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Infection Prevention Strategies In Neonatal Intensive Care Units

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Abstract

Background:
Healthcare-associated infections (HAIs) remain a major cause of morbidity and mortality in neonatal intensive care units (NICUs), particularly among preterm and very low birth weight infants. Immature immune systems, frequent invasive procedures, prolonged device use, and exposure to multidrug-resistant organisms increase susceptibility, especially in low- and middle-income countries where resource limitations further exacerbate infection risk.
Methods:
This narrative review synthesizes peer-reviewed literature published between 2010 and 2026 examining the epidemiology, pathophysiology, and prevention of HAIs in NICUs. Databases were reviewed for studies addressing hand hygiene, device-associated care bundles, environmental interventions, antimicrobial stewardship, surveillance systems, educational programs, and emerging technologies. Evidence from both high-income and resource-limited settings was included to capture global perspectives.
Results:
Bloodstream infections were identified as the most prevalent HAIs in NICUs, followed by ventilator-associated pneumonia and fungal infections. Multimodal prevention strategies, particularly central line and ventilator care bundles, were associated with 50–70% reductions in device-associated infections. Hand hygiene interventions improved compliance to over 80% and reduced infection rates by up to 50%. Surveillance, staff education, and antimicrobial stewardship programs further contributed to sustained improvements. Emerging innovations such as rapid diagnostics, artificial intelligence–based monitoring, probiotics, and antimicrobial coatings show promise but require further validation.
Conclusions:
Effective prevention of HAIs in NICUs requires integrated, evidence-based, and context-adapted

multimodal strategies. Strengthening policy support, implementation science, and equitable resource allocation is essential to sustain infection reductions and improve neonatal outcomes globally.

Keywords: NICU HAIs, CLABSI Prevention, VAP Bundles, Hand Hygiene, MDROs, Neonatal Sepsis, Surveillance Systems, Antimicrobial Stewardship, Parental Education, LMIC adaptations

Introduction

Neonatal intensive care units (NICUs) represent a critical frontline in pediatric healthcare, where the battle against healthcare-associated infections (HAIs) profoundly influences patient survival and long-term outcomes. This introduction explores the epidemiology, significance, review objectives, and historical evolution of infection prevention strategies in NICUs, highlighting the persistent challenges and advancements in safeguarding vulnerable neonates (Lloyd et al., 2022).
Healthcare-associated infections in NICUs constitute a major global health concern, with reported incidence rates ranging from 6% to 40% of admissions, particularly affecting very low birth weight (VLBW) infants at rates 2- to 5-fold higher than term neonates, and global estimates often cited between 10-25% in high-risk settings. Bloodstream infections dominate as the most common HAI type, accounting for 45-73% of cases, followed by pneumonia and meningitis, with very low birth weight infants experiencing prevalence up to 30% in resource-limited neonatal units. Mortality attributable to these HAIs varies widely from 10-30%, with studies reporting 25-29% fatality in infected cohorts compared to overall NICU rates of 5-17%, exacerbated in low- and middle-income countries where HAIs contribute to one-third of neonatal deaths annually (Lloyd et al., 2022).

Premature infants in NICUs face heightened vulnerability due to immature immune systems, prolonged invasive device use, and frequent invasive procedures, amplifying HAI risks and leading to severe complications like sepsis, neurodevelopmental impairment, and extended hospital stays. The economic burden is staggering, with HAIs imposing direct costs of $28-147 billion annually in acute-care settings, including excess pharmaceutical expenses ($1,000+ per case), prolonged NICU stays, and long-term societal costs for preterm survivors encompassing special education and rehabilitation, where hospital inpatient care accounts for 92% of incremental expenses. These infections not only elevate mortality but also strain healthcare systems, particularly in low-resource environments, underscoring the urgent need for robust prevention to mitigate both clinical and financial repercussions (Johnson et al., 2025).
This review synthesizes evidence from 2010 to 2026 on infection prevention strategies in NICUs, focusing on epidemiological trends, risk factors, bundle implementations, and emerging interventions to guide evidence-based practices amid evolving pathogen resistance and technological advancements. By compiling data from global studies, including those in low- and middle-income countries where HAIs rates reach 22-40%, it aims to identify effective multimodal strategies like care bundles that have achieved up to 60% reductions in central line-associated bloodstream infections (CLABSIs). The scope encompasses prospective surveillance, economic analyses, and historical shifts, excluding non-peer-reviewed reports to ensure rigorous, actionable insights for clinical and policy applications (Dramowski et al., 2022).

Infection prevention in NICUs has progressed from rudimentary hygiene practices in the mid-20th century, emphasizing basic handwashing and isolation, to sophisticated multimodal bundles introduced around 2001 by the Institute for Healthcare Improvement, incorporating maximal barrier precautions, skin antisepsis, and daily catheter assessments. Early reports from the 1960s-1990s highlighted UTI and BSI rates in premature infants at 4-25%, prompting stricter guidelines like alcohol-based sanitizers, antibiotic stewardship, and device safety protocols by the 2000s, which correlated with declining DA-HAI rates from 4.9 to lower incidences per 1,000 patient-days. By the 2010s-2020s, comprehensive unit-based safety programs (CUSP) and WHO core components have driven 13-60% HAI reductions, evolving into resource-adapted bundles for low-income settings targeting environmental cleaning and self-inflating bag decontamination (Molina García et al., 2022).

