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Neonatal Bloodstream Infections: A Narrative Review on Diagnostic and Therapeutic Challenges and Prospects in Developing Countries

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ABSTRACT

Background: Bloodstream infections (BSIs) pose a significant global health challenge, particularly in developing countries. Neonates are highly vulnerable due to underdeveloped immune systems and immature physical barriers, a risk amplified by poor hygiene and limited healthcare access in low- and middle-income countries (LMICs), leading to an estimated incidence of 5.5 cases per 1000 live births. This review aims to provide insight into the diagnostic and therapeutic challenges of neonatal BSIs in developing countries and to identify prospects for improving their diagnosis and