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Targeting host adaptation in *Streptococcus pneumoniae*: A narrative review of biological strategies beyond antibiotics

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Abstract

Streptococcus pneumoniae remains a leading cause of severe respiratory disease in U.S. adults despite expanded conjugate vaccination and guideline-directed antibiotic therapy. Rising antimicrobial resistance, serotype replacement, and rapid within-host evolutionary adaptation collectively undermine the long-term effectiveness of conventional antibiotic-centric strategies, motivating complementary non-antibiotic interventions that attenuate pneumococcal virulence rather than directly targeting viability. This review examines emerging host adaptation mechanisms in S. pneumoniae and evaluates biological targets for antivirulence therapy with the potential to reduce pneumococcal pneumonia and invasive disease burden in the United States. Focusing on literature from 2020 onward, the review synthesizes advances in understanding of pneumolysin-mediated immune modulation, complement evasion by capsular and surface proteins, metabolic and regulatory adaptation in the host niche, and small molecule or biologic antivirulence candidates that interfere with these processes. Unresolved questions include the durability of antivirulence-driven selective pressures, optimal combination with vaccines and antibiotics, and host-specific factors that determine therapeutic windows. Addressing these gaps will be essential for integrating antivirulence agents into future pneumonia prevention and treatment frameworks aimed at substantially lowering the pneumococcal disease burden in the United States.

Keywords: *Streptococcus pneumoniae*; Antivirulence Therapy; Pneumolysin Inhibitors; Host Adaptation; Complement Evasion; Pneumococcal Pneumonia; Vaccine Escape.

1. Introduction

Invasive and noninvasive pneumococcal disease remain major causes of morbidity and mortality in the United States (U.S), particularly among older adults and individuals with comorbidities. Recent analyses estimate that vaccine-preventable diseases (VPDs) cause 40,000–50,000 adult deaths annually in the United States, with *pneumococcal pneumonia* accounting for a substantial fraction, and with an economic burden estimated at 27 billion USD (Durusu-Tanrıöver et al., 2025). According to two US datasets used in 2020, it has been estimated that twenty important pneumococcal serotypes can cause up to 1.2 million cases of pneumococcal infections in children under five years of age and 250,000 infections in adults (Mohanty, Cossrow, White, et al., 2024; Shi et al., 2021). Even with the introduction of more valent conjugate vaccines in adults, the IPD Case Fatality Rate in people aged over 65 years has been shown to reach up to 35%, highlighting the residual risk. Additionally, surveillance carried out between 2018 and 2022 has demonstrated that serotypes such as CAPVAXIVE, which are only contained in more recently developed vaccines, cause a disproportionate number of IPD cases among adults aged ≥65 years, with nonsusceptibility common across multiple serotypes. From the indications of these findings, it is not expected that *pneumococcal pneumonia* IPD-related cases will be eliminated as major public health threats in the ageing populations of the US with the expanded vaccine approach (Durusu-Tanrıöver et al., 2025), and new treatment strategies will be key.

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Notably, resistance to beta-lactams, macrolides, and fluoroquinolones is rapidly reducing the effectiveness of treatment strategies for pneumococcal pneumonia. Current isolates tend to be multidrug-resistant, with frequent reports of treatment failures in severe disease with the known conventional drugs. Conventional antibiotics exert strong selective pressure that favors resistant strains and do not effectively reduce virulence factors such as toxin production, complement evasion, and biofilm formation (Zou et al., 2023). Interestingly, genomic studies have provided insight into how adaptable *S. pneumoniae* can be during a human infection. In a 2025 study of the genetic diversity of *S. pneumoniae* serotype 3, it was estimated that a base substitution occurs approximately every 15 weeks of carriage, with an average of 72 nucleotide sequence changes resulting from recombination events. These mechanisms enable *S. pneumoniae* to adapt to antibiotics and to the immune system, which is affected by vaccination. The adaptability of *S. pneumoniae* calls into question the long-term success of bactericidal and bacteriostatic approaches, thereby supporting the antivirulence approach to infections, which has already been discussed (Sibale et al., 2025)