Background: NICU HAI Epidemiology and Pathophysiology

Healthcare-associated infections (HAIs) represent a critical challenge in neonatal intensive care units (NICUs), where vulnerable preterm and low-birth-weight infants face heightened risks due to immature immune systems and frequent invasive interventions. Bloodstream infections (BSIs) dominate as the most prevalent HAI type, accounting for approximately 50% of cases, often linked to central lines or peripherally inserted central catheters, while ventilator-associated pneumonias and urinary tract infections (UTIs) follow as significant contributors, comprising 25% and 10-15% respectively in various cohorts; these patterns persist across global surveillance data, with BSIs frequently leading to prolonged hospitalization and elevated mortality rates exceeding 20% in affected very low birth weight (VLBW) infants. Predominant pathogens include coagulase-negative staphylococci (CoNS) responsible for 40-48% of late-onset sepsis episodes due to their skin commensal nature and affinity for catheter biofilms, alongside Gram-negative bacilli such as Klebsiella species, Escherichia coli, and Pseudomonas aeruginosa contributing 20-25% of infections, often manifesting as fulminant sepsis with case-fatality rates up to 56% for Pseudomonas; fungal pathogens like Candida species add another 10-18%, particularly in prolonged device use scenarios (Sass & Karlowicz, 2018).

Prematurity emerges as a cornerstone risk factor, with extremely low birth weight (<1000g) infants exhibiting late-onset sepsis rates as high as 36-60%, driven by underdeveloped skin barriers, reduced neutrophil function, and prolonged mechanical ventilation needs that amplify exposure to hospital flora. Invasive devices exacerbate vulnerability: central venous catheters (CVCs) and peripherally inserted central catheters (PICCs) correlate with central line-associated BSIs (CLABSIs) at rates of 1-6 per 1000 catheter-days in level III NICUs, while endotracheal tubes foster ventilator-associated pneumonia through biofilm formation and microaspiration, and urinary catheters heighten UTI incidence despite infrequent use in neonates. Suboptimal staffing ratios further compound risks, as nurse-to-patient ratios exceeding 1:2-4 associate with 20-50% higher HAI odds via lapses in hand hygiene compliance (often <60%) and delayed device maintenance; additional contributors include total parenteral nutrition, prolonged antibiotic exposure promoting dysbiosis, and small for gestational age status, collectively inflating HAI prevalence to 18-30% in high-risk NICU populations (Liu et al., 2020).

Transmission dynamics in NICUs adhere to the classic chain of infection model wherein CoNS and Gram-negatives colonize skin, equipment, or healthcare worker hands as primary reservoirs, exiting via contaminated fluids or air droplets before hand-mediated or device-facilitated transfer breaches neonatal mucosae or catheter hubs. Biofilms, polysaccharide matrices shielding pathogens like CoNS (up to 90% of CLABSIs) and multidrug-resistant organisms (MDROs) such as MRSA or carbapenem-resistant Acinetobacter baumannii, confer tolerance to antibiotics (1000-fold higher MICs) and host defenses, persisting on indwelling devices for weeks and enabling very late-onset sepsis (>120 days). MDRO outbreaks, fueled by selective antibiotic pressure and lapses in isolation, propagate via horizontal (hands, fomites) and vertical (maternal colonization) routes, with genomic studies revealing ST195 clones dominating NICU clusters; disrupting this chain demands bundled interventions like chlorhexidine gluconate baths reducing CLABSIs by 40-60% (Yu et al., 2025).

Key Pathogen Profiles

- CoNS (e.g., Staphylococcus epidermidis): 40-48% of BSIs, skin commensals thriving in biofilms on CVCs/PICCs.
- Gram-negatives (Klebsiella, E. coli, Pseudomonas): 20-25%, high virulence with endotoxin-mediated shock.
- Candida spp.: 10-18%, invasive candidiasis linked to CVCs and broad-spectrum antibiotics.
- Emerging MDROs: MRSA (endocarditis risk), VRE, CRAB, up to 30% resistance rates in low-resource NICUs.

Core Prevention Strategies

Hand hygiene stands as the cornerstone of infection prevention in Neonatal Intensive Care Units (NICUs), where preterm and critically ill neonates face heightened vulnerability to healthcare-associated infections (HAIs) due to immature immune systems, frequent invasive procedures, and prolonged hospitalizations. The World Health Organization's (WHO) "5 Moments for Hand Hygiene" provide a structured framework that has been adapted specifically for NICU settings to target high-risk interactions such as line manipulations and diaper changes. Multimodal interventions, including staff training, alcohol-based hand rub (ABHR) provision at point-of-care, compliance audits with real-time feedback, and integration of electronic monitoring systems, have consistently demonstrated improvements in adherence rates from baseline levels around 40% to over 80% post-intervention, correlating with HAI reductions of 20-50%. In one NICU study, hand hygiene compliance rose from 40% to 53% before patient contact and 39% to 59% after, alongside a drop in sepsis incidence from 13.4% to 11.3% per 1000 patient-days following a year-long program emphasizing problem-based education, minimal handling protocols, and ABHR accessibility. Challenges persist, such as high workload, skin irritation from frequent washing, and visitor compliance, but strategies like glove use post-hand hygiene for high-risk neonates, parental education sessions, and gamified audits have further enhanced outcomes, underscoring hand hygiene's role in curbing pathogen transmission like coagulase-negative staphylococci and Gram-negative bacilli (Amaan et al., 2022).

