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Economic and Clinical Impact of Optimizing Antimicrobial Stewardship Programs in U.S. Hospitals: A Comprehensive Review

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Abstract: Antimicrobial stewardship programs (ASPs) have become essential components of modern healthcare systems to combat the growing threat of antimicrobial resistance while optimizing patient outcomes. This paper examines the economic and clinical impact of optimizing ASPs in U.S. hospitals. A comprehensive literature review was conducted examining peer-reviewed studies published between 2010-2025 that evaluated the economic and clinical outcomes of ASP optimization in U.S. hospital settings. Studies were analyzed for implementation strategies, cost-effectiveness measures, clinical outcomes, and barriers to optimization. Results showed that optimized ASPs demonstrate significant economic benefits, with average cost savings of $732 per patient in U.S. studies (range: $2.50-$2,640) and annual hospital savings averaging $435,000. Clinical outcomes show consistent improvements, with 85% of studies reporting decreased length of stay and 14-92% reduction in antibiotic expenditure. Implementation of CDC Core Elements increased from 41% in 2014 to 91% in 2020, with prospective audit and feedback achieving 60-90% acceptance rates. In conclusion, optimized ASPs provide substantial value to U.S. hospitals through improved clinical outcomes and significant cost savings. The primary economic driver is a reduction in length of stay, while clinical benefits include decreased inappropriate antibiotic use, reduced healthcare-associated infections, and improved patient safety. Successful optimization requires comprehensive implementation of evidence-based strategies, adequate resources, and sustained leadership commitment.

Keywords: Antimicrobial stewardship, economic evaluation, clinical outcomes, healthcare optimization, United States hospitals.

INTRODUCTION

The emergence of antimicrobial resistance (AMR) represents one of the most significant threats to modern healthcare, with the Centers for Disease Control and Prevention (CDC) estimating that treating six major antimicrobial-resistant threats contributes to more than $4.6 billion in healthcare costs annually in the United States (Centers for Disease Control and Prevention. 2024). The magnitude of inappropriate antibiotic prescribing in U.S. hospitals is substantial, with approximately 30-50% of antibiotics prescribed being either inappropriate or unnecessary (Centers for Disease Control and Prevention. 2019; Markley, D). This concerning statistic creates an urgent need for systematic approaches to optimize antimicrobial use across healthcare institutions. Challenges in patient adherence to prescribed treatment regimens significantly influence antimicrobial effectiveness, and strategies involving digital health tools and culturally tailored education have shown promise in improving adherence and outcomes in the United States (Amofah, A. D. *et al.*, 2024). Concurrent initiatives aimed at enhancing antimicrobial stewardship programs and stimulating antimicrobial innovation continue to evolve as critical components in combating resistance and supporting public health (Gyasi-Darko, K. *et al.*, 2024).

Antimicrobial stewardship programs have evolved as the cornerstone strategy to address this multifaceted challenge. The Infectious Diseases Society of America (IDSA) defines antimicrobial stewardship as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen, including dosing, duration of therapy, and route of administration"(Barlam, T. F. 2016). The scope of ASP objectives extends beyond mere cost reduction to encompass optimizing clinical outcomes while minimizing unintended consequences, including toxicity, selection of pathogenic organisms such as *Clostridioides difficile*, and emergence of resistance (Centers for Disease Control and Prevention. 2019; Markley, D).

The regulatory landscape surrounding ASP implementation has undergone significant strengthening in recent years. The Joint Commission established comprehensive ASP standards for accredited hospitals that became effective in January 2017(Stenehjem, E. A. *et al.*, 2023). Subsequently, the Centers for Medicare and Medicaid Services (CMS) added federal regulations for hospital antibiotic stewardship programs as conditions of participation in 2019 (Centers for Disease Control and Prevention. 2019; Shrestha, J. *et al.*, 2023). These regulatory mandates, combined with the updated CDC Core Elements published in 2019)(CDC), have established a robust framework for ASP development and optimization across U.S.

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healthcare systems. Moreover, sustainable pharmaceutical practices are bolstered by policy frameworks and advocacy strategies at the federal and state levels, which facilitate responsible antibiotic use and stewardship implementation (Amofah, A. D. *et al.*, 2024).

The evolution of ASPs from optional quality improvement initiatives to mandatory regulatory requirements reflects the growing recognition of their importance in addressing antimicrobial resistance and improving patient care. However, the transition from basic compliance with structural requirements to comprehensive program optimization presents ongoing challenges that require careful examination of both economic and clinical outcomes to guide evidence-based implementation strategies.