Antivirulence therapy is an approach that aims to target and neutralise virulence factors and host-adaptation strategies while maintaining bacterial viability. In *Streptococcus pneumoniae*, antivirulence targets include its major virulence factor, pneumolysin, a cholesterol-dependent cytolysin; surface proteins that inhibit host immune responses by interfering with the complement cascade; and enzymes and regulatory systems that regulate adhesion, biofilm formation, and metabolic fitness within its host niche. Notably, a growing number of recent studies show that inhibitors of pneumolysin, either small molecules or natural products, substantially reduce disease outcomes and animal mortality without causing appreciable decreases in bacterial loads. (Brooks & Mias, 2018; Pipkins et al., 2017; Zou et al., 2023). Concurrently, there is a growing focus on the host side of this interaction. Over the past five years, a growing number of studies have helped refine the understanding of how the host immune system, via activation of the complement cascade, pattern-recognition receptors, and cell-mediated immune responses, limits pneumococcal infection, and how *S. pneumoniae* responds to this pressure by varying its capsule and surface proteins and its metabolic pathways (Gu et al., 2023)

Most of these reviews preceded recent high-resolution studies of host genomes and the discovery of antivirulence candidates. Some have examined pneumococcal virulence factors or pneumolysin biology separately. There is a clear need for an integrated, trend-focused synthesis that connects molecular host adaptation processes to specific non-antibiotic targets and considers the unique epidemiological context of pneumococcal respiratory illness in US adults. This review aims to summarize recent progress (2020 onward) in understanding *S. pneumoniae* host-adaptation mechanisms related to respiratory disease; critically evaluate emerging non-antibiotic targets like pneumolysin and complement-evasion systems; highlight key antivirulence candidates; analyse how serotype shifts, vaccination trends, and resistance patterns in U.S. adults influence antivirulence strategies; and identify critical knowledge gaps. It also proposes future research directions to develop clinical tools that can lessen the severe burden of pneumococcal respiratory diseases in the US.

2. Methodology

This is a narrative, theme-driven review that prioritizes conceptual integration over exhaustive coverage. We searched PubMed, Web of Science, and Scopus for English-language articles published between January 2010 and December 2025, using combinations of the following terms: *Streptococcus pneumoniae*, pneumolysin, virulence factor, host adaptation, complement evasion, antivirulence, non-antibiotic, sortase A, biofilm, quorum sensing, and CRISPRi. We preferentially included peer-reviewed primary studies and reviews that provided mechanistic insight or in vivo efficacy data relevant to pneumococcal virulence and host adaptation, with an emphasis on work from 2020 onward; seminal earlier studies were cited where necessary to contextualise recent findings (Falagas et al., 2008; Gusenbauer & Haddaway, 2020). Conference abstracts, trade-press reports, and preprints were used only to illustrate emerging trends and are clearly identified as such. Because this was not a systematic review, we did not apply formal PRISMA criteria or perform risk-of-bias scoring; instead, we critically appraised study design (in vitro versus in vivo, strain diversity, controls, endpoints) when interpreting the strength and generalisability of the evidence (Yepes-Nuñez et al., 2021)

3. Results and discussion

3.1. Translational context in U.S. adults: vaccines, serotypes, and resistance

Although adult vaccination with higher-valency conjugate vaccines is cost-effective and reduces IPD, coverage remains suboptimal and substantial as disease persists, particularly in older adults and those with chronic conditions (Durusu-Tanrıöver et al., 2025). Recent analyses using U.S. surveillance and claims data show that, even after the introduction of higher-valency conjugate vaccines, adults ≥65 years continue to experience substantial residual IPD and

non-bacteremic pneumococcal pneumonia, with case-fatality rates of 10–20% depending on comorbidity burden (Lu et al., 2025). Notably, serotype distribution has shifted toward types newly targeted by expanded-valency vaccines and non-vaccine serotypes, several of which exhibit high rates of β-lactam and macrolide nonsusceptibility(Brooks & Mias, 2018; Du et al., 2021). These patterns underscore that vaccination alone is unlikely to eliminate severe pneumococcal disease in older adults and highlight a potential niche for adjunctive antivirulence interventions (Brooks & Mias, 2018; Lu et al., 2025; Mohanty, Cossrow, White, et al., 2024)

Antivirulence strategies are generally perceived as having a lower risk of resistance, at least compared with killing antibiotics (Cools et al., 2021). Agents targeting the host, such as the complement system, might, in theory, exacerbate immune disease or provide an opportunity for other pathogens if not properly balanced. Finally, agents that reduce disease but not the causative agent might sustain carriage longer and alter the mode of transmission. Accordingly, as with all antibiotic interventions, the first human studies should assess carriage and include models of transmission (Mohanty, Cossrow, White, et al., 2024).

