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Defending The Frontline: Infection Prevention And Stewardship Against Multidrug-Resistant Organisms

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Abstract

Background
Multidrug-resistant organisms (MDROs) pose a major threat to healthcare systems worldwide, causing increased morbidity, mortality, and economic costs, with rises in healthcare-associated (up to two-thirds) and community-acquired infections. Sentinel pathogens like MRSA, VRE, ESBL-Enterobacterales, CRE, and MDR Pseudomonas/Acinetobacter drive invasive infections, particularly in ICUs where mortality exceeds 35-40%.

Methods
This narrative review synthesizes evidence from global epidemiologic studies, systematic reviews, meta-analyses, and surveillance data on MDRO burden, transmission, infection prevention/control (IPC), antimicrobial stewardship (ASP), and emerging strategies across ICU, non-ICU, community, and special settings.

Results
MDROs show high colonization (10-60%), elevated mortality (20-50%), prolonged stays, and costs (e.g., $1.9 billion/year). Horizontal IPC (hand hygiene, bundles) and ASP (de-escalation, rapid diagnostics) reduce incidence by 15-50%; universal decolonization cuts MRSA by 37%; barriers persist in LMICs.

Conclusions
Strengthening integrated AID stewardship, One Health approaches, and novel diagnostics/therapeutics is essential to bolster MDRO defenses; future RCTs and implementation science are needed for resilient strategies.

Keywords Multidrug-resistant organisms, Infection prevention, Antimicrobial stewardship, Healthcare-associated infections, Carbapenem-resistant Enterobacterales, One Health approach.

Introduction

Multidrug-resistant organisms (MDROs) have emerged as a defining threat to modern healthcare systems, driving substantial global morbidity, mortality, and economic burden in both intensive care unit (ICU) and non-ICU settings through infections that are increasingly difficult to treat and prevent. Recent global estimates indicate a sharp rise in multidrug-resistant infections, with one large synthesis reporting approximately a 43% overall increase and disproportionate growth in healthcare-associated infections, which rose by about two-thirds, and community-acquired infections, which increased by nearly two-fifths, particularly in regions with high antibiotic misuse and fragile infection prevention infrastructures. Invasive MDRO infections such as bloodstream infections and ventilator-associated pneumonias are linked to prolonged hospital stays, higher rates of organ dysfunction, and excess mortality, with ICU mortality for patients with MDRO infections approaching or exceeding 35–40% in some cohorts, compared with substantially lower mortality for non-MDRO infections. Economic evaluations in high-income settings have shown that six major multidrug-resistant pathogens can together account for nearly 1.9 billion US dollars in attributable costs, more than 400,000 excess inpatient days, and over 10,000 deaths in a single year among older adult populations, underscoring the enormous direct and indirect costs associated with these organisms across levels of care. Importantly, emerging surveillance data suggest that the burden of MDROs is no longer confined to hospital wards; community reservoirs are expanding, and in some countries fewer than half of MDRO infections are now strictly hospital-acquired, blurring traditional epidemiologic boundaries and challenging classical control paradigms that focused primarily on acute-care facilities (Marino et al., 2025).

The clinical impact of MDROs is driven by a relatively small but critical group of sentinel pathogens that act as markers of system failure in infection prevention and antimicrobial stewardship, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL)–producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), and multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. MRSA remains one of the most frequently reported MDROs in both ICU and non-ICU environments, although some high-income countries have documented declines following aggressive infection control interventions, while ESBL-producing Escherichia coli and Klebsiella pneumoniae have surged in prevalence and are increasingly recognized as an equal or greater threat due to their ubiquity and limited oral treatment options. CRE, often carrying carbapenemase enzymes such as KPC, NDM, or OXA-48-like variants, represents a particularly urgent threat, with case-fatality rates that can exceed 50% in vulnerable populations and frequent association with clonal outbreaks in ICUs, hematology-oncology units, and long-term care facilities. In parallel, multidrug-resistant P. aeruginosa and A. baumannii have become emblematic ICU pathogens, dominating ventilator-associated pneumonia and bloodstream infection epidemiology in many regions, with several Southeast Asian and Mediterranean studies documenting high incidence, prolonged length of stay, and substantial attributable mortality and costs linked to these organisms. Beyond hospitals, community-associated MRSA lineages and ESBL-producing E. coli have firmly established themselves as frequent causes of skin and soft tissue infections, urinary tract infections, and occasionally invasive disease in otherwise healthy individuals, demonstrating the capacity of MDROs to disseminate into the community via person-to-person spread, food chains, animal reservoirs, and environmental contamination (Gould et al., 2014).