FRAMEWORKS FOR ASP OPTIMIZATION IN THE UNITED STATES

CDC Core Elements as the Foundation for Success

The CDC's Core Elements of Hospital Antibiotic Stewardship Programs, comprehensively updated in 2019, provide the fundamental framework for ASP optimization across U.S. healthcare institutions (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs),12]. These seven core elements represent evidence-based structural components that have demonstrated effectiveness in improving antimicrobial use when implemented systematically.

Leadership Commitment constitutes the foundational element that involves dedicating necessary human, financial, and information technology resources while establishing formal statements of support and regular reporting mechanisms to senior leadership and hospital boards (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs,12). This commitment must be tangible and sustained, as evidenced by resource allocation decisions and organizational priority setting that demonstrate genuine support for stewardship activities.

Accountability requires appointing a leader or co-leaders responsible for program activities and outcomes, with the most effective model being physician-pharmacist co-leadership based on 2019 National Healthcare Safety Network (NHSN) hospital survey data(CDC). This collaborative leadership approach leverages complementary expertise while ensuring adequate clinical and pharmaceutical knowledge to guide program decisions effectively.

Pharmacy Expertise emphasizes appointing a pharmacist, ideally as co-leader, to spearhead implementation efforts for improving antibiotic use. This requirement reflects the critical role of pharmacy engagement in successful stewardship programs, given pharmacists' specialized knowledge of antimicrobial pharmacokinetics, pharmacodynamics, and drug interactions (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs),12].

Action encompasses implementing priority interventions, including prospective audit and feedback, preauthorization, and facility-specific treatment recommendations. Evidence consistently demonstrates that these strategies improve antibiotic use as core components of any stewardship program, with prospective audit and feedback showing particularly strong effectiveness (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs),12].

Tracking involves comprehensive monitoring of antibiotic prescribing, intervention impact, and important outcomes such as C. difficile infection rates and resistance patterns. The CDC emphasizes electronic submission of antibiotic use data to the NHSN Antimicrobial Use Option to facilitate benchmarking and quality improvement efforts (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs,12].

Reporting ensures regular dissemination of information on antimicrobial use and resistance patterns to healthcare providers and relevant staff. This communication maintains awareness and engagement while providing feedback on program effectiveness and areas requiring improvement (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs,12].

Education provides ongoing training to clinicians about local resistance patterns and optimal prescribing practices to support evidence-based decision-making. Educational interventions must be tailored to specific clinical contexts and updated regularly to reflect evolving evidence and resistance patterns (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs,12).

Implementation Success Metrics and Current Status

The widespread adoption of CDC Core Elements has been remarkable in scope and speed. Self-

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reported NHSN data revealed that 91% of acute-care hospitals had all seven Core Elements in place in 2020, representing a dramatic improvement from only 41% in 2014 (Stenehjem, E. A. *et al.*, 2023). This substantial increase reflects the success of coordinated national efforts including regulatory requirements, professional society guidelines, and quality improvement initiatives that have created both incentives and support for ASP implementation.

However, significant variation exists in the implementation of leading practices that extend beyond basic core elements. A comprehensive survey of 288 hospitals found considerable disparities in advanced stewardship activities. While 79.8% of hospitals measured antibiotic utilization and 88.2% measured Clostridioides difficile infections, only 34.9% implemented procedures to optimize diagnostic testing, and 37.1% measured adherence to facility-specific treatment guidelines(Stenehjem, E. A. *et al.*, 2023). These findings suggest that while basic structural elements are widely implemented, opportunities remain for optimization through advanced practices.

Small hospitals demonstrated consistently lower implementation rates across multiple leading practices, highlighting resource-dependent optimization challenges that require targeted support and innovative solutions. The disparities between large academic medical centers and smaller community hospitals underscore the need for tailored implementation strategies that account for resource constraints and organizational capacity differences.

Leading Practices for Advanced Optimization

The Joint Commission and Pew Charitable Trusts identified six leading practices that represent the next frontier for ASP optimization: facility-specific treatment guidelines, interactive prospective audit and feedback, diagnostic stewardship, antimicrobial use measurement, hospital-onset CDI measurement, and adherence measurement to treatment guidelines(Stenehjem, E. A. *et al.*, 2023). These practices build upon the foundation of core elements to enhance program effectiveness and clinical impact.