3.2. Within-host evolution, metabolic adaptation, and regulatory networks

Recent high-resolution genomic studies have found *S. pneumoniae* evolving quickly within individual hosts. A 2025 study on *S. pneumoniae* serotype 3 using functional genomics strategy and found base substitution mutations occur at a rate of one for every 15 weeks of carriage and concluded that such changes can drive adaptation to antibiotics and host immune effects, such as antibodies induced by vaccines (Sibale et al., 2025) presenting a classic example of how evolutionary routes may reduce acute virulence but increase persistence and transmission, complicating clinical outcomes. Further related research is the use of genome-wide CRISPR interference (CRISPRiSeq), which is now showing promise for identifying genes required for survival within a host under specific conditions. Recently, *S. pneumoniae* was used *in-vivo* genome-wide CRISPRiSeq and identified genes required for survival within a lung environment but not required for survival within a standard lab environment. Such research shows promise to identify antivirulence targets within genes required for nutrient acquisition and metabolism that help the S. *pneumoniae* bacteria thrive within a host environment. Antivirulence strategies hold promise for future development and use but also have several hurdles. The use of antivirulence strategies may disable the *S. pneumoniae* bacteria without impacting on the microbiome but may also enable the bacteria to quickly adapt to such a strategy, therefore may require the use of multiple antivirulence strategies such as PLY, biofilm regulation, and metabolic enzymes.

Table 1 Pneumococcal antivirulence candidates targeting pneumolysin and related pathways (2010–2025)

Target	Compound (class)	Primary mechanism	In vitro potency	In vivo model & dosing	PK/toxicity notes	Development stage
Pneumolysin	Wogonin (flavonoid)	Inhibits PLY hemolysis; inhibits sortase A, reducing surface protein anchoring	IC50 for hemolysis ~X μM (human RBCs)	Murine pneumonia; 50 mg/kg i.p. post-infection; ↑ survival, ↓ lung damage, minimal CFU change	No significant acute toxicity; no PK data reported	Preclinical, proof-of-concept.onlinelibrary.wiley
Pneumolysin	Isorhamnetin (flavonoid)	Inhibits PLY-mediated hemolysis	IC50 ~X μM	Murine infection; 50–100 mg/kg improves survival and lung pathology	Limited toxicity assessment; PK not reported	Preclinical.sciencedirect

Pneumolysin	Statins (e.g., simvastatin)	Modulate cholesterol-dependent cytolysins; dampen inflammation	Variable; indirect	Murine pneumococcal models show reduced lung inflammation and improved survival	Well-characterized human PK and safety	Repurposing candidate.pmc.ncbi.nlm.nih
PLY + others	PLY toxoid vaccines	Induce neutralizing antibodies	High titers; strong neutralization	Mouse models show protection against lethal challenge; often combined with other antigens	Vaccine-type reactogenicity; no human PLY-only data	Preclinical.pmc.ncbi.nlm.nih

3.3. Pneumolysin-Centred Host Adaptation and Antivirulence Targeting

Recent studies have highlighted pneumolysin (PLY) as the key factor in the induction of tissue damage in pneumococcal pneumonia amid complex regulation of the immune response. Apart from the known pore-forming activity of PLY, the toxin also acts on host cell receptors, including the mannose receptor MRC1 in dendritic cells, enhancing intracellular survival of the bacterium and reducing the production of pro-inflammatory cytokines, thus allowing the pneumococcus to evade the immune system at sublytic concentrations of the toxin. The dual role of PLY makes the pneumococcal toxin more susceptible to antivirulence strategies (Gu et al., 2023; Nishimoto et al., 2020)

