking and susceptibility to SARS-CoV-2 infection. Across multiple populations, study designs, and time periods, active smokers were repeatedly reported to be less likely to test positive for SARS-CoV-2 or to show serological evidence of prior infection compared with never-smokers (1). This observation contrasts with reports associating smoking with severe COVID-19 and mortality once infection is established.

A critical distinction is therefore necessary. The epidemiological signal concerns infection probability (attack rate), not clinical severity among infected individuals. These two domains are biologically distinct. Failure to maintain this distinction has contributed to the premature abandonment of the question, which has received limited mechanistic investigation, driven partly by public-health communication priorities rather than by biological refutation.

This Perspective does not claim that smoking is beneficial. Smoking remains a leading cause of preventable morbidity and mortality worldwide. Instead, we pose a narrower scientific question: if a harmful behavior contains a biological factor that reduces risk of infection, scientific responsibility requires identifying and separating that factor from harm.

This question extends beyond COVID-19. SARS-CoV-2 will not be the last airborne virus. Understanding mechanisms operating at the earliest stage of infection could inform future prophylactic strategies independent of tobacco exposure.

2 The epidemiological paradox and why it matters

The relationship between smoking and COVID-19 involves two biologically distinct questions: susceptibility to SARS-CoV-2 infection and severity of disease once infected. Most literature has focused on the latter. Meta-analyses and large cohort studies consistently report that smoking is associated with worse clinical outcomes among infected individuals, although interpretation is limited by residual confounding, smoking misclassification, and selection bias (2–4).

Evidence regarding infection risk is more heterogeneous, and the so-called "smoking paradox" remains controversial. Several analyses report an inverse association between current smoking and SARS-CoV-2 infection or seropositivity, while methodological reviews emphasize the potential role of bias and unmeasured confounding, including misclassification of smoking status, selection bias, and differences in healthcare-seeking behavior (1). Inverse associations have been described in population-based serosurveys, healthcare-worker cohorts, and large administrative datasets across Europe, North America, and Asia (1, 5–7). A recent pooled Nordic analysis similarly observed reduced risk of COVID-19 diagnosis among current smokers, but no protective association for non-inhaled nicotine use (snus) (8).

Across diverse study designs and populations, an inverse association confined largely to current smokers has been reported in several quantitative analyses. In a Bayesian meta-analysis, Simons et al. reported a pooled risk ratio (RR) of 0.67 (95% credible interval CI 0.60–0.75) for current smokers (1). The corresponding E-values were approximately 2.36 for the point estimate and ~2.0 for the interval limit closest to the null, indicating that an unmeasured confounder associated with both smoking status and infection risk by a risk ratio of this magnitude—above and beyond measured covariates—would be required to explain away the association under the assumptions of the sensitivity model (9). In contrast, data for former smokers were inconclusive (RR = 0.99; 95% CI 0.94–1.05).

In a large health-system cohort, Young-Wolff et al. similarly observed lower adjusted hazard ratio (aHR) of SARS-CoV-2 infection among current smokers (aHR = 0.64; 95% CI 0.61–0.67), corresponding to E-values of approximately 2.5 for the point estimate and ~2.36 for the confidence limit closest to the null (6). The association among former smokers, however, was weak and highly sensitive to residual confounding.

Consistent findings have been reported across several datasets. In the Troina serosurvey, current smoking was associated with lower odds of IgG seropositivity (OR 0.23; 95% CI 0.12–0.45; E-values ~8.2 for the point estimate and ~3.9 for the confidence limit closest to the null) (5). A nationwide Korean study reported lower infection odds among current smokers (OR 0.51; 95% CI 0.48–0.54; E-values of ~3.35 and ~3.0 for the point estimate and interval limit) but not former smokers (7), while pooled Nordic analyses observed reduced risk of COVID-19 diagnosis among exclusive current smokers (RR 0.75; 95% CI 0.72–0.79; E-values of ~2.0 for the point estimate and ~1.85 for the confidence limit closest to the null) without similar effects for snus (8).

Such findings must be interpreted cautiously. Prior reviews have underscored substantial methodological limitations and the potential for residual bias in the observed associations (1, 3, 4).

The present hypothesis does not assume that the epidemiological signal is definitive; rather, it proceeds from the premise that, if a recurring reduction in infection probability among current smokers is observed across independent datasets, mechanistic investigation may be justified.