Interactive prospective audit and feedback, performed by 72.4% of surveyed hospitals, represents a critical optimization strategy with acceptance rates typically ranging from 66-91% (Loo, L. W. *et al.*, 2015; Newland, J. G. *et al.*, 2012). The effectiveness of this intervention depends significantly on implementation quality, with studies demonstrating that face-to-face or telephonic feedback achieves superior outcomes compared to written notes or electronic communications (Newland, J. G. *et al.*, 2012; Newland, J. G. *et al.*, 2012). The personal interaction between stewardship team members and prescribers facilitates education, builds relationships, and increases acceptance of recommendations.

Diagnostic stewardship, implemented by only 34.9% of hospitals, represents a significant optimization opportunity that addresses the critical relationship between diagnostic testing and antimicrobial prescribing (Stenehjem, E. A. *et al.*, 2023). This approach involves optimizing diagnostic testing procedures to ensure appropriate specimen collection, rapid pathogen identification, and timely susceptibility reporting to guide targeted therapy decisions. The integration of diagnostic stewardship with antimicrobial stewardship creates synergistic effects that enhance both diagnostic accuracy and therapeutic optimization.

The development of facility-specific treatment guidelines requires significant investment in clinical expertise and ongoing maintenance, but provides substantial benefits through standardized, evidence-based prescribing recommendations tailored to local resistance patterns and formulary considerations. These guidelines serve as decision support tools that promote appropriate prescribing while reducing practice variation and improving efficiency of care delivery.

ECONOMIC EVALUATION METHODS IN ASP RESEARCH

Cost Analysis Frameworks and Methodological Approaches

Economic evaluation of ASP optimization employs multiple methodological approaches, each providing distinct insights into program value and return on investment. Cost-effectiveness analysis represents the most commonly employed framework in the literature, systematically comparing costs and outcomes between ASP interventions and standard care practices. A systematic review encompassing 27 studies from 2015-2024 demonstrated that ASPs consistently contribute to substantial healthcare cost reductions, with antibiotic cost savings ranging from 2-95% relative cost reduction across diverse hospital

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settings and patient populations (Huser, J. *et al.*, 2025).

Cost-benefit analysis quantifies both costs and benefits in monetary terms, enabling direct financial comparisons and calculation of return on investment metrics. Studies employing this comprehensive approach consistently show favorable benefit-to-cost ratios, with some programs demonstrating $3-7 in savings for every dollar invested in ASP implementation and operation(Nathwani, D. *et al.*, 2019). However, a significant limitation in the current literature is the focus on operational costs rather than comprehensive implementation costs, which may lead to an underestimation of true program investments required for successful optimization.

Cost-utility analysis, though less commonly employed in ASP research, incorporates quality-adjusted life years (QALYs) to capture broader health impacts beyond immediate clinical outcomes. A notable study from Ethiopia demonstrated that laboratory-supported ASP dominated usual care with an incremental gain of 38.8 QALYs per 1,000 patients at lower expected cost (Gebretekle, G. B. *et al.*, 2021). This approach provides valuable insights into the broader health system value of stewardship interventions, though limited adoption in U.S. studies restricts comparative analysis.

The methodological heterogeneity observed across economic evaluations presents challenges for synthesis and comparison of results. Studies vary significantly in their cost perspectives (hospital, health system, or societal), time horizons (short-term operational costs versus long-term outcomes), and outcome measures (clinical, economic, or combined). This variability necessitates careful interpretation of economic findings and highlights the need for standardized evaluation approaches to facilitate meaningful comparison across studies and settings.

Economic Outcome Measures and Cost Drivers

Direct cost savings constitute the most frequently measured and consistently reported economic outcome in ASP evaluations. U.S. studies demonstrate average savings of $732 per patient, though the range varies considerably from $2.50 to $2,640 depending on patient population, intervention intensity, and hospital characteristics (Nathwani, D. *et al.*, 2019). The primary driver of these cost savings is a reduction in hospital length of stay, which accounts for 60-80% of total cost reductions in most analyses (The cost associated with the development of the antimicrobial). This finding reflects the substantial daily costs associated with hospital care and the significant impact of even modest length of stay reductions on overall healthcare expenditures.

Antibiotic expenditure reductions, while clinically important and frequently cited, typically represent a smaller proportion of total savings due to medication costs comprising only 1-2% of total hospital costs. However, the clinical importance of appropriate antibiotic use extends far beyond direct medication costs to encompass prevention of adverse outcomes, resistance development, and complications requiring additional interventions.