Interestingly, a review in 2020 aimed to consolidate preclinical data related to pneumolysin (PLY)-targeting interventions, which include toxoid-based vaccines, statins that target cholesterol-dependent cytolysins, and early-stage small molecule inhibitors(Nishimoto et al., 2020). The outcomes suggested that PLY neutralization would attenuate diseases in a meaningful manner without necessarily imposing strong bactericidal selective pressure. This has moved away from abstract concepts and towards more defined chemical structures. Zou et al (2024) identified that isorhamnetin is a potent inhibitor of PLY-induced hemolytic activity and that this compound was able to protect mice from lethal *S. pneumoniae* infection with improved survival and decreased lung damage despite modest reductions in bacterial load. Another recent study by Gu et al. (2023) identified that the flavonoid compound wogonin can attenuate pneumococcal pathogenicity by simultaneously inhibiting PLY and SrtA, a transpeptidase enzyme that is crucial for the anchorage of important surface proteins in *S. pneumoniae*. Pneumonia models in mice showed that treatment with wogonin resulted in significant reductions in tissue damage and improved clinical scores. (Gu et al., 2023; Zou et al., 2023). Collectively, this indicates that a few areas are being explored: there is a reliance on natural product structures as starting points for discovering PLY inhibitor while there is increasing interest in compounds that inhibit two targets simultaneously, reducing toxin release and interfering with the final location of surface proteins; and there is an increasing focus on functional outcomes relevant to the host, such as the death of immune cells, cytokine patterns, and the maintenance of the host barrier, rather than just on the minimum inhibitory concentration. However, no clinical trials have been conducted with these compounds, and nothing is known about the long-term development of resistance to PLY inhibition. (Durusu-Tanrıöver et al., 2025)

3.4. Complement evasion, capsule, and surface proteins as intervention nodes

Complement evasion is particularly noteworthy as a characteristic of pneumococcus adaptation to the human host, allowing the organism to coexist with a raging innate immune response. The capsule of the bacterium prevents binding C3b, and surface-expressed proteins such as PspA and PspC on regulators such as factor H and C4b binding protein (Brooks & Mias, 2018). Taken together, this reduces opsonophagocytosis. Much of this mechanism was elucidated prior to 2020, but more recent work has clarified the interplay between these mechanisms and antibodies induced by

vaccination and highlighted the importance of serotype-specific vulnerabilities, which are important for U.S. adults. The challenge is that serotypes have a potent capsule-mediated mechanism of complement evasion, combined with poor cross-protection by current vaccines. Current surveillance in U.S. adults shows that some serotypes included in new vaccines are disproportionately represented in cases of IPD, suggesting that these serotypes have highly effective mechanisms of immune evasion.

From a therapeutic standpoint, there are two distinct approaches. One is to use monoclonal antibodies or engineered fragments of antibodies targeted to PspA, PspC, or specific capsular targets to enhance complement deposition and phagocytosis, particularly in high-risk adults whose immune responses to the vaccine are suboptimal(Kristian et al., 2016). The other is to develop small molecules or biologics that inhibit the binding of factor H or C4b binding protein to the bacterial surface, thereby restoring effective complement killing the bacteria. While there are few specific candidates in this area, progress in structural biology and the development of protein-protein interaction inhibitors in other pathogens suggests that there may be productive avenues of research (Brooks & Mias, 2018). The primary concern is safety and accuracy. Modifying the host's complement system may result in undesirable inflammatory reactions. In contrast, inhibitors that target bacterial side factors must avoid interfering with microorganisms that employ the complement system. A middle ground between these extremes could be to develop pathogen-specific therapeutics, such as monoclonal antibodies that identify conformational epitopes unique to pneumococcal surface proteins.

3.5. Natural products and small molecules as antivirulence leads

Another trend that has been clear since 2020 is that natural products, particularly flavonoids, have become a starting point for antivirulence strategies targeting pneumococcus. Wogonin and isorhamnetin, for example, are flavonoids derived from natural products that show potent inhibition of PLY-induced hemolysis and provide protection in mouse infection models, with wogonin also targeting sortase A and inhibiting anchoring of surface proteins (Gu et al., 2023; Nishimoto et al., 2020; Zou et al., 2023). These generally have low direct antibacterial activity, consistent with antivirulence strategies, and often come with a prior safety profile from non-infectious studies, which will be beneficial in moving these into further development.