Framing MDROs as a “last line of defense” problem reflects the confluence of microbiological, clinical, and health-system dynamics in which therapeutic options, preventive measures, and operational resilience are simultaneously being eroded, leaving clinicians with progressively narrower margins for error in the management of serious infections. Many of the sentinel MDROs now exhibit resistance not only to first-line agents but also to traditional “reserve” drugs such as carbapenems, glycopeptides, and even polymyxins, so that success increasingly depends on newer or highly specialized agents that are expensive, toxic, or only marginally supported by clinical trial data, effectively transforming each treatment decision into a high-stakes choice at the edge of available pharmacologic defenses. At the same time, increased global connectivity, medical tourism, and inter-facility patient transfers facilitate rapid cross-border dissemination of high-risk clones and resistance determinants, enabling local lapses in stewardship or infection control to reverberate internationally and making it difficult for individual institutions to rely on isolated interventions without broader regional collaboration. The risk is

particularly acute in critical care and high-dependency units, where invasive devices, high antibiotic consumption, and complex care pathways create ideal conditions for MDRO selection and transmission, so that failures to prevent colonization or promptly identify carriers can rapidly translate into outbreaks with severe clinical and operational consequences, including unit closures and diversion of patients. Moreover, the expansion of MDROs into community and One Health reservoirs means that healthcare facilities increasingly confront a constant influx of colonized patients, eroding the protective boundary once assumed between community and hospital and reinforcing the notion that the system is defending its remaining lines of protection on multiple fronts simultaneously (Teerawattanapong et al., 2018).
Despite decades of guidance, major gaps persist in infection control and antimicrobial stewardship approaches for MDROs, creating a persistent implementation–effectiveness divide that undermines the impact of existing tools and best-practice recommendations. Evidence syntheses highlight that successful MDRO control typically relies on implementing multi-component bundles but many institutions, especially in low- and middle-income countries, struggle to operationalize such comprehensive packages due to deficits in staffing, infrastructure, isolation capacity, and information systems. Barriers reported across diverse settings include lack of trained infection prevention personnel, weak governance structures, inconsistent access to microbiology and rapid diagnostics, inadequate data to guide local policies, and limited IT support for real-time surveillance, all of which constrain the ability to detect emerging resistance, monitor adherence, and evaluate interventions. Antimicrobial stewardship programs face parallel challenges: insufficient protected time and training for pharmacists and infectious disease physicians, poor integration with infection prevention and diagnostic stewardship, and weak regulatory frameworks that fail to curb inappropriate prescribing in hospitals, outpatient clinics, and agriculture, particularly in regions where antibiotics remain over-the-counter or are viewed as substitutes for structural investments in sanitation and vaccination. Additionally, many national action plans against antimicrobial resistance remain under-funded and fragmented, with limited coordination between human health, veterinary, and environmental sectors, leading to patchy implementation of policies and missed opportunities to address MDRO emergence at its ecological roots, further reinforcing the perception that health systems are perpetually reacting at the last defensive layer rather than proactively shaping upstream determinants of resistance (Y. Geng et al., 2025).

Within this complex landscape, the objective of this review is to synthesize current evidence on the global burden and clinical impact of healthcare-associated and community-associated MDROs, with a specific emphasis on the challenges that constrain effective infection prevention, control, and antimicrobial stewardship across diverse health-system contexts. The review will examine epidemiologic trends and sentinel pathogens in both ICU and non-ICU settings, exploring how MDROs reshape patterns of morbidity, mortality, and resource use, and will integrate data from hospital-based and community-based studies to illustrate the increasingly porous boundary between these spheres. Particular attention will be given to implementation barriers that limit the effectiveness of existing infection prevention and control (IPC) measures as well as to gaps in antimicrobial and diagnostic stewardship that permit ongoing selection and silent dissemination of resistant strains. By mapping these challenges onto emerging frameworks such as integrated “AID” (Antimicrobial, Infection-prevention, Diagnostic) stewardship and One Health approaches, the review aims to identify practical leverage points for strengthening the last lines of defense at the bedside, ward, institutional, and policy levels, thereby informing future research priorities and guiding policymakers, clinicians, and infection control teams toward more resilient and context-appropriate strategies for MDRO containment(Abbas, 2024).

Definitions, Epidemiology, and Drivers

Multidrug-resistant organisms (MDROs) represent a critical threat in healthcare settings, with standardized definitions established by international consensus to guide surveillance and treatment. Multidrug-resistant (MDR) bacteria are defined as isolates showing acquired non-susceptibility to at least one agent in three or more antimicrobial categories, while extensively drug-resistant (XDR) isolates exhibit non-susceptibility to at least one agent in all but two or fewer categories, leaving only one or two susceptible classes, and pandrug-resistant (PDR) strains demonstrate non-susceptibility to all agents across all categories. These classifications, proposed by the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention, emphasize comprehensive

antimicrobial susceptibility testing across relevant categories to avoid selective reporting errors, ensuring accurate identification for clinical and epidemiological purposes. A key distinction exists between colonization and infection, which involves tissue invasion, inflammation, or positive cultures from sterile sites with attributable signs like fever or elevated white cell counts; colonization drives silent transmission, necessitating active surveillance screening upon admission, weekly checks in high-risk units like ICUs, and isolation precautions to prevent progression to infection in 20-50% of cases, as seen in ICU cohorts where 51% developed colonization leading to 28% infections. Misclassifying colonization as infection risks unnecessary antibiotics, fueling resistance, while under-detection hampers outbreak control; thus, standardized criteria like CDC definitions and high concordance (κ=0.902) between clinical and retrospective assessments underscore the need for robust microbiologic surveillance and isolation protocols in transmission hotspots (Magiorakos et al., 2012).
Gram-positive MDROs dominate certain infections, with methicillin-resistant Staphylococcus aureus (MRSA) prevalent in skin/soft tissue and bloodstream cases, vancomycin-resistant Enterococcus (VRE, mainly E. faecium with VanA phenotype) surging in ICUs due to selective antibiotic pressure, and penicillin-resistant Streptococcus pneumoniae rising globally (≥25% in regions like Romania, France), complicating community-acquired pneumonia empiric therapy. Gram-negative threats include extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales like Klebsiella pneumoniae and E. coli, carbapenem-resistant Enterobacterales (CRE), multidrug-resistant Pseudomonas aeruginosa (MDR-PA, often difficult-to-treat or DTR), and MDR Acinetobacter baumannii (CRAB), with 40-60% MDR rates in ICUs, biofilm-mediated persistence, and high mortality from ventilator-associated pneumonia or bloodstream infections. Emerging non-bacterial MDROs like Candida auris challenge antifungal therapy, showing near-universal fluconazole resistance (90-100%), 35% amphotericin B resistance, and 5-10% echinocandin resistance across clades, thriving in ICUs via skin colonization and medical devices, with limited breakpoints complicating management. These pathogens interconnect in networks, where primary colonization (e.g., VRE) heightens secondary risks like CAUTI from MDR-GNB, amplified by antibiotic exposures (Rivera & Boucher, 2011).