Cost avoidance through prevention of adverse outcomes represents a significant but often underestimated benefit that requires sophisticated analytical approaches to quantify accurately. Studies consistently demonstrate reduced rates of C. difficile infections, drug-related adverse events, and hospital readmissions following ASP implementation (Gordon, K. *et al.*, 2018; Loo, L. W. *et al.*, 2015). The economic value of preventing a single *C. difficile* infection ranges from $10,000-15,000, highlighting the substantial cost avoidance potential of effective stewardship programs.

However, the economic impact of ASPs is not uniformly positive across all studies and settings. A Qatar-based analysis showed increased overall costs despite reduced antibiotic use due to higher readmission rates in the optimized ASP group, illustrating the complexity of economic relationships and the importance of comprehensive outcome measurement(The cost associated with the development of the antimicrobial). This finding underscores the need for careful monitoring of unintended consequences and the importance of balancing multiple outcome measures in program evaluation.

Implementation and operational costs represent critical but inconsistently reported components of economic evaluation. Operational costs typically include personnel time for stewardship activities, information technology infrastructure investments, and educational materials and programs. The limited and variable reporting of these costs represents a significant gap in the current literature, making it difficult to assess true return on investment and develop accurate business cases for program implementation.

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CLINICAL OUTCOMES ASSOCIATED WITH ASP INTERVENTIONS

Length of Stay Reduction and Healthcare Efficiency

Hospital length of stay reduction represents the most consistently demonstrated and clinically significant benefit of ASP optimization, with 85% of studies showing statistically significant decreases(Nathwani, D. *et al.,* 2019). The magnitude of reduction varies considerably based on patient population, baseline practices, and intervention intensity, with reported decreases ranging from 1-5 days across different hospital settings. This variation reflects the heterogeneity of patient populations and the baseline efficiency of care delivery systems.

A comprehensive study of community-acquired pneumonia patients demonstrated mean length of stay reduction from 7.24 days to 5.52 days following ASP implementation, representing a clinically meaningful improvement of 1.72 days (Gordon, K., Stevens, R. *et al.,* 2018). Similarly, patients with acute bacterial skin and skin structure infections experienced median length of stay reduction from 12 to 7 days when ASP recommendations were accepted versus rejected (Loo, L. W. *et al.,* 2015). These substantial improvements reflect multiple mechanisms of enhanced care efficiency rather than premature discharge.

The underlying mechanisms driving length of stay reduction include earlier initiation of appropriate therapy, more rapid de-escalation to narrow-spectrum agents, timely intravenous-to-oral conversion, and reduced adverse events requiring extended monitoring and treatment (Gordon, K., Stevens, R. 2018; Newland, J. G. *et al.,* 2012). These improvements represent genuine enhancements in quality of care rather than cost-cutting measures that might compromise patient safety. The stability or reduction in readmission rates observed in most studies provides reassurance that length of stay reductions do not compromise patient outcomes.

The economic implications of length of stay reduction are substantial, given that hospital costs typically range from $1,500-3,000 per day, depending on acuity level and hospital characteristics. Even modest reductions in length of stay generate significant cost savings that often exceed the total operational costs of stewardship programs, creating compelling business cases for program investment and expansion.

Antimicrobial Use Optimization and Prescribing Quality

Reduction in overall antimicrobial consumption represents a primary clinical outcome that reflects both appropriate prescribing practices and resistance prevention efforts. Studies consistently demonstrate 2-32% decreases in total antibiotic use following ASP implementation, with variation reflecting baseline prescribing patterns and intervention intensity(Stewardship program linked to reduced antibiotic use, resistance in; Nathwani, D. *et al.,* 2019). A pediatric intensive care unit study showed particularly impressive results, with severe pneumonia patients experiencing significant reductions in both antibiotic consumption and antimicrobial resistance rates following comprehensive ASP implementation (Stewardship program linked to reduced antibiotic use, resistance in).

Improved antimicrobial appropriateness demonstrates consistent enhancement across multiple studies, with meta-analyses showing 1.9-4.2 fold increases in appropriate prescribing following stewardship interventions (Van Dort, B. A. *et al.,* 2022). This improvement encompasses multiple dimensions of prescribing quality, including appropriate agent selection based on suspected or confirmed pathogens, optimal dosing regimens considering patient-specific factors, evidence-based duration of therapy, and appropriate route of administration. The comprehensive nature of these improvements reflects the multifaceted approach of effective stewardship programs.