Collectively, the literature describes a qualitative pattern: an inverse association largely confined to current smokers and attenuated or absent in former smokers. This pattern has been observed across outbreak investigations and population-based analyses (10–13). Such observations are consistent with ongoing exposure, rather than smoking history per se, being relevant to the association.

3 Alternative explanations: behavior, demographics and nicotine

Behavioral and demographic explanations, including differences in testing uptake, healthcare-seeking behavior, symptom perception, or healthcare access, likely contribute to variability in observational data. However, several observations suggest behavioral factors alone may not fully account for the pattern. First, serological studies designed to minimize dependence on testing behavior have also reported reduced seropositivity among current smokers. Second, studies incorporating biochemical validation of smoking status retain an inverse association. Third, similar patterns have been observed in occupational cohorts with systematic testing protocols.

Nicotine-based mechanisms have also been proposed, including modulation of ACE2 expression and engagement of cholinergic anti-inflammatory pathways. Nicotine could, in principle, influence mucosal immune responses through systemic or neuroimmune pathways. However, available human data do not consistently demonstrate reduced infection probability associated with non-combustible nicotine exposure. In particular, large cohort studies indicate that e-cigarette use and snus use are not associated with lower rates of COVID-19 diagnosis (8, 14, 15).

While mechanistic exclusion of nicotine is not possible on current evidence, current data provide limited support for nicotine alone being sufficient to induce a sustained epithelial antiviral state capable of reducing early susceptibility to infection. Taken together, these considerations suggest that nicotine may not be a sufficient standalone explanation and that other components specific to combustible tobacco exposure warrant consideration.

4 Viral interference and innate mucosal priming: a paradigm shift

Recent translational evidence demonstrates that early epithelial interferon-stimulated genes (ISG) programs can limit SARS-CoV-2 infection independently of adaptive immunity, underscoring the biological plausibility of mechanisms acting at the mucosal surface prior to viral establishment (16).

One such mechanism is viral interference, a well-described phenomenon in respiratory virology, whereby infection or exposure to one virus can transiently reduce susceptibility to infection by another virus, often through interferon-mediated antiviral states in host cells (17–19).

Importantly, not all interferon responses are equivalent. Type III interferons (IFN-λ) play a dominant role in antiviral defense at epithelial barriers, providing potent local protection while limiting

systemic inflammation (20). Early and localized IFN-λ responses are associated with reduced viral replication, whereas impaired interferon signaling predisposes to severe COVID-19 (21).

Crucially, induction of an antiviral epithelial state may not require productive viral replication. As early as the 1970s, Tobacco Mosaic Virus (TMV) was shown to possess substantial interferon-inducing and antiviral activity in mammalian systems, comparable to synthetic interferon inducers, despite its inability to replicate in vertebrate cells (22). Modern studies have formalized this paradigm: defective viral genomes and defective interfering particles, incapable of replication, can robustly activate innate immunity and protect against SARS-CoV-2 (23). Defective viral RNA sensing has emerged as a critical determinant of COVID-19 severity (24), and a prenylated double-stranded RNA sensor has been shown to protect against severe disease (25).

Consistent with this framework, prophylactic induction of interferon responses can reduce susceptibility to SARS-CoV-2. An attenuated influenza virus vaccine lacking the interferon antagonist NS1 conferred interferon-mediated protection against SARS-CoV-2 in animal models (26). At the population level, recent common-cold episodes have been associated with reduced risk of subsequent SARS-CoV-2 infection (27). Together, these observations suggest that mucosal exposure to immunostimulatory viral material, even in the absence of replication competence, can meaningfully alter susceptibility to SARS-CoV-2 infection.

5 Tobacco mosaic virus in the smokers' airways: an overlooked viral presence

TMV is a structurally stable and environmentally persistent plant RNA virus that is abundant in tobacco products (28).

Direct mucosal exposure to TMV in smokers has been empirically demonstrated. TMV remains viable in a substantial proportion of commercially available cigarettes, underscoring the remarkable stability of this virus (28, 29), and TMV RNA is detectable in the saliva of active smokers but not in non-smokers (30); viral particles may potentially reach the airways via airflow through unburned tobacco or via oral contact with contaminated filters. Humans possess circulating IgG, IgM, and IgA antibodies against TMV, indicating repeated exposure and immune recognition (31).

Experimental work further demonstrates that TMV can enter and persist in mammalian pulmonary tissue. In a murine intratracheal inoculation model, TMV was detected within lung tissue and localized in the cytoplasm of alveolar macrophages, persisting for up to 14 days despite the absence of productive replication (32).