MDRO prevalence escalates in hospitals (4-20% infections), ICUs (20-40% HAIs, peaking post-COVID at 44/1000 days for some), and communities, with Gram-negatives like CRAB and KPC-CRE endemic in Southern Europe, Latin America, and Asia, while MRSA/VRE dominate high-income settings but surge globally via networks. High-income countries report lower ICU HAI rates (1-5%) with robust surveillance, versus LMICs' 10-30% due to understaffing, poor diagnostics, and HAI surveillance gaps, where MDROs like ESBL-E exceed 50% in some African/Asian ICUs. Patient transfers amplify spread: sparse, centralized networks show acute/post-acute hospitals as hubs, with 4,864 transfers linking 326 Florida facilities disseminating KPC-CRE, medical tourism seeding outbreaks, and regional flows prioritizing screening/inter-facility communication. Post-COVID rebounds (mortality 10.7/1000 ICU days) highlight vulnerabilities (Wang et al., 2025).
Antibiotic overuse/misuse exerts selective pressure, yielding 40-50% ESBL in livestock-human interfaces, zoonotic transfers, and stalled AMR progress. Inadequate IPC infrastructure (handwashing deficits, overcrowding, low HCW ratios), staffing shortages, and poor training enable persistence, especially LMICs lacking isolation/WASH. Environmental biofilms on catheters/ventilators harbor 80% colonized devices, shielding MDROs like P. aeruginosa/CRAB from disinfectants, while drains/devices amplify HAIs. LMIC socioeconomic gaps fuel 2-10x higher rates versus high-income nations (Jayatilleke, 2020).

Pathogenesis, Transmission, and Clinical Impact

Multi-drug resistant organisms (MDROs) pose a formidable challenge in healthcare due to their intricate mechanisms of resistance, efficient transmission dynamics, and profound clinical consequences, making them the last line of defense in infection control efforts. These pathogens evade standard treatments through genetic and biochemical adaptations while spreading rapidly in vulnerable hospital environments, leading to heightened morbidity, mortality, and economic strain (Bhat et al., 2023).
Multi-drug resistant organisms develop resistance primarily through genetic mechanisms such as spontaneous mutations and horizontal gene transfer, where mobile genetic elements like plasmids, transposons, and integrons facilitate the rapid dissemination of resistance genes across bacterial populations, enabling pathogens to acquire multiple resistance determinants simultaneously and evolve

into "superbugs" capable of withstanding a broad spectrum of antibiotics. Biochemically, these organisms employ strategies including the production of hydrolytic enzymes like β-lactamases and carbapenemases that degrade antibiotics before they reach their targets, modifications to essential cellular targets such as penicillin-binding proteins to prevent drug binding, active efflux pumps that expel antibiotics from the cell, and reduced outer membrane permeability via porin alterations, collectively rendering conventional therapies ineffective even when initially susceptible strains are exposed to sublethal antibiotic concentrations. Biofilm-associated resistance further exacerbates the problem in indwelling devices and hospital surfaces, where bacterial communities encased in a protective extracellular polymeric matrix exhibit up to 1,000-fold greater tolerance to antimicrobials due to slow growth rates, limited antibiotic penetration, and persistent cells that serve as reservoirs for recurrent infections, significantly complicating eradication efforts in clinical settings like catheters, ventilators, and prosthetics (Wachino, 2025).