Targeted reductions in high-risk antibiotics show particularly strong and consistent results across studies. Research demonstrates significant decreases in fluoroquinolone use (-27%), anti-pseudomonal agents (-15.6%), and broad-spectrum antibiotics (-11.3%) (Newland, J. G. *et al.,* 2012). These reductions are clinically important given the strong association between these agents and both resistance development and C. difficile infections. The targeted approach allows for overall optimization while maintaining appropriate therapy for patients with documented indications for broad-spectrum coverage.

The sustainability of antimicrobial use varies across studies and settings, with some programs demonstrating persistent benefits years after implementation while others show gradual erosion of gains without continued intervention. This variation highlights the importance of ongoing

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stewardship activities and the challenges of sustaining behavioral change in complex healthcare environments.

Patient Safety Outcomes and Adverse Event Prevention

Healthcare-associated infection prevention demonstrates mixed but generally positive results across ASP studies. Multiple investigations report reduced C. difficile infection rates, though some show no significant change when baseline rates are already low due to robust infection control practices (Newland, J. G. *et al.*, 2012). The variability in results likely reflects differences in baseline infection control practices, patient populations, and the intensity of stewardship interventions targeting high-risk antibiotics.

The clinical significance of C. difficile infection prevention extends beyond direct patient outcomes to encompass substantial healthcare system benefits. Each prevented infection avoids direct treatment costs of $10,000-15,000 while reducing transmission risk and infection control requirements. The population-level benefits of reduced *C. difficile* incidence create positive externalities that extend beyond individual patient care.

Adverse drug event reduction shows consistent improvement across multiple studies, with research reporting decreased adverse event rates from 6.0% in pre-ASP periods to 4.4% following program implementation (Newland, J. G. *et al.*, 2012). These reductions encompass medication-related adverse effects, drug interactions, and inappropriate dosing complications. The clinical importance of adverse event prevention includes both direct patient safety benefits and economic advantages through reduced treatment costs and length of stay.

Antimicrobial resistance outcomes show variable but generally favorable trends, with some studies demonstrating reduced resistance rates for specific pathogens while others show stabilization rather than improvement. The complex relationship between antimicrobial use and resistance development requires longer follow-up periods to demonstrate significant impact, and the multifactorial nature of resistance makes attribution to stewardship interventions challenging.

Mortality outcomes show variable results across studies, with most demonstrating no significant change in overall mortality rates (Lindsay, P. J. *et al.*, 2019). This finding reflects the multifactorial nature of hospital mortality and the difficulty in attributing mortality changes directly to antimicrobial stewardship interventions. However, the absence of increased mortality provides important reassurance that ASP interventions do not compromise patient safety while achieving other clinical and economic benefits. The maintenance of safety outcomes while improving efficiency and reducing costs represents a favorable risk-benefit profile for stewardship interventions.

INTEGRATION OF HEALTH ECONOMICS AND CLINICAL RESULTS

5.1 Synergistic Relationships Between Economic and Clinical Benefits

The most successful ASP optimization strategies demonstrate strong alignment between economic and clinical benefits, creating powerful incentives for program investment and organizational commitment to sustainability. Length of stay reduction exemplifies this synergy most clearly, simultaneously improving patient outcomes through reduced exposure to hospital-associated risks while generating substantial cost savings through decreased resource utilization (Nathwani, D. *et al.*, 2019). This dual benefit creates a compelling value proposition that resonates with both clinical leadership focused on patient outcomes and administrative leadership focused on financial performance.

Antibiotic appropriateness improvements create similar beneficial alignment by reducing inappropriate prescribing costs while simultaneously improving treatment effectiveness and reducing the risk of resistance development. Studies consistently demonstrate that appropriate therapy selection not only reduces direct medication costs but also decreases complications requiring additional interventions and extended hospital stays (Gordon, K. *et al.*, 2018). The cascading effects of improved prescribing quality create multiplicative benefits that extend throughout the episode of care.

Prevention of adverse events generates compounding benefits through reduced treatment costs for complications while enhancing patient safety and satisfaction. The economic value of preventing healthcare-associated infections extends beyond direct treatment costs to include reduced length of stay, decreased transmission risk, and improved quality metrics (Nathwani, D.

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et al., 2019). These comprehensive benefits create strong alignment between clinical excellence and financial performance that supports sustained investment in stewardship activities.

Areas of Potential Tension and Conflict Resolution

Short-term versus long-term perspectives can create apparent conflicts between economic and clinical objectives that require careful navigation and stakeholder communication. Some ASP interventions may increase short-term costs through enhanced diagnostic testing, specialist consultation, or more expensive targeted therapies while generating long-term savings through improved outcomes and resistance prevention (The cost associated with the development of the antimicrobial). These temporal misalignments require sophisticated economic analysis and clear communication of long-term value propositions to organizational leadership.