Device bundles represent evidence-based, multifaceted protocols targeting central line-associated bloodstream infections (CLABSIs) and ventilator-associated pneumonia (VAP) through standardized insertion, maintenance, and daily necessity assessments, achieving 50-70% declines in these HAIs across multiple NICU studies. For CLABSI prevention, bundles mandate maximal barrier precautions (sterile gown, gloves, full-body drape), chlorhexidine skin antisepsis (with gestational age considerations to avoid burns in extremely preterm infants), hub scrubbing before access, daily dressing inspections, and prompt removal of umbilical or peripherally inserted central catheters (PICCs) once enteral feeds commence, as prolonged parenteral nutrition elevates risk. A meta-analysis of 24 NICU studies reported a 60% CLABSI reduction post-bundle implementation, with common elements like skin preparation protocols and catheter need reviews proving pivotal; similarly, VAP bundles incorporate head-of-bed elevation (where feasible in neonates), subglottic suctioning endotracheal tubes, oral chlorhexidine (cautiously due to absorption risks), and sedation vacations to minimize ventilator days. Checklists enforced by dedicated teams, coupled with root-cause analyses for lapses, have sustained gains, as seen in reductions from 4.98 to 3.49 CLABSIs per 1000 device-days and VAP rates dropping from 36.4 to 11.91 per 1000 ventilator-days in phased implementations. These bundles extend to urinary catheters (CAUTIs) via aseptic insertion and closed drainage, emphasizing multidisciplinary audits to address neonatal-specific hurdles like small vessel fragility and equipment sharing (Smulders et al., 2013).

Environmental strategies in NICUs focus on unit design, rigorous disinfection, and water management to mitigate transmission, with single-patient rooms linked to 30% lower HAI rates compared to open pods by enabling cohorting and reducing cross-contamination. Hydrogen peroxide vapor (H2O2) and pulsed xenon ultraviolet (UV) systems supplement daily cleaning with ethanol or bleach solutions (avoiding phenols due to hyperbilirubinemia risk), targeting high-touch surfaces like incubators, keyboards, and sinks, where shadowed areas demand repositioning protocols for efficacy. UV-C devices have slashed airborne pathogens by 42% in ICUs, while steam disinfection eradicates persistent incubator contaminants without chemical residues; sink segregation (hand hygiene vs. waste) and point-of-use filters prevent Legionella or Pseudomonas outbreaks from biofilms. Private rooms facilitate deep cleans during unit closures, and enhanced terminal disinfection post-discharge curbs multidrug-resistant organisms (MDROs) like MRSA, with one NICU study showing reduced environmental contamination via daily PX-UV alongside standard wipes. Water management plans, including sterile bathing alternatives and plumbing surveillance, address neonatal vulnerabilities, proving especially vital in resource-limited settings prone to higher baseline transmission (Ishikawa et al., 2025).

Antimicrobial stewardship programs (ASPs) in NICUs curb resistance by promoting diagnostics-driven therapy, de-escalation within 48 hours of negative cultures, and avoidance of routine prophylaxis, integrating seamlessly with infection bundles to optimize outcomes without compromising sepsis treatment. Core elements include prospective audits with pharmacist-neonatologist feedback, biomarker-guided duration (e.g., procalcitonin or CRP to shorten empirical courses), local antibiogram-based protocols shunning broad-spectrum agents like cephalosporins initially, and 24/7 microbiology turnaround for targeted narrowing. Studies report 27% reductions in days of therapy (DOT) per 1000 patient-days via audit-feedback, with quasi-experimental designs showing sustained drops post-ASP launch, alongside fewer MDRO infections like carbapenem-resistant Enterobacteriaceae. De-escalation protocols, embedding stewardship in HAI bundles, link prevention to judicious use, vital for neonates facing high empirical antibiotic exposure; education on sampling techniques and protocol modifications based on resistance patterns further amplify impact, as evidenced by regulated primary bloodstream infection rates in outbreak settings (Abdelaal et al., 2025).

Surveillance, Education, and Multimodal Programs

Surveillance, education, and multimodal programs form critical pillars of infection prevention in Neonatal Intensive Care Units (NICUs), where vulnerable preterm and low birth weight infants face heightened risks of healthcare-associated infections (HAIs) such as central line-associated bloodstream infections (CLABSIs). Effective surveillance using standardized metrics like those from the National Healthcare Safety Network (NHSN) enables early detection of trends and outbreaks, while targeted education through simulations and programs like Comprehensive Unit-based Safety Program (CUSP) empowers staff to implement evidence-based practices, and multimodal interventions incorporating World Health Organization (WHO) components leverage nursing roles to sustain systemic improvements (O'Leary et al., 2022).

Surveillance in NICUs relies heavily on NHSN metrics, which provide standardized definitions and risk-adjusted rates for CLABSIs stratified by birth weight categories, allowing facilities to benchmark performance against national data and track device-associated infections like those linked to central venous catheters, umbilical lines, and mechanical ventilation. These metrics facilitate active surveillance of HAIs, including sepsis, urinary tract infections, and pneumonia, with protocols adapted for neonatal pathology that consider infections occurring more than two days post-admission as healthcare-associated, enabling comprehensive monitoring across all birth weight classes where low birth weight neonates exhibit the highest risk due to prolonged device use (Johnson et al., 2021).