Patient-to-patient transmission of MDROs occurs predominantly via the contaminated hands of healthcare workers and shared equipment, with studies showing that up to 70% of interactions involving colonized patients result in hand or glove contamination, underscoring the critical role of hand hygiene compliance in breaking this chain, as genetic typing via PFGE often links identical strains across patients touched by the same personnel during routine care. Environmental reservoirs amplify spread through persistent contamination of high-touch surfaces, sinks, water systems, and shared devices, where biofilms in drain traps harbor diverse MDROs including carbapenem-resistant Enterobacteriaceae, acting as long-term niches that aerosolize pathogens during use and contaminate air, hands, and patients even months after initial outbreaks. Asymptomatic colonization in high-risk populations such as ICU, transplant, and oncology patients serves as an amplification hub, with colonization rates exceeding 10-30% in these groups leading to progression to infection in up to 20-50% of cases, particularly under immunosuppression or invasive procedures, thereby sustaining nosocomial epidemics through silent reservoirs that evade routine screening (Mody et al., 2025).
Infections with MDROs drastically elevate mortality risks, with 30-day rates often reaching 20-45% compared to susceptible counterparts, driven by treatment failures and delays to effective therapy averaging 1-2 extra days, during which septic shock develops in nearly 40% of cases, as inappropriate empirical antibiotics allow unchecked pathogen proliferation. Prolonged hospitalization, extended ICU stays, and frequent readmissions compound the crisis, with MDRO cases associated with 1.3-fold longer lengths of stay exceeding 10-20 days and readmission rates up to 32-68% within a year, often due to recurrent infections or complications from limited therapeutic options. The economic burden is staggering, imposing 1.3-1.6-fold increases in direct costs from extended resource use, specialized antibiotics, and isolation measures totaling thousands per case in high-income settings and catastrophic expenditures in resource-limited environments where access to novel agents is scarce, amplifying global health disparities (Dicks et al., 2017).

Current Infection Prevention and Control Strategies

Current strategies for controlling multi-drug-resistant organisms (MDROs) in healthcare settings emphasize a multifaceted approach combining universal and pathogen-specific measures to mitigate transmission risks. These strategies form the cornerstone of infection prevention and control (IPC) programs, aiming to reduce both colonization and infection rates amid rising antimicrobial resistance challenges (Lemmen & Lewalter, 2018).
Horizontal strategies encompass broad, pathogen-agnostic interventions such as standard precautions, rigorous hand hygiene protocols, meticulous environmental cleaning, and device care bundles, which collectively target multiple transmission routes and have demonstrated superior cost-effectiveness and wider applicability across diverse healthcare-associated infections, including MDROs. In contrast, vertical strategies focus on specific MDROs through active surveillance screening, contact precautions for identified carriers, and targeted decolonization therapies, offering precision in high-prevalence scenarios but often limited by resource intensity, incomplete eradication success, and potential for fostering resistance or overlooking non-targeted pathogens. Evidence from systematic reviews and meta-analyses supports horizontal approaches for their sustained reductions in MDRO incidence due to higher compliance feasibility and broader impact, while vertical methods excel in outbreak yet face limitations like screening variability, isolation-related errors, and lack of definitive proof for preventing

all transmissions, prompting recommendations for hybrid models tailored to local epidemiology (McDonald, 2013).

Core IPC components integrate hand hygiene programs which have consistently correlated with MDRO reductions, alongside contact precautions involving single-room placement or cohorting of colonized patients and mandatory personal protective equipment (PPE) use to interrupt direct and indirect transmission. Device-associated prevention bundles for central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), and ventilator-associated pneumonia (VAP) further bolster these efforts by standardizing insertion, maintenance, and removal practices, yielding significant declines in MDRO-linked incidences, such as CLABSI rates dropping from 7.4 to 4.78 per 1000 device-days post-implementation. Multimodal hand hygiene initiatives, achieving compliance increases via WHO strategies, outperform isolated measures, with studies showing 6-14% HAI reductions per 10% compliance gain, while bundles and precautions demonstrate additive effects in ICUs, though sustained adherence remains challenged by workload and behavioral factors (Boyce, 2024).

Environmental hygiene relies on systematic cleaning and disinfection of high-touch surfaces, monitored via fluorescent markers or ATP bioluminescence to ensure thoroughness, complemented by engineering controls addressing water systems, HVAC filtration, and sink designs to curb MDRO reservoirs like biofilms in drains that propel aerosols up to 1 meter. Advanced no-touch technologies, including UV-C irradiation and hydrogen peroxide vapor (HPV), augment manual efforts by achieving near-complete log reductions in surface contaminants post-terminal cleaning, with randomized trials reporting HAI declines and MDRO acquisition drops, particularly for Clostridium difficile, VRE, and Gram-negatives. Sink redesign mitigates splash contamination, while HVAC optimizations reduce airborne dissemination; evidence underscores these as vital in endemic settings, though integration with horizontal IPC maximizes efficacy amid challenges like implementation costs and operator dependency (Huttner & Harbarth, 2015).

Active surveillance cultures target high-risk patients (e.g., prior MDRO carriers, ICU admissions) via nares, groin, and rectal swabs processed by culture or PCR for timely MDRO detection, enabling prompt isolation; decolonization employs daily chlorhexidine gluconate (CHG) baths and intranasal mupirocin, achieving ~15% per-application MRSA clearance but grappling with emerging resistance, high costs, and adherence issues. Isolation via contact precautions in single rooms or cohorts yields mixed outcomes yet incurs unintended consequences like psychological distress, increased medical errors, falls, and delayed care due to PPE barriers and stigma. Balancing benefits requires risk-stratified screening and universal decolonization in select units, with network meta-analyses favoring combined CHG-contact bundles over standalone vertical tactics for colonization control (Landelle et al., 2013).