These findings indicate that TMV is not merely an environmental contaminant but can access the respiratory microenvironment in vertebrate hosts.

Early observations suggesting biological interactions between TMV and mammalian cells date back several decades (33), but were necessarily limited by pre-molecular methodologies. More recently, Li et al. demonstrated that TMV-derived RNA introduced into human epithelial cells can trigger conserved innate cellular stress responses, including endoplasmic reticulum stress and autophagy (34). Complementary studies show that TMV particles can interact with dendritic cells, induce co-stimulatory molecule expression, and promote downstream immune activation (29, 35).

Beyond TMV, plant virus–derived single-stranded RNA nanoparticles analogous to tobamoviruses can be internalized by primary human dendritic cells and induce type I interferon responses via TLR7/8-dependent pathways, showing that plant viral RNA can activate canonical innate antiviral signaling in human immune cells (36). Collectively, these data show that plant viral particles can engage vertebrate immune pathways.

Independent metagenomic studies have further demonstrated that TMV can be detected in the human respiratory tract (37). Although this study does not allow causal inferences—and the authors themselves emphasize that the functional significance of these viruses remains unclear—the findings provide independent evidence that TMV can be present within the human respiratory microenvironment and detected under conditions of epithelial and immune perturbation. However, these observations should be interpreted cautiously, as detection of TMV RNA does not necessarily indicate active biological interaction with airway epithelial cells and may reflect environmental exposure or methodological limitations.

Taken together, these observations support the notion that exposure to TMV is not a rare or artifactual event, but rather represents a genuine environmental exposure with demonstrated capacity for cellular entry and innate immune engagement in vertebrate systems.

Importantly, plant viruses do not replicate in vertebrate hosts and are generally regarded as biologically non-infectious for humans (38). Within this framework, TMV emerges not as a pathogen but as a persistent, replication-incompetent source of viral RNA exposure—conceptually analogous to defective viral genomes capable of inducing antiviral programs without productive infection. The possibility that plant viruses present in tobacco or related Solanaceae may exert biological effects distinct from nicotine has previously been raised in other disease contexts (39), suggesting that TMV may represent a biologically relevant non-nicotine tobacco component.

6 A mechanistic hypothesis: TMV-mediated epithelial pre-activation

We propose that chronic exposure to TMV-containing aerosols may function as a non-infectious, persistent, low-intensity pathogen-associated exposure at the respiratory mucosa. Importantly, there is no direct evidence that TMV exposure in smokers induces antiviral interferon responses in human airway epithelium. Theoretically, recognition of TMV-derived RNA by epithelial RNA sensors, e.g. TLR3, TLR7, melanoma differentiation-associated protein (MDA5), or retinoic acid-inducible gene RIG-I, could elevate baseline interferon signaling, particularly type III interferon responses at epithelial barriers, maintaining

partial activation of interferon-stimulated genes without overt inflammation. However, the concentration of TMV particles inhaled during smoking and whether these levels are sufficient to activate epithelial pattern-recognition receptors remain unknown.

Such a low-level epithelial pre-activation state, if present, could increase the threshold required for SARS-CoV-2 to establish productive infection. Within this framework, a reduction in infection probability (attack rate), without modification of disease severity among infected individuals, would be consistent with the epidemiological pattern described above.

Experimental models of acute cigarette smoke exposure in human airway epithelial air-liquid interface cultures have reported increased viral permissivity accompanied by blunted interferon responses (40, 41). However, cigarette smoke exposure can also alter epithelial antiviral immunity in complex and context-dependent ways across respiratory viral models, including influenza systems (42). Importantly, experimental findings have not been uniform: some *in vitro* models have also reported reduced SARS-CoV-2 replication following acute cigarette smoke pre-exposure (43), underscoring the composite and context-dependent biological effects of smoke exposure.

These studies indicate that combustion-derived smoke constituents exert context-dependent effects on epithelial antiviral programs. Most experimental models capture the acute biological impact of smoke particulates rather than the full spectrum of exposures associated with tobacco use and do not isolate the contribution of structurally intact, replication-incompetent viral particles within tobacco. Controlled epithelial assays comparing TMV-derived stimuli with smoke-conditioned media are therefore required to determine whether TMV-associated priming occurs independently of smoke-induced effects.