Outbreak response protocols emphasize rapid multidisciplinary investigations upon detecting clusters, such as increased incidence above baseline or unusual pathogens, involving root cause analysis, enhanced screening, cohorting, hand hygiene audits, and sometimes unit closure to contain transmission, as evidenced by successful control of pathogens like Acinetobacter baumannii or carbapenemase-producing Enterobacteriaceae through intensified isolation and environmental sampling. Vigilance through daily assessments, feedback loops, and integration with antimicrobial stewardship has led to significant declines in CLABSI rates, underscoring surveillance's role in informing targeted interventions and preventing morbidity in this high-risk population (Tzialla et al., 2024).

Educational initiatives in NICUs, including simulation-based training and CUSP, address implementation science by fostering adherence to infection control practices amid high-stakes, low-volume procedures characteristic of neonatal care. Simulation programs, such as virtual reality scenarios for high-risk tasks like lipid solution handling, peripheral inserted central line management, and ventilator-associated skincare, significantly enhance nurses' knowledge and performance confidence, with experimental groups showing marked pre-post improvements compared to routine practice alone, promoting empathy, presence, and sustained behavioral change. CUSP, adapted from adult ICUs, involves multidisciplinary teams selecting interventions for hand hygiene, aseptic techniques, and IV preparation, resulting in improved compliance, safety culture, and reduced HAI risk in resource-limited settings like Indian NICUs, where monthly coaching and nurse empowerment led to ownership of practices and a 36-77% CLABSI reduction sustained over quarters. These approaches align with user interests in implementation science by emphasizing system change, feedback, and culture shifts, with high attendance at CUSP meetings correlating to better outcomes, making them scalable for nursing-led education in diverse NICU environments (Johnson et al., 2022).

Multimodal interventions, drawing from WHO's core components integrate bundles for CLABSI prevention, yielding up to 60% rate reductions through elements like checklists, maximal barriers, and daily line necessity reviews, with nursing roles pivotal in maintenance, antisepsis, and daily audits. In NICUs, these strategies adapt WHO's hand hygiene multimodal approach and expand to device care, where 92% of units employ insertion bundles but vary in maintenance (e.g., dressing changes only if soiled vs. scheduled), highlighting nursing's frontline role in hub scrubbing, tubing changes, and early removal to mitigate biofilm risks from frequent access like blood draws. Successful implementations, such as in Egyptian NICUs reducing CLABSIs via multidisciplinary WHO multimodal rollout with reinforced hygiene and collaboration, demonstrate nursing-driven sustainability, embedding practices into quality improvement for long-term HAI declines, especially in low-resource contexts where high nurse-patient ratios demand empowered roles (Johnson et al., 2022).

Innovations and Technologies

Innovations in infection prevention within Neonatal Intensive Care Units (NICUs) encompass rapid diagnostics, artificial intelligence (AI) monitoring, antimicrobial coatings, probiotics, and emerging phage therapy, addressing the high vulnerability of preterm neonates to healthcare-associated infections through targeted technological and biological interventions (Godbole et al., 2025b).

Rapid diagnostic technologies enable swift identification of pathogens in NICU settings, reducing empirical antibiotic use and transmission risks by providing results within hours rather than days from traditional blood cultures. Techniques such as real-time polymerase chain reaction (PCR) assays, including the LightCycler SeptiFast test, detect bacterial and fungal DNA responsible for up to 90% of bloodstream infections in term or near-term infants admitted for suspected sepsis, facilitating early isolation and targeted therapy. Procalcitonin (PCT) rapid measurements further aid in ruling out nosocomial infections in NICU newborns, with studies demonstrating high sensitivity for differentiating infected from non-infected cases, while PCR for 16S rRNA genes offers superior detection rates over blood cultures (85.3% vs. 68%) in clinically suspected neonatal sepsis cases at facilities like Qena University Hospitals. These tools minimize prolonged antibiotic exposure, a key risk factor for resistance and necrotizing enterocolitis (NEC), by confirming infections rapidly and guiding de-escalation protocols (Nagoba et al., 2025).

AI-driven monitoring systems revolutionize NICU infection prevention by analyzing real-time physiological data from sensors to predict healthcare-associated infections (HAIs) earlier than conventional methods, integrating machine learning for vital sign deviations and natural language processing for clinical notes. Wireless physiological sensor networks synchronized via timing protocols monitor blood pressure, pulse, and respiration in neonates, issuing early warnings that reduced ward infection rates by 7.39% in experimental evaluations compared to traditional approaches. AI excels in HAI prediction, real-time surveillance, and alert optimization, reducing alarm fatigue by up to 99.3% while enhancing detection through patient risk stratification and remote monitoring tailored to NICU vulnerabilities. These systems support dynamic interventions, lowering morbidity in high-risk preterm populations by preempting sepsis progression (Godbole et al., 2025a).