Antimicrobial Stewardship

Antimicrobial stewardship programs (ASPs) serve as a critical parallel defense against multi-drug-resistant organisms (MDROs) by promoting the optimal selection, dose, duration, and route of antimicrobial therapy to improve patient outcomes, minimize toxicity, and curb resistance emergence. The primary objectives of ASPs include optimizing antimicrobial therapy through evidence-based prescribing, reducing unnecessary utilization to limit selective pressure on bacterial populations, minimizing the development of resistance by preserving the efficacy of existing agents, and decreasing adverse events such as Clostridioides difficile infections and other complications associated with prolonged exposure. Core components encompass strong leadership commitment from hospital executives to allocate resources including dedicated personnel and budgets, formation of multidisciplinary teams comprising infectious disease specialists, pharmacists, microbiologists, infection control experts, and nurses to oversee program implementation, formulary restriction strategies to prioritize narrow-spectrum agents and control broad-spectrum use via preauthorization, prospective audit and feedback mechanisms where teams review prescriptions post-initiation to recommend de-escalation or discontinuation, development and adherence to facility-specific guidelines derived from local antibiograms and national recommendations, and comprehensive education initiatives targeting prescribers, pharmacists, and frontline staff to foster a culture of prudent use. These elements, as outlined in foundational frameworks like those from the CDC and international adaptations, ensure coordinated interventions that have demonstrated reductions in antimicrobial consumption by up to 20-30% in various hospital settings without compromising clinical efficacy, while

also addressing system-level barriers such as high patient loads and resource constraints prevalent in diverse global contexts including low- and middle-income countries (LMICs) (Shrestha et al., 2023). Key stewardship interventions tailored for MDRO control emphasize de-escalation strategies, where empirical broad-spectrum therapy is narrowed to pathogen-specific agents based on culture results, antimicrobial susceptibility testing (AST), and clinical response indicators like fever resolution or biomarker trends, alongside short-course therapy protocols that limit treatment duration to the shortest effective period supported by evidence for specific infections such as uncomplicated bacteremia or pneumonia, thereby reducing cumulative exposure and resistance selection. Additional tactics include intravenous-to-oral (IV-to-PO) switches once hemodynamic stability is achieved and gastrointestinal function is restored, dose optimization using pharmacokinetic/pharmacodynamic (PK/PD) principles adjusted for patient factors like renal function or obesity, and therapeutic drug monitoring (TDM) for narrow-spectrum agents like vancomycin or beta-lactams to achieve target attainment and avoid subtherapeutic levels that foster resistance. Prospective audit and feedback involves real-time review of high-risk prescriptions with direct prescriber communication, preauthorization requirements for restricted agents like carbapenems or colistin in MDRO-endemic settings, and syndrome-specific pathways for common MDRO-prone conditions such as sepsis, ventilator-associated pneumonia, and intra-abdominal infections, which integrate rapid diagnostics, local resistance patterns, and predefined escalation/de-escalation criteria to expedite targeted therapy and avert inappropriate broad coverage. These interventions collectively form a multifaceted approach, with studies showing 20-50% reductions in MDRO isolation rates and shorter lengths of stay when bundled, particularly in high-pressure environments where empirical therapy overuse drives clonal expansion of pathogens like carbapenem-resistant Enterobacterales or vancomycin-resistant Enterococcus (S. Geng et al., 2025).

Rapid diagnostic tests (RDTs) such as multiplex PCR panels (e.g., BioFire FilmArray), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), and molecular resistance gene detection platforms dramatically shorten the time to targeted therapy by providing pathogen identification and preliminary resistance profiles within hours rather than days, directly impacting MDRO outcomes through earlier de-escalation from broad-spectrum agents, reduced empirical overtreatment, and lower mortality in bloodstream infections where delays exceed 1-2 hours. Antimicrobial susceptibility testing (AST) advancements, including local antibiograms updated quarterly with cumulative data from institutional isolates and real-time surveillance dashboards, empower stewardship teams to guide empirical choices and track resistance trends, enabling predictive modeling for outbreak-prone MDROs like extensively drug-resistant Acinetobacter baumannii. However, in LMICs, implementation faces substantial limitations including high upfront costs for RDT platforms exceeding equipment budgets, inadequate infrastructure such as unreliable power supply and cold chain logistics for reagents, shortages of skilled personnel for operation and interpretation, and training gaps that hinder integration into stewardship workflows, resulting in underutilization despite proven benefits in resource-rich settings like 20-30 hour reductions in time-to-optimal therapy. Despite these hurdles, hybrid models combining low-cost phenotypic AST with selective RDT deployment have shown feasibility, underscoring the need for subsidized access and capacity-building to bridge the diagnostic divide in MDRO control (Baum et al., 2025).

In high MDRO-pressure environments like intensive care units (ICUs), oncology, transplant, and burn units, stewardship grapples with complexities such as frequent empirical broad-spectrum use due to high colonization rates (up to 50% for MDROs), invasive devices amplifying infection risk, and immunocompromised hosts necessitating prolonged therapy, where interventions like daily audits and biomarker-guided discontinuation face resistance from prescribers prioritizing survival over stewardship metrics. Deployed military or austere settings exacerbate challenges with limited laboratory capacity restricting AST to basic cultures, inconsistent antibiotic supply chains leading to stockouts of last-line agents, transient patient populations complicating follow-up, and overcrowding that accelerates transmission, as evidenced by surveys revealing only 67% formal programs and minimal training among personnel. Pediatric, neonatal, and obstetric contexts present unique hurdles with scarce pharmacokinetic data for neonates leading to off-label dosing, complex risk-benefit balances in vulnerable populations where MDRO sepsis mortality exceeds 20%, limited syndrome-specific trials, and high empirical starter rates for early-onset sepsis, compounded by diagnostic limitations like blood

volume constraints for cultures. Addressing these demands tailored, context-specific adaptations such as mobile RDT units in austere environments, pediatric-focused pathways, and multidisciplinary training, yet persistent gaps in LMIC infrastructure, funding, and policy integration hinder scalable success (Ture et al., 2022).