7 Limitations of the hypothesis

Several limitations should be acknowledged. The epidemiological associations motivating this hypothesis remain heterogeneous and potentially affected by residual bias. Direct evidence that TMV exposure induces antiviral interferon responses in the human airway epithelium is currently lacking. In addition, quantitative data regarding the concentration of TMV particles inhaled during smoking and their capacity to activate epithelial pattern-recognition receptors remain unknown.

8 What would count as evidence? A hierarchically structured experimental framework

To move from hypothesis to evidence, we propose a hierarchically structured set of experimentally feasible approaches. Demonstration of TMV-induced interferon responses in primary human airway epithelial cells is the essential prerequisite for subsequent investigations.

8.1 Airway epithelial priming at the mucosal interface (primary experiment)

Primary human airway epithelial cells cultured at air–liquid interface could be exposed to standardized TMV particles or TMV-associated material, followed by a challenge with a SARS-CoV-2 pseudovirus. Exposure models could include purified TMV virions or TMV-derived RNA preparations, with appropriate controls such as heat-inactivated virus, RNA degradation, or mock-treated cultures. A smoke-exposure condition may serve as a comparator to distinguish TMV-specific effects from combustion-related interferon modulation. Primary outcomes could include IFN-λ production and downstream interferon-stimulated gene expression, together with measures of viral entry or early replication.

This design would test whether TMV-associated exposure induces epithelial interferon priming and alters susceptibility to viral establishment.

8.2 Human serological and mucosal correlation studies (contingent step)

If epithelial priming is demonstrated *in vitro*, TMV-specific IgA (saliva) and IgG (serum) could be used as indirect markers of exposure and correlated with documented SARS-CoV-2 infection or serostatus in smokers and non-smokers.

8.3 Prospective pilot cohorts (conditional extension)

Cohorts characterized by baseline TMV exposure markers and mucosal innate immune signatures could then be followed prospectively to assess whether exposure-related profiles predict subsequent SARS-CoV-2 infection.

In this framework, anti-TMV antibodies are not proposed as mechanistic effectors, but as accessible biomarkers of exposure. All proposed experiments are feasible using existing platforms and do not require high-containment facilities when TMV and pseudovirus systems are employed.

9 Ethical and public-health considerations

Scientific responsibility lies in examining unexpected observations and extracting insights that can be rendered safe and beneficial. Smoking remains harmful, and any potential reduction in infection probability would be outweighed by its well-established adverse health effects; it has no relevance as a preventive strategy.

If a specific component within tobacco exposure modulates viral susceptibility, identifying and isolating that component represents a legitimate scientific objective. This perspective aligns with a “One Health” framework, in which human behavior, plant viruses, and emerging respiratory pathogens intersect in ways that may inform protection of human health.

10 Conclusion

Reduced SARS-CoV-2 attack rates among active smokers remain an unresolved observation. Much of the apparent contradiction arises from conflating susceptibility to infection with progression to severe disease—distinct biological processes operating at different stages.

While smoking is associated with worse outcomes among infected individuals, this does not address mechanisms governing initial viral acquisition at the mucosal surface. Reduced susceptibility to viral establishment could coexist with increased vulnerability to severe disease.

Within this framework, chronic exposure to non-replicating viral particles capable of inducing low-level innate immune activation represents one biologically plausible mechanism acting at the stage of viral entry. Tobacco mosaic virus, due to its stability and documented immunological activity in vertebrate systems, warrants focused experimental evaluation.

This hypothesis is testable using existing experimental platforms. Whether confirmed or refuted, investigation would advance understanding of respiratory mucosal host–virus interactions. Exploring such mechanisms does not imply endorsement of harmful behaviors but reflects a commitment to scientific inquiry. Smoking remains harmful to health, and this hypothesis should not be interpreted as evidence of protective effects of tobacco use, but rather as an attempt to explore a specific biological mechanism that could ultimately be investigated independently of smoking exposure.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

EB: Conceptualization, Writing – original draft, Writing – review & editing. FL: Validation, Writing – original draft, Writing – review & editing. LB: Writing – original draft, Writing – review & editing. GP: Writing – original draft, Writing – review & editing. RM: Funding acquisition, Writing – original draft, Writing – review & editing.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. Generative AI tools were used to assist with English language editing and the preparation of the figure. No generative AI was used to generate scientific content, formulate hypotheses, interpret data, or draw conclusions. All scientific responsibility remains with the authors.

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