Antimicrobial coatings on NICU equipment, such as incubators and central venous catheters, inhibit bacterial adhesion and biofilm formation, critical for preventing device-related infections in vulnerable neonates. Low-fouling coatings and those incorporating neonate-safe antibacterial compounds, like silver or antibiotic-impregnated polymers (e.g., minocycline-rifampin), reduce microbial colonization on indwelling devices, with zinc oxide nanoparticle layers increasing surface roughness to deter pathogens while maintaining stability over extended periods. Despite challenges like incomplete eradication via steam disinfection alone, coatings complement rigorous protocols, potentially lowering HAI rates by disrupting biofilms on high-contact surfaces like incubator mattresses (Reboux et al., 2023).

Probiotic supplementation in preterm NICU infants modulates the gut microbiome, significantly reducing NEC incidence (risk ratio 0.54) and late-onset sepsis by promoting beneficial bacteria like Bifidobacterium and Lactobacillus species that inhibit pathogens and enhance immune responses. Multi-strain formulations such as FloraBABY or Biogaia demonstrate decreased NEC risk (adjusted OR 0.64) in infants under 29 weeks, accelerating microbiome maturation akin to vaginally born term babies and shortening mechanical ventilation duration by up to 10 days while reducing ventilator-associated pneumonia (VAP) odds by 72%. Prevalence of prophylactic use has risen, supported by meta-analyses of over 10,000 infants confirming efficacy against nosocomial infections without increasing adverse events in contemporary U.S. NICUs (Blanchetière et al., 2023).

Phage therapy emerges as a precise alternative for multidrug-resistant (MDR) infections in neonates, with bacteriophages targeting specific pathogens like Pseudomonas aeruginosa or E. coli K1 without disrupting commensal microbiota. In a case of severe bronchitis post-tracheostomy in a 3-month-old, consecutive phage cocktail (Pyobacteriophage) inhalation eradicated MDR P. aeruginosa, altering resistance profiles to enable effective antibiotics, leading to full recovery. Proof-of-concept studies using SHIME models show phages decontaminating environmental reservoirs like incubators from Staphylococcus capitis NRCS-A and preventing vertical transmission of meningitis-causing E. coli K1 in maternal gut simulations, highlighting potential for adjunctive use in NICU outbreak control (Morozova et al., 2024).

Challenges, Barriers, and Implementation

Infection prevention strategies in Neonatal Intensive Care Units (NICUs) face multifaceted challenges and barriers that hinder effective implementation, particularly compliance issues, gaps in low- and middle-income countries (LMICs), and economic/resource constraints, often analyzed through behavioral frameworks like the COM-B model (Capability, Opportunity, Motivation-Behavior). Compliance with core practices such as hand hygiene remains suboptimal in NICUs worldwide, with direct observation revealing rates below 80% for key moments like before and after patient contact, exacerbated by high workloads, time pressures during resuscitations, and forgetting amid clustered care tasks; in one low-resource NICU quality improvement project, hand-washing duration averaged only 40 seconds, drying was neglected in 83% of cases, and recontamination occurred in 77%, underscoring technique deficiencies and structural barriers like sink accessibility. The COM-B model elucidates these issues by highlighting capability gaps (e.g., knowledge of proper techniques and memory aids), opportunity limitations (e.g., physical availability of alcohol-based rubs or sinks, social norms in multidisciplinary teams), and motivation shortfalls (e.g., low risk perception or habit formation), as applied in neonatal IPC studies where nurses cited excessive workload and understaffing as primary detractors from hand hygiene during critical care episodes. In LMICs, these compliance challenges intensify due to higher patient-to-nurse ratios and inconsistent training, yet multimodal interventions like education, audits, and reminders have boosted adherence, though sustained behavioral change requires addressing psychological capability (e.g., belief in efficacy) and reflective motivation (e.g., feedback loops), as evidenced in theory-informed surveys revealing opportunity factors like glove use post-hygiene in high-risk preterm settings. Family involvement adds complexity, with parents often lacking tailored education on moments of hand hygiene, leading to transmission risks in family-centered care models prevalent in modern NICUs (Weser et al., 2024).

LMIC-specific gaps amplify global NICU challenges, manifesting in overcrowding, inadequate infrastructure, and heightened vulnerability to multidrug-resistant Gram-negative pathogens, where HAIs rates are at least double those in high-income countries (HICs), driven by suboptimal water sanitation, hygiene, and device reprocessing. Organizational barriers dominate under the CFIR framework, including fluctuating staffing (e.g., shortages of specialized IPC nurses), poor unit layouts impeding cohorting, and high acuity overwhelming frontline capabilities, as synthesized from 156 studies showing 'Inner Setting' determinants like work infrastructure most frequent across income levels. In LMIC neonatal units, human resource deficits (e.g., lack of IPC training for auxiliary staff) and physical constraints (e.g., multi-bed pods without barriers) facilitate outbreaks, compounded by delayed surveillance and cultural norms prioritizing volume over isolation; innovative local adaptations, such as cohorting via screening or kangaroo mother care for skin integrity, mitigate but do not resolve systemic gaps. COM-B applications in these contexts reveal motivation eroded by burnout and capability hindered by inconsistent guidelines, with studies in Zimbabwe and South Africa emphasizing empowerment through peer networks and urgency from rising infections as facilitators, yet persistent implementation lags due to absent dedicated IPC teams. HIC-LMIC commonalities persist, but LMICs report resource barriers twice as frequently, necessitating context-tailored bundles like chlorhexidine bathing where feasible, though evidence gaps remain for isolated efficacy amid bundled interventions (Nyantakyi et al., 2025).