The main roadblocks for these antivirulence strategies targeting pneumococcus include pharmacokinetics and pharmacodynamics. Flavonoids, for example, generally have low bioavailability, rapid metabolism, and difficulty penetrating to adequate tissue concentrations, particularly into the lung interstitium, which may limit their utility in the treatment of existing pneumonia (DIckey et al., 2017). To advance these antivirulence strategies into viable therapeutic candidates, structural optimization, advanced delivery systems, and development of synthetic analogs will be required. A second issue is that most existing studies focus on treatment in animal models, while very few studies have been conducted on using these as a preventative strategy in high-risk adults or as a combination with antibiotic therapy (Zou et al., 2023). Nonetheless, these studies provide critical proof of principle that selective interference with host-adaptation mechanisms can attenuate disease in vivo. Over time, a diversified portfolio of small-molecule, peptide, and biologic antivirulence agents targeting distinct mechanisms (toxin activity, complement evasion, metabolic adaptation, biofilm regulation) may enable personalized combination regimens for patients at high risk for severe pneumococcal pneumonia.

3.6. Mechanistic detail for pneumolysin and inhibitors

Pneumolysin has been shown to act as a cholesterol-dependent cytolysin, binding cholesterol through its interaction with domain 4, followed by oligomerisation into large pre-pore structures, and finally a conformational transition into β-hairpins that result in the formation of a pore (Aziz et al., 2024). In relation to the above, small-molecule inhibitors characterised in scientific literature have been shown primarily to target early steps of the process, such as binding and oligomerisation. For example, a review by Subramanian et al. (2022) has highlighted evidence that compounds such as statins and flavonoids interact at a site close to domain 4, as well as at inter-monomer sites, and therefore limit the formation of a pore, although they do not limit bacterial growth and proliferation. In more recent studies, flavonoids such as wogonin and isorhamnetin have been shown, through docking and mutagenesis, to interact with domains 3 and 4 of pneumolysin, thereby limiting oligomer formation. Although structural data on complexes of pneumolysin and its inhibitors have been limited, it has been shown that antivirulence compounds act by stabilising a pre-pore structure and therefore inhibiting oligomerisation. (Gu et al., 2023; Zou et al., 2023)

From an evolutionary standpoint, PLY faces strong selective pressure due to its role in transmission and immune detection by the host. At the individual host level, pneumococci tend to accumulate point mutations and undergo recombination at rates that could produce PLY variants during prolonged carriage, potentially allowing the bacteria to evade inhibitors. However, large loss-of-function mutations that fully disable PLY seem to reduce bacterial fitness, indicating that completely knocking out the toxin may not be beneficial in certain environments unless other virulence

factors compensate. Current research focuses on whether clinically relevant sequence changes affect inhibitor binding and on strategies, such as combining PLY inhibitors with antibodies targeting other virulence factors like PspA and PspC, to reduce the likelihood of inhibitor escape (Sibale et al., 2025; Zaborskytė et al., 2025)

3.7. Pharmacologic details: doses, routes, PK, toxicity

In the wogonin study, mice received intraperitoneal injections of wogonin at 50 mg/kg, starting 2 h post-infection and continuing daily for three days; this regimen significantly improved survival and reduced lung pathology compared with vehicle-treated controls, without notable changes in bacterial loads (Gu et al., 2023). Similarly, isorhamnetin, given at 50–100 mg/kg intraperitoneally or orally in murine models, reduced PLY-mediated haemolysis and protected against lethal challenge, with only modest effects on CFU. Both compounds appeared acceptable for acute toxicity in mice. No significant changes were observed in body weight, liver enzymes, or tissue histology for possible organ damage. However, no pharmacokinetic studies were conducted for these compounds, and lung tissue concentrations were not measured. The spectrum was limited to only a few serotypes, raising the need for a broader spectrum evaluation and PK/PD studies (Gu et al., 2023).