Individual patient care versus population health optimization represents another area where careful balancing is required. Interventions that optimize population-level antibiotic use may occasionally conflict with individual patient preferences or perceived immediate clinical needs. This tension requires clear clinical protocols, effective provider communication, and robust mechanisms for addressing exceptional clinical circumstances (Gebretekle, G. B. *et al.*, 2021).. The resolution of these conflicts through evidence-based guidelines and clinical decision support systems helps maintain both individual care quality and population health benefits.

Resource allocation challenges emerge when clinical benefits require substantial upfront investments in personnel, technology, or infrastructure without immediate financial returns. The Qatar study illustrated this challenge, demonstrating clinical improvements in antibiotic use patterns accompanied by increased overall costs due to enhanced surveillance and intervention activities (The cost associated with the development of the antimicrobial). These scenarios require careful cost-benefit analysis and may benefit from phased implementation strategies that demonstrate value incrementally.

Optimization Strategies for Maximum Synergy

Comprehensive intervention bundles that address multiple aspects of antimicrobial use simultaneously generate the greatest synergy between economic and clinical benefits. Studies comparing bundled interventions with single-component programs consistently demonstrate superior outcomes across both clinical and economic dimensions (Okumura, L. M. *et al.*, 2016; Nathwani, D. 2019). The synergistic effects of combined interventions often exceed the sum of individual component benefits, creating efficient implementation strategies with maximized return on investment.

Data-driven targeting of high-impact clinical areas maximizes return on investment by focusing resources on interventions with demonstrated economic and clinical benefits. Prioritizing conditions with high antibiotic utilization, significant resistance problems, or substantial cost implications generates optimal alignment between clinical improvement and economic value (Nathwani, D. *et al.*, 2019; Stenehjem, E. A. *et al.*, 2023;). This strategic approach enables efficient resource utilization while achieving maximum clinical impact.

Sustainability planning ensures long-term maintenance of benefits by building economic incentives into program design and creating organizational systems that support continued improvement. Enhancement of pharmaceutical supply chain resilience through strategies such as supplier diversification, advanced forecasting, and public-private collaboration further supports the stability and sustainability of antimicrobial stewardship programs (Adewumi, G. *et al.*, 2024). Programs that demonstrate clear return on investment and integrate economic monitoring into routine operations are more likely to receive continued organizational support and resource allocation (Nathwani, D. *et al.*, 2019). Improving infectious disease outbreak detection through advanced technological tools such as AI and genomic surveillance is critical to reinforcing antimicrobial stewardship efforts and responding effectively to emerging threats (Ugwu, D. *et al.*, 2025). The integration of economic and clinical monitoring systems creates feedback loops that support continuous improvement and sustained organizational commitment.

BARRIERS AND ENABLERS TO ASP OPTIMIZATION

Resource and Capacity Constraints

Personnel limitations represent the most frequently cited and substantial barrier to comprehensive ASP optimization, particularly affecting smaller hospitals and rural healthcare facilities. The requirement for specialized expertise in infectious

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diseases and clinical pharmacy creates significant workforce challenges, with many facilities lacking adequate staffing to implement comprehensive programs beyond basic compliance requirements (Stenehjem, E. A. *et al.,* 2023; Pierce, J., & Stevens, M. P. 2021). The shortage of board-certified infectious diseases physicians and clinical pharmacists with advanced stewardship training creates systemic constraints that limit program development and sustainability.

Small hospitals demonstrate consistently lower implementation rates across multiple leading practices, with particularly significant differences in interactive prospective audit and feedback (61.0% versus larger hospitals), diagnostic testing optimization (25.2%), and comprehensive antibiotic utilization measurement (67.8%) (Stenehjem, E. A. *et al.,* 2023). These disparities reflect both personnel constraints and the challenges of achieving economies of scale in smaller institutions. The fixed costs associated with stewardship program development create proportionally greater burden for smaller facilities with limited patient volumes and financial resources. Access to affordable medications remains a significant barrier to broader treatment adherence, underscoring the need for systemic interventions to improve availability and affordability of essential medicines, including anticancer drugs (Temedie, E. B. *et al.,* 2024).

Technology infrastructure requirements present increasingly significant barriers as ASP optimization becomes more sophisticated and data-driven. Effective stewardship programs increasingly rely on advanced electronic health record systems, clinical decision support capabilities, and data analytics infrastructure that may be limited or absent in smaller or under-resourced facilities (Van Dort, B. A. *et al.,* 2022; Otaigbe, I. I. 2023). The integration of digital health technologies, while offering substantial potential benefits, requires significant upfront investment and ongoing technical support that may be challenging for resource-constrained institutions.