Emerging and Advanced Strategies

Recent developments in antimicrobial agents have introduced novel compounds such as cefiderocol, ceftazidime/avibactam, and imipenem/relebactam, which demonstrate activity against multidrug-resistant organisms (MDROs) like carbapenem-resistant Enterobacterales and metallo-β-lactamase producers, necessitating integrated stewardship programs to optimize their use and prevent rapid resistance emergence through restricted access in hospitals with antimicrobial stewardship committees and mandatory surveillance reporting. Non-traditional approaches, including bacteriophage therapy, have shown promise in compassionate use cases for recalcitrant MDRO infections in transplant recipients and other high-risk patients, with reported safety and efficacy in small series, though randomized controlled trials are needed to confirm benefits and address phage resistance. Monoclonal antibodies targeting bacterial virulence factors, such as those against Pseudomonas aeruginosa toxins or Staphylococcus aureus clumping factor A, enhance opsonophagocytosis and neutralize pathogens without bactericidal activity, reducing selective pressure for resistance, while anti-virulence agents inhibit pathogenic mechanisms and microbiome-modulating therapies like fecal microbiota transplantation or probiotics aim to restore gut dysbiosis caused by MDRO colonization. Combination therapies, pairing antibiotics with adjuvants or multiple agents, suppress resistance evolution by requiring multiple simultaneous mutations and lowering bacterial load, as evidenced in treatments for tuberculosis and HIV analogs applied to MDROs, with examples like cefepime-aminoglycoside showing zero mortality in small cohorts. Optimized dosing strategies incorporating pharmacokinetic/pharmacodynamic modeling and therapeutic drug monitoring further minimize resistance risk in intensive care settings(S. Geng et al., 2025).

Universal decolonization using chlorhexidine or octenidine body washes in intensive care units has significantly reduced MDRO transmission and bloodstream infections in large cluster-randomized trials, outperforming targeted strategies in high-prevalence settings by preventing acquisition in non-colonized patients, though targeted octenidine washes showed mixed results in endemic MRSA environments. Combining body washes with nasal mupirocin decolonization enhances efficacy against gram-positive MDROs like MRSA, with body-surface decolonization broadly adopted for high-risk populations due to reductions in carriage and infections. Selective digestive decontamination (SDD), involving non-absorbable antibiotics in the oropharynx and gut, decreases catheter-related bacteremias and ventilator-associated pneumonia without significantly increasing MDRO colonization in long-term studies spanning decades, challenging concerns over resistance ecology through ecological analyses showing no rise in resistant flora despite rising admission rates. Controversies persist due to potential ecological shifts, but modified SDD protocols adapted to local flora effectively control outbreaks of MRSA or gram-negative MDROs in ICUs (Harris et al., 2015).

Whole-genome sequencing (WGS) enables precise outbreak investigation, transmission mapping, and source attribution for MDROs like vancomycin-resistant Enterococcus and ESBL-producing Enterobacterales, revealing hospital transmissions underestimated by traditional epidemiology in multi-site prospective studies across thousands of isolates. Real-time PCR surveillance of environmental and patient samples integrates with infection prevention dashboards for rapid gene detection, such as carbapenemases, facilitating early isolation and outbreak containment without reliance on culture delays. Predictive analytics using machine learning models, like random forest algorithms on ICU data, achieve high accuracy (AUC 0.83) in identifying high-risk patients for MDRO infections by prioritizing factors such as catheterization, ventilation, and prior antibiotics, with SHAP interpretability guiding interventions (Sherry et al., 2022).

The One Health approach highlights interconnections where antibiotic use in food animals drives higher MDRO prevalence, such as MDR E. coli in livestock exceeding human rates, disseminating via food chains, runoff, and waste to human populations. Wastewater surveillance serves as an early warning

system, detecting MDRO genes and organisms like carbapenem-resistant pathogens in hospital and community effluents through qPCR and digital PCR, reflecting clinical patterns and enabling population-level monitoring beyond clinical cases. Policy measures at national levels include restricting new antimicrobials to stewardship-certified hospitals with surveillance mandates, while global efforts emphasize harmonized One Health surveillance, antimicrobial stewardship, and infection control standards to curb dissemination (Al-Khalaifah et al., 2025).