3.8. Other non-antibiotic strategies and computational pipelines

In addition to the classical toxin and complement evasion targets, a variety of non-antibiotic approaches against S. *pneumoniae* and other respiratory pathogens have started to gain significant traction in the past decade(Cools et al., 2021). Approaches targeting adhesins, such as antibodies against choline-binding proteins and pilus proteins, have shown potential in improving clearance and reducing bacterial colonization in preclinical models(Aziz et al., 2024). Another promising antivirulence approach that has gained significant interest in the past decade is the disruption of quorum sensing and biofilm regulation(Gonzales et al., 2024), for example, by inhibiting the Com and Rgg systems, which has been shown to reduce biofilm formation and modulate competence. Another approach that has been suggested, although with a significant risk of immunopathology, is the use of inhaled cytokines and modulators that can enhance bacterial clearance, while host-directed approaches, such as inhaled cytokines and modulators that can enhance neutrophil recruitment, have also been suggested as a potential approach that can enhance bacterial clearance, although there is a significant risk of immunopathology if these are not tightly controlled(Junges et al., 2017). Finally, bacteriophage-derived lysins and synthetic endolysins have been shown to rapidly lyse pneumococci in vitro and in animal models, and a variety of engineered lysins are in early-phase trials against a variety of Gram-positive pathogens, providing a potential alternative approach in the fight against bacterial pathogens (Lu et al., 2025).

3.9. Computational pipelines for antivirulence lead discovery

Significantly, computational tools are assuming a progressively central part in accelerating the pace of antivirulence compound discovery and development. By applying structure-based virtual screening and molecular docking tools, researchers have begun to explore antivirulence agents like PLY and sortase A, revealing promising flavonoid-like compounds and synthetic small molecules that dock into potential binding sites of viral toxins/enzymes. In recent years, researchers have proposed various machine learning-based computational tools like reinforcement learning-based molecular docking and natural product-focused representation learning that have been proposed as efficient tools to navigate through vast chemical spaces with promising pharmacokinetic/pharmacodynamic properties, as well as low off-target potential. The integration of these tools with antivirulence compound development will certainly reduce the distance between initial discovery and final development stages with regard to antivirulence compounds like PLY, sortase A, and complement-binding proteins, as well as alleviate pharmacokinetic issues with first-generation flavonoids inhibitors. (Lu et al., 2025)

3.10. Knowledge Gap and Future directions

Two areas for clinical development hold particular promise for pneumococcal disease in U.S. adults. The first involves an adjunctive therapeutic for hospitalized adults with severe community-acquired pneumococcal pneumonia, especially when resistant serotypes are suspected or identified. It may demonstrate whether the use of a PLY inhibitor as adjunctive therapy with antibiotics reduces mortality rate, the need for mechanical ventilation, or shortens the length of stay. The primary endpoints may be 28-day mortality rate and time to clinical stability, with secondary endpoints including changes in inflammatory markers and rate of radiographic clearing.

The second area for development involves high-risk, vaccinated older adults with conditions such as COPD and heart failure presenting with early lower respiratory tract symptoms. It may demonstrate whether antivirulence agents can delay progression to severe pneumococcal pneumonia or reduce the risk of hospitalization. In all cases, safety assessments should include immune profiling, colonization status, and careful evaluation for adverse events related to immunopathology and opportunistic infection risk. Interestingly, no PLY-targeting compound has yet entered human

trials; dose, route, and timing in relation to antibiotic administration remain undefined. (Nishimoto et al., 2020) and would critical as next step in intensive research.

4. Conclusion

Pneumococcal pneumonia and invasive disease remain major causes of hospitalization and death among U.S. adults despite expanded conjugate vaccination and optimized antibiotic use. By focusing on host-adaptation mechanisms most prominently pneumolysin-driven tissue injury and complement evasion by the capsule and surface proteins, this review argues that antivirulence interventions can attenuate disease severity without intensifying classical resistance selection. Recent small-molecule and natural-product inhibitors that block pneumolysin oligomerization, together with emerging insights into complement-evasion networks and within-host genomic plasticity, demonstrate both the feasibility and the complexity of targeting virulence rather than viability. To realize their potential, future antivirulence agents will need to be optimized for pharmacokinetics and safety, deployed in rational combinations with vaccines and antibiotics, and evaluated in trials that incorporate colonization, transmission, and evolutionary endpoints alongside clinical outcomes. If these scientific and translational challenges are met, non-antibiotic biological strategies directed at *S. pneumoniae* host adaptation could substantially reduce the burden of severe respiratory disease in U.S. adults and help reshape the broader antimicrobial landscape.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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