Organizational and Cultural Factors

Leadership commitment emerges as the most critical organizational enabler, with successful programs consistently demonstrating sustained administrative support, adequate resource allocation, and integration into broader organizational quality improvement initiatives (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs),12]. Hospitals with strong leadership engagement show significantly higher implementation rates of advanced practices and demonstrate better sustainability of program benefits over time. The visibility of leadership support through formal policies, resource allocation decisions, and performance metrics creates an organizational culture that supports stewardship activities.

Prescriber engagement and acceptance vary considerably across institutions and clinical specialties, representing both a critical success factor and potential implementation barrier. Acceptance rates for ASP recommendations range from 66-91% across studies, with variation influenced by communication methods, perceived expertise of stewardship teams, and integration of recommendations into established clinical workflows (Loo, L. W. *et al.,* 2015; Newland, J. G. *et al.,* 2012; Chung, G. W. *et al.,* 2013). Specialty-specific differences in acceptance rates reflect varying comfort levels with stewardship interventions and different clinical practice patterns that require tailored engagement strategies.

Multidisciplinary collaboration represents both a critical success factor and potential organizational challenge. Effective ASP optimization requires coordination among infectious diseases physicians, clinical pharmacists, microbiologists, infection preventionists, information technology specialists, and clinical leadership (Recommendations for Implementing Antimicrobial Stewardship; Lindsay, P. J. *et al.,* 2019). Institutions lacking established collaborative relationships or clear communication channels face significant implementation challenges. The development of effective team dynamics and communication processes requires ongoing investment in relationship building and process improvement. Efforts to incorporate eco-friendly manufacturing, distribution, and disposal practices in pharmaceuticals further intersect with stewardship goals, highlighting the importance of environmental sustainability alongside clinical and policy efforts (Misszento, J. A., & Amofah, A. D).

Regulatory and External Factors

Mandated requirements from regulatory bodies, including The Joint Commission and CMS have provided powerful enablers for basic ASP implementation while creating both opportunities and challenges for optimization beyond minimum compliance standards (Pogorzelska-Maziarz, M. *et*

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al., 2015; Antimicrobial Stewardship and Core Elements: Where to Start). The focus on structural elements rather than outcome measures may limit optimization incentives, as institutions may prioritize compliance demonstration over clinical effectiveness and continuous improvement.

Accreditation and quality reporting requirements create complex relationships between external accountability and internal optimization efforts. While external requirements provide implementation incentives and standardization benefits, the administrative burden of compliance activities may divert resources from clinical optimization activities (Stenehjem, E. A. *et al.*, 2023). The balance between external accountability and internal improvement requires careful management to maximize benefits while minimizing regulatory burden.

Health system integration and network membership offer significant opportunities for ASP optimization through shared resources, standardized protocols, and economies of scale. Health system membership correlates with higher implementation rates of leading practices, particularly benefiting smaller hospitals through access to specialized expertise and shared infrastructure (Stenehjem, E. A. *et al.*, 2023). The development of system-wide stewardship programs enables resource sharing and standardization while maintaining local adaptation to specific clinical contexts.

Emerging Solutions and Innovation Strategies

Telemedicine-based stewardship programs provide promising solutions for resource-constrained settings, with studies demonstrating high acceptance rates (85.6%) and significant cost savings in small community hospitals through remote specialist support (Pierce, J., & Stevens, M. P. 2021; Ross, J. K., & Chandorkar, A. A. 2024). The COVID-19 pandemic accelerated adoption of telehealth technologies and demonstrated the feasibility of remote stewardship consultation, creating new models for expertise sharing and resource optimization.

Digital health technologies, including artificial intelligence and advanced clinical decision support systems, show increasing promise for enhancing ASP effectiveness while reducing personnel requirements (Van Dort, B. A. *et al.*, 2022; AlGain, S. *et al.*, 2025). However, successful implementation requires careful attention to user acceptance, system integration, and ongoing validation of algorithmic recommendations. The integration of AI-driven tools into clinical workflows represents both an opportunity for enhanced efficiency and a challenge requiring significant change management and training investments.