Special Populations and Settings

Community-associated multi-drug resistant organisms (MDROs), particularly methicillin-resistant Staphylococcus aureus (CA-MRSA), have emerged as significant pathogens outside traditional healthcare environments, affecting otherwise healthy individuals and challenging conventional infection control paradigms. The epidemiology of CA-MRSA reveals a dramatic rise since the mid-1990s, with strains distinct from healthcare-associated MRSA in their genetic profiles, virulence factors like Panton-Valentine leukocidin (PVL), and clinical manifestations, which often present as skin and soft-tissue infections (SSTIs) but can progress to severe syndromes such as necrotizing pneumonia, bacteremia, and sepsis in community settings. Other CA-MDR pathogens, including vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E), are increasingly reported in community-onset infections, with notification rates for CA-MRSA in regions like Western Australia's Kimberley escalating from 250 to over 3,600 cases per 100,000 population between 2003 and 2023, disproportionately impacting younger Aboriginal populations and straining emergency services. Risk factors in seemingly healthy hosts extend beyond overt comorbidities to subtle immune deficiencies, such as undiagnosed HIV or transient neutropenia, and social determinants of health including overcrowding, poor housing, homelessness, low socioeconomic status, and limited healthcare access, which facilitate transmission through close contact and suboptimal hygiene. Community-level prevention strategies emphasize household hygiene practices like regular surface disinfection and laundry protocols, targeted decolonization with mupirocin nasal ointment and chlorhexidine baths for carriers, and setting-specific interventions in high-risk environments such as sports facilities (e.g., shared equipment cleaning in wrestling gyms), prisons (enhanced screening and cohorting), and long-term care transitions, where modeling shows decolonization can reduce MRSA prevalence by up to 24% regionally. These multifaceted approaches, including education on hand hygiene and avoiding antibiotic overuse, are crucial as CA-MDR pathogens spread rapidly among healthy populations, often evading standard prophylaxis due to unique resistance patterns like retained susceptibility to clindamycin or trimethoprim-sulfamethoxazole in CA-MRSA (David & Daum, 2010).

Long-term care facilities (LTCFs), including nursing homes, rehabilitation centers, and outpatient dialysis clinics, exhibit alarmingly high MDRO colonization prevalence driven by frequent healthcare contacts, indwelling devices, recurrent antibiotic exposure, and patient sharing with acute care hospitals, positioning these settings as reservoirs for pathogens like MRSA, VRE, carbapenem-resistant Enterobacteriaceae (CRE), and multidrug-resistant Acinetobacter. Studies confirm that recent nursing home residency independently predicts MDRO carriage upon hospital readmission, with over 57% of recently admitted residents acquiring new colonization during stays, exacerbated by shared environments and limited resources. Adapted infection prevention and control (IPC) models for nursing homes incorporate core elements like dedicated infection preventionists with at least 20 weekly IPC hours, quality assurance performance improvement (QAPI) processes for surveillance, and universal decolonization protocols using chlorhexidine gluconate (CHG) bathing combined with nasal iodophor, which have reduced MDRO prevalence from 64% to 50% in collaborative programs spanning hospitals and LTCFs. Antimicrobial stewardship in these venues focuses on pharmacist-led reviews, restricting broad-spectrum agents like vancomycin in dialysis (where 30-40% of chronic hemodialysis patients receive antibiotics annually), and prospective audit-feedback to curb Clostridium difficile and MDRO infections, yielding substantial cost savings and mortality reductions. In ambulatory clinics and dialysis centers, bundled interventions including hand hygiene compliance, environmental cleaning with sporicidal agents, and minimizing invasive device use further mitigate transmission, as evidenced by multisociety guidelines prioritizing chlorhexidine bathing, active surveillance, and MDRO status communication across facilities (Cassone & Mody, 2015).

Surgical and transplant patients face elevated MDRO risks due to prolonged perioperative antibiotic prophylaxis, invasive procedures, and immunosuppression, with liver, heart, and lung recipients experiencing MDRO bloodstream infections (BSIs) in 31-57% of cases post-transplant, linked to donor-derived colonization, mechanical ventilation, and high-dose corticosteroids that impair neutrophil function and mucosal barriers. In surgical site infections (SSIs), MDROs emerge from endogenous flora amplified by prophylaxis overuse, with risk factors like low transthyretin levels, prior hospitalization, and device utilization mirroring community predictors but compounded by procedure complexity. Intensive care units (ICUs) report distinct MDRO epidemiology, dominated by Gram-negative pathogens like CRE and MDR Acinetobacter in southern Europe, where bundles integrating antimicrobial restriction, CHG daily bathing, contact precautions, and hand hygiene compliance achieve 15% reductions in overall MDRO rates, alongside universal decolonization cutting MRSA clinical cultures by 37%. Transplant-specific strategies include preoperative MDRO screening and targeted prophylaxis (e.g., vancomycin for known MRSA carriers), donor risk assessment, and stewardship to limit empirical carbapenems, as MDRO BSIs confer 15-82% crude mortality and graft failure risks. ICU bundles, such as the four-component model (antimicrobial use optimization, environmental cleaning, isolation, hygiene), prove most effective in adult settings, averting transmissions while addressing cocolonization common in device-heavy patients (Septimus & Schweizer, 2016).

Future Directions and Research Priorities in MDRO Control

High-quality randomized controlled trials evaluating comprehensive infection prevention and control (IPC) bundles, including isolation strategies, remain essential to establish evidence-based practices for multidrug-resistant organisms (MDROs) across diverse healthcare settings, particularly in long-term care facilities where current meta-analyses show inconsistent reductions in MRSA colonization despite multifaceted interventions like barrier precautions, decolonization, education, and environmental cleaning. These trials must prioritize rigorous methodological designs, such as clustered RCTs with concurrent controls, to address high risks of bias identified in prior studies, including small sample sizes, unadjusted confounders, and short intervention durations that limit generalizability; subgroup analyses indicate vertical strategies (active surveillance plus decolonization) may yield better MRSA reductions in smaller cohorts, but horizontal approaches like hand hygiene and performance improvement show null effects, underscoring the need for long-term (over 12 months) assessments incorporating administrative engagement, which correlates with success in all effective programs. Future studies should integrate cost-effectiveness analyses, patient-centered outcomes (e.g., adverse events from isolation like social stigma or reduced care time), and real-world adherence metrics, as compliance often wanes under resource constraints in low staff-to-resident ratios, while exploring adaptive bundles tailored to pathogen-specific transmission dynamics, such as contact precautions for CRE or VRE, to overcome current evidence gaps where pooled risk ratios hover near unity (e.g., RR 0.81 for long-term interventions) (Wong et al., 2022).