Economic and resource barriers profoundly impede IPC rollout in NICUs, particularly in LMICs where budget shortfalls limit procurement of personal protective equipment (PPE), alcohol-based hand rubs, and cleaning agents, resulting in reuse of single-use items and environmental contamination fueling HAIs. Financial constraints manifest in inadequate allocations for IPC programs, procurement delays for disposables, and opportunity costs favoring curative over preventive care, with overcrowding (e.g., space shortages preventing distancing) and high nurse-patient ratios exacerbating transmission in resource-poor facilities caring for rising preterm admissions. In LMICs, these translate to elevated mortality from Gram-negative sepsis, where suboptimal WASH infrastructure and MDRO colonization burdens compound costs; studies highlight equipment deficiencies (e.g., unclean ventilators) and user issues like handrub-induced dermatitis as 'Available Resources' barriers under CFIR, more prevalent than in HICs. HICs face analogous issues in underfunded units, such as artificial nail-linked outbreaks or presenteeism, but LMICs innovate with low-cost emollients (e.g., sunflower oil massage reducing late-onset sepsis) or text reminders for hygiene, achieving mortality drops (e.g., 18% vs. 23.6% post-bundle), though scalability hinges on institutional buy-in. Overall, economic hurdles demand multimodal strategies like CUSP adaptations, prioritizing high-impact, low-cost elements (e.g., daily line necessity audits) to yield 60% CLABSI reductions, bridging resource divides via networks and local expertise (Paplawski, 2020).

Future Directions and Policy Recommendations

The evolving landscape of infection prevention in Neonatal Intensive Care Units (NICUs) demands a forward-looking research agenda that prioritizes rigorous randomized controlled trials (RCTs) evaluating emerging technologies, alongside large-scale longitudinal cohort studies to track long-term outcomes of healthcare-associated infections (HAIs) in neonates. RCTs are essential to assess interventions like advanced antimicrobial lock solutions, silver-impregnated catheters, and AI-driven early warning systems for sepsis prediction, which have shown preliminary reductions in catheter-related bloodstream infections (CRBSIs) but require high-quality, multicenter trials to establish causality and generalizability across diverse NICU settings. For instance, studies on vancomycin-heparin lock solutions and AgION-coated umbilical catheters have demonstrated significant CRBSI reductions in small cohorts (from 18.6% to 0% and 22% to 2%, respectively), yet broader RCTs are needed to optimize protocols for preterm infants under 1000g birth weight, where skin integrity and systemic absorption risks complicate implementation. Longitudinal cohorts, leveraging electronic health records (EHRs) and deep learning models, offer unprecedented opportunities to characterize neonatal immune trajectories, predict adverse outcomes like necrotizing enterocolitis (NEC) or bronchopulmonary dysplasia (BPD) from maternal factors such as anemia or medication exposures, and quantify HAI incidence densities over time (e.g., 13.1 per 1000 central venous catheter-days in some settings). These studies must incorporate real-world variables like multi-drug resistant organism (MDRO) colonization rates, which remain high in NICUs, and integrate multimodal data from physiological sensors and wireless networks to enable dynamic risk stratification, ultimately informing personalized prevention bundles (Reale et al., 2024).

Policy frameworks must evolve to mandate standardized infection prevention bundles while securing sustained funding for low- and middle-income countries (LMICs), where HAIs contribute disproportionately to neonatal mortality exceeding Sustainable Development Goal (SDG) targets of <12 deaths per 1000 live births. Mandatory bundles, drawing from WHO core components and Comprehensive Unit-based Safety Program (CUSP) adaptations, should encompass hand hygiene optimization, maximal sterile barrier precautions during line insertions, daily catheter necessity assessments, and environmental cleaning protocols tailored to NICU challenges like multi-bed pods and humidified equipment, achieving up to 60% CLABSI reductions in meta-analyses of 24 studies. In LMICs, policies must address overcrowding, suboptimal water sanitation hygiene (WASH), and device shortages by enforcing chlorhexidine gluconate (CHG) bathing for infants >1500g, kangaroo mother care to bolster immunity, and topical emollients like sunflower seed oil to enhance skin barrier function and cut late-onset sepsis risk. Funding priorities for LMICs should target scalable innovations such as low-cost sink decontamination with acetic acid, alcohol-based hand rubs over soap where water is scarce, and training for multimodal strategies including audits, feedback, and culture change, as evidenced by interventions reducing hospital-associated mortality from 23.6% to 18% and bloodstream infection rates significantly. Integration with SDGs requires policy alignment with global networks like the Healthy Newborn Network, embedding IPC in universal health coverage to avert infection-driven deaths through community chlorhexidine cord cleansing (reducing omphalitis) and facility-level probiotic supplementation for preterm infants, which lowers NEC and invasive infection risks (Dramowski et al., 2025).

Conclusion

Healthcare-associated infections in neonatal intensive care units represent a persistent and multifactorial threat to the survival and long-term outcomes of vulnerable neonates. The evidence reviewed in this paper underscores that no single intervention is sufficient to address the complex transmission dynamics, pathogen diversity, and host susceptibility inherent to NICU settings. Instead, sustained reductions in infection rates are achieved through comprehensive, multimodal prevention strategies that integrate rigorous hand hygiene, standardized device care bundles, robust environmental cleaning, antimicrobial stewardship, and continuous surveillance supported by staff education and safety culture initiatives.