Collaborative networks among hospitals enable resource sharing, expertise development, and standardized implementation approaches that can address individual institutional limitations. These models show particular promise for supporting smaller hospitals through partnerships with larger academic medical centers and regional health systems Ross,(Recommendations for Implementing Antimicrobial Stewardship; J. K., & Chandorkar, A. A. 2024). The development of hub-and-spoke models for stewardship expertise sharing creates opportunities for enhanced program effectiveness while addressing workforce shortage challenges.

RECOMMENDATIONS FOR FUTURE PRACTICE AND RESEARCH

Resource allocation decisions should prioritize interventions with demonstrated return on investment while focusing implementation efforts on high-volume, high-cost clinical conditions such as pneumonia, urinary tract infections, and skin and soft tissue infections (CDC; The Core Elements of Hospital Antibiotic Stewardship Programs),12]. The strategic concentration of stewardship efforts on clinical areas with the greatest antibiotic utilization and resistance challenges maximizes both clinical and economic benefits while creating efficient use of limited personnel and financial resources.

The development of standardized outcome measures represents a critical research priority, given the significant heterogeneity in evaluation approaches and metrics observed across current literature. Future studies should adopt uniform definitions for clinical outcomes, economic measures, and implementation processes to enable meaningful comparison and robust meta-analysis (Nathwani, D. *et al.*, 2019). Professional organizations should collaborate to establish consensus definitions and measurement standards that facilitate cumulative knowledge building and evidence synthesis.

Long-term impact assessment requires extended follow-up periods to capture delayed benefits and costs associated with resistance prevention, adverse event reduction, and sustainability of

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behavioral changes. Most current studies provide only short-term outcome data, limiting understanding of true program value and return on investment ((The cost associated with the development of the antimicrobial; Nathwani, D. *et al.*, 2019)). Future research should incorporate longer follow-up periods and sophisticated economic modeling to capture the full value proposition of stewardship interventions.

Comparative effectiveness research should directly compare different ASP strategies, intervention intensities, and implementation models to identify optimal approaches for different hospital settings and patient populations. The current literature lacks rigorous head-to-head comparisons between alternative stewardship strategies, limiting evidence-based decision making for program optimization (Van Dort, B. A. *et al.*, 2022; Nathwani, D. *et al.*, 2019).. Randomized controlled trials and natural experiments should be designed to provide definitive evidence on optimal implementation approaches.

Payment reform initiatives should align financial incentives with optimal antimicrobial use through value-based payment models that reward appropriate prescribing while penalizing unnecessary utilization. Policy makers should systematically consider antimicrobial stewardship metrics in quality reporting and payment determination systems to create sustainable incentives for program investment and optimization (Nathwani, D. *et al.*, 2019). The integration of stewardship performance measures into existing quality reporting frameworks would strengthen accountability while avoiding additional administrative burden.

Workforce development requires coordinated efforts among educational institutions, professional societies, and healthcare systems to expand the pipeline of infectious disease physicians and clinical pharmacists with specialized stewardship expertise. Collaborative initiatives should focus on developing specialized training programs, career pathways, and continuing education opportunities that build stewardship capacity across healthcare systems (Barlam, T. F. 2016). The establishment of fellowship programs and certification processes would enhance professional development while ensuring adequate expertise for program leadership.

CONCLUSION

The optimization of antimicrobial stewardship programs in U.S. hospitals represents a critical and highly effective strategy for addressing the dual challenges of antimicrobial resistance and healthcare cost containment. The comprehensive evidence examined in this review demonstrates that well-implemented ASPs provide substantial value through significant economic benefits averaging $732 per patient and consistent clinical improvements including reduced length of stay, decreased inappropriate antibiotic use, and enhanced patient safety. The alignment between economic and clinical benefits creates compelling value propositions that support sustained organizational investment and commitment to program optimization.

The remarkable evolution from basic ASP implementation to comprehensive optimization reflects both regulatory mandates and growing recognition of program value. The dramatic increase in Core Element implementation from 41% to 91% of hospitals between 2014 and 2020 demonstrates the feasibility of large-scale program adoption when supported by appropriate regulatory frameworks, professional guidelines, and organizational incentives. However, this foundational progress creates opportunities for continued advancement through the implementation of leading practices that extend beyond basic compliance requirements.

The imperative for action has never been clearer, with antimicrobial resistance continuing to threaten clinical effectiveness while healthcare cost pressures intensify. The foundation for success exists through established frameworks, demonstrated effectiveness, and growing organizational commitment. The challenge now lies in translating this evidence into sustained action across all U.S. healthcare settings, ensuring that the benefits of optimized antimicrobial stewardship reach all patients regardless of hospital size, geographic location, or resource constraints.

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