Implementation science frameworks, such as the Consolidated Framework for Implementation Research (CFIR), offer critical tools to bridge gaps in antimicrobial stewardship programs (ASPs) and IPC deployment in low- and middle-income countries (LMICs), where chronic resource deficits, inadequate infrastructure, and low adherence exacerbate MDRO burdens despite promising pharmacy-driven ASPs demonstrating audit-feedback efficacy. Research must dissect contextual barriers like leadership disengagement, supply chain disruptions, and cultural adaptations, employing pre-implementation feasibility assessments to generate sustainable, resource-maximizing interventions; for instance, multimodal IPC-ASPs in Latin American ICUs synergistically curbed CRE infections through interdisciplinary teams and senior commitment, yet scalability falters without national curricula or relicensing mandates for HCWs. Priorities include comparative effectiveness trials of tailored multimodal strategies (e.g., education, surveillance, stewardship) versus universal decolonization, incorporating CFIR domains to evaluate outcomes like mortality reduction (up to 36% with rapid diagnostics in bloodstream infections) and economic viability, while fostering cross-sectoral collaborations to embed IPC in broader health priorities like sepsis prevention and WASH in LMICs (Ojo et al., 2021).

The pipeline for novel diagnostics and therapeutics demands accelerated development and pragmatic evaluations, focusing on rapid tools like multiplex PCR, MALDI-TOF MS, and metagenomic next-

generation sequencing (mNGS) to enable prompt de-escalation and PK/PD-optimized dosing in critically ill patients, alongside non-antibiotic innovations such as bacteriophages, monoclonal antibodies, and bispecific engineering showing synergy in preclinical models against MDROs. Phase IV trials for agents like dalbavancin in high-risk populations (e.g., dialysis patients) and combinatorial therapies (phage-antibiotic hybrids) must assess clinical translation, resistance evolution, and cost-effectiveness, as current meta-analyses affirm mRDT-ASP bundles shorten hospital stays by 2.48 days and cut mortality by 36% in MDRO bloodstream infections. Longitudinal studies should validate dynamic TDM frameworks and bedside biomarkers (e.g., procalcitonin) for 5-7 day treatments, prioritizing MDR-GNB like CRAB, XDRPA, and Candida auris where few options exist, with RCTs needed on decolonization bundles (e.g., glycerin enemas plus lactobacillus for VRE/CRE) despite uncertain long-term efficacy (Fanelli et al., 2024).

Integrating One Health principles with digital health and behavioral sciences promises holistic MDRO frameworks by linking human-animal-environmental surveillance via interoperable ICT systems for real-time data fusion, genomic tracking (e.g., WGS for transmission chains), and behavioral nudges to curb misuse across sectors. Research agendas should pioneer One Digital Health models to forecast outbreaks via AI-driven R0 modeling (e.g., triggered by 3 cases/5 days), while trials test scalable environmental-behavioral interventions like fluorescent-guided cleaning (92% compliance boost) and PCR surveillance reducing nosocomial risks by 40%. Priorities encompass joint data governance for zoonotic-AMR hotspots, policy harmonization for cross-sectoral policies, and RCTs validating digital twins for ecosystem monitoring, addressing gaps where LMICs lag in IPC programs (S. Geng et al., 2025).
Shifting to sustainable, prevention-centric systems necessitates a paradigm from antibiotic reliance to "de-antibiotization," emphasizing IPC multimodality (surveillance, isolation, WGS), stewardship de-escalation, and non-pharmacological pillars like microbiome restoration and phage therapies to mitigate post-antibiotic crises. Visionary research must pioneer genetic engineering, regulatory-aligned combinatorials, and global stewardship with behavioral science for adherence, targeting resilient infrastructures where bundles halved MDRO rates in adult ICUs via antimicrobial optimization, cleaning, and hygiene. Long-term trials should quantify shifts via metrics like recolonization rates (high for MRSA at 86% within 90 days) and economic models proving IPC cost-savings, fostering universal protocols amid rising threats like C. auris reservoirs (S. Geng et al., 2025).

Conclusion

Multidrug-resistant organisms represent an existential threat to healthcare systems worldwide, eroding therapeutic options and overwhelming infection prevention efforts across ICU, community, and long-term care settings. While multicomponent bundles in IPC, antimicrobial stewardship, and rapid diagnostics have shown promise in reducing transmission and mortality, persistent barriers like resource limitations in LMICs, implementation gaps, and emerging community reservoirs demand urgent, context-adapted innovations. Prioritizing high-quality RCTs, One Health integration, novel therapeutics such as phages and monoclonal antibodies, and digital surveillance will fortify these last lines of defense, ensuring resilient strategies that safeguard patient outcomes and global health security.

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