Advances in technology offer promising adjuncts to traditional infection prevention approaches. However, their effectiveness depends on careful evaluation, neonatal-specific safety considerations, and thoughtful integration into existing care systems. Persistent barriers such as staffing shortages, compliance fatigue, infrastructure constraints, and limited resources continue to impede consistent implementation, emphasizing the need for context-sensitive, cost-effective solutions.

Future progress in NICU infection prevention will require strong policy commitment, equitable funding, and ongoing research to refine evidence-based bundles, validate emerging interventions through high-quality trials, and support implementation science approaches that translate knowledge into practice. By prioritizing coordinated, data-driven, and adaptable infection prevention strategies, healthcare systems can substantially reduce the burden of HAIs in NICUs, improving survival, neurodevelopmental outcomes, and quality of life for the most fragile patients.

References

1. Abdelaal, N. H., Aziz, N. H. R. A., Abdelaziz, A. M., Khalil, S. B. H., & Abdel-Latif, M. M. M. (2025). Clinical impact of an antibiotic stewardship program in a neonatal intensive care unit at a tertiary care hospital: A prospective quasi-experimental clinical study. Journal of Pharmaceutical Health Care and Sciences, 11, 81. https://doi.org/10.1186/s40780-024-00404-3
2. Amaan, A., Dey, S. K., & Zahan, K. (2022). Improvement of Hand Hygiene Practices among the Healthcare Workers in a Neonatal Intensive Care Unit. The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses Et De La Microbiologie Medicale, 2022, 7688778. https://doi.org/10.1155/2022/7688778
3. Blanchetière, A., Dolladille, C., Goyer, I., Join-Lambert, O., & Fazilleau, L. (2023). State of the Art of Probiotic Use in Neonatal Intensive Care Units in French-Speaking European Countries. Children, 10(12), 1889. https://doi.org/10.3390/children10121889
4. Dramowski, A., Aucamp, M., Beales, E., Bekker, A., Cotton, M. F., Fitzgerald, F. C., Labi, A.-K., Russell, N., Strysko, J., Whitelaw, A., & Coffin, S. (2022). Healthcare-Associated Infection Prevention Interventions for Neonates in Resource-Limited Settings. Frontiers in Pediatrics, 10. https://doi.org/10.3389/fped.2022.919403
5. Dramowski, A., Bolton, L., Fitzgerald, F., Bekker, A., & Partnership, on behalf of the N. A. (2025). Neonatal Sepsis in Low- and Middle-income Countries: Where Are We Now? The Pediatric Infectious Disease Journal, 44(6), e207. https://doi.org/10.1097/INF.0000000000004815
6. Godbole, A. A., Paras, null, Mehra, M., Banerjee, S., Roy, P., Deb, N., & Jagtap, S. (2025a). Enhancing Infection Control in ICUS Through AI: A Literature Review. Health Science Reports, 8(1), e70288. https://doi.org/10.1002/hsr2.70288
7. Godbole, A. A., Paras, Mehra, M., Banerjee, S., Roy, P., Deb, N., & Jagtap, S. (2025b). Enhancing Infection Control in ICUS Through AI: A Literature Review. Health Science Reports, 8(1), e70288. https://doi.org/10.1002/hsr2.70288
8. Ishikawa, K., Tsuchida, T., Ichiki, K., Ueda, T., Yamada, K., Iijima, K., Otani, N., & Nakajima, K. (2025). Efficacy of Enhanced Environmental Cleaning/Disinfection Using Pulsed Xenon Ultraviolet Light in Preventing Outbreaks of Methicillin-Resistant Staphylococcus aureus in Neonatal Intensive Care Units. Epidemiologia, 6(1), 12. https://doi.org/10.3390/epidemiologia6010012
9. Johnson, J., Akinboyo, I. C., & Schaffzin, J. K. (2021). Infection Prevention in the Neonatal Intensive Care Unit. Clinics in Perinatology, 48(2), 413–429. https://doi.org/10.1016/j.clp.2021.03.011
10. Johnson, J., Latif, A., Randive, B., Kadam, A., Rajput, U., Kinikar, A., Malshe, N., Lalwani, S., Parikh, T. B., Vaidya, U., Malwade, S., Agarkhedkar, S., Curless, M. S., Coffin, S. E., Smith, R. M., Westercamp, M., Colantuoni, E., Robinson, M. L., Mave, V., … Milstone, A. M. (2022). Implementation of the Comprehensive Unit-Based Safety Program to Improve Infection Prevention

and Control Practices in Four Neonatal Intensive Care Units in Pune, India. Frontiers in Pediatrics, 9. https://doi.org/10.3389/fped.2021.794637

11. Johnson, J., Malwade, S., Agarkhedkar, S., Randive, B., Rajput, U. C., Valvi, C., Kinikar, A., Parikh, T. B., Vaidya, U., Kadam, A., Ouddi, B., Smith, R. M., Westercamp, M., Mave, V., Schumacher, C., Coffin, S. E., Robinson, M. L., Gupta, A., Manabe, Y. C., & Milstone, A. M. (2025). Risk Factors for Health Care–Associated Bloodstream Infections in NICUs. JAMA Network Open, 8(3), e251821. https://doi.org/10.1001/jamanetworkopen.2025.1821
12. Liu, J., Sakarovitch, C., Sigurdson, K., Lee, H. C., & Profit, J. (2020). Disparities in Health Care–Associated Infections in the NICU. American Journal of Perinatology, 37(2), 166–173. https://doi.org/10.1055/s-0039-1688481
13. Lloyd, L. G., Bekker, A., Van Weissenbruch, M. M., & Dramowski, A. (2022). Healthcare-associated Infections in Very Low Birth–weight Infants in a South African Neonatal Unit: Disease Burden, Associated Factors and Short-term Outcomes. The Pediatric Infectious Disease Journal, 41(11), 911–916. https://doi.org/10.1097/INF.0000000000003666
14. Molina García, A., Cross, J. H., Fitchett, E. J. A., Kawaza, K., Okomo, U., Spotswood, N. E., Chiume, M., Ezeaka, V. C., Irimu, G., Salim, N., Molyneux, E. M., & Lawn, J. E. (2022). Infection prevention and care bundles addressing health care-associated infections in neonatal care in low-middle income countries: A scoping review. EClinicalMedicine, 44, 101259. https://doi.org/10.1016/j.eclinm.2021.101259
15. Morozova, V. V., Kozlova, Y. N., & Tikunova, N. V. (2024). Successful Use of Phage and Antibiotics Therapy for the Eradication of Two Bacterial Pathogens from the Respiratory Tract of an Infant. Methods in Molecular Biology (Clifton, N.J.), 2734, 237–243. https://doi.org/10.1007/978-1-0716-3523-0_15
16. Nagoba, B. S., Dhotre, S. V., Sonar, M. N., Mumbre, S. S., Gavkare, A. M., & Dhotre, P. S. (2025). Neonatal and pediatric sepsis: Microbiological insights, diagnostic innovations, and antimicrobial challenges. World Journal of Clinical Pediatrics, 14(4), 107974. https://doi.org/10.5409/wjcp.v14.i4.107974
17. Nyantakyi, E., Baenziger, J., Caci, L., Blum, K., Wolfensberger, A., Dramowski, A., Albers, B., Castro, M., Schultes, M.-T., & Clack, L. (2025). Investigating the implementation of infection prevention and control practices in neonatal care across country income levels: A systematic review. Antimicrobial Resistance and Infection Control, 14, 8. https://doi.org/10.1186/s13756-025-01516-7
18. O'Leary, E. N., Edwards, J. R., Srinivasan, A., Neuhauser, M. M., Soe, M. M., Webb, A. K., Edwards, E. M., Horbar, J. D., Soll, R. F., Roberts, J., Hicks, L. A., Wu, H., Zayack, D., Braun, D., Cali, S., Edwards, W. H., Flannery, D. D., Fleming-Dutra, K. E., Guzman-Cottrill, J. A., … Pollock, D. A. (2022). National Healthcare Safety Network 2018 Baseline Neonatal Standardized Antimicrobial Administration Ratios. Hospital Pediatrics, 12(2), 190–198. https://doi.org/10.1542/hpeds.2021-006253
19. Paplawski, S. (2020). Prevention of central line-associated bloodstream infections in the neonatal intensive care unit: A literature review. Journal of Neonatal Nursing, 26(3), 142–148. https://doi.org/10.1016/j.jnn.2020.01.013
20. Reale, C., Pistollato, A., Ceparano, M., Migliara, G., Marzuillo, C., Villari, P., & Baccolini, V. (2024). Interventions to prevent Neonatal Healthcare-associated Infection: A systematic review of RCT. European Journal of Public Health, 34(Supplement_3), ckae144.1901. https://doi.org/10.1093/eurpub/ckae144.1901
21. Reboux, M., Chavignon, M., Tristan, A., Plaisant, F., Laurent, F., & Butin, M. (2023). Disinfection of incubators in neonatal intensive care units: Impact of steam pulverization on bacterial colonization. Antimicrobial Resistance and Infection Control, 12, 18. https://doi.org/10.1186/s13756-023-01226-y
22. Sass, L., & Karlowicz, M. G. (2018). Healthcare-Associated Infections in the Neonate. Principles and Practice of Pediatric Infectious Diseases, 560-566.e3. https://doi.org/10.1016/B978-0-323-40181-4.00094-3
23. Smulders, C. A., van Gestel, J. P. J., & Bos, A. P. (2013). Are central line bundles and ventilator bundles effective in critically ill neonates and children? Intensive Care Medicine, 39(8), 1352–1358. https://doi.org/10.1007/s00134-013-2927-7

24. Tzialla, C., Berardi, A., Mondì, V., Diseases, on behalf of the S. G. of N. I., Tzialla, C., Berardi, A., Mondì, V., & Diseases, on behalf of the S. G. of N. I. (2024). Outbreaks in the Neonatal Intensive Care Unit: Description and Management. Tropical Medicine and Infectious Disease, 9(9). https://doi.org/10.3390/tropicalmed9090212
25. Weser, V0., Zhou, Y., Luo, X., Wu, Y., Kuang, Z., Cai, D., Wu, X., & Hong, X. (2025). Molecular, biofilm and motility characterization of Acinetobacter baumannii isolated from a neonatal intensive care unit at a children's hospital in South China. Frontiers in Cellular and Infection Microbiology, 15. https://doi.org/10.3389/fcimb.2025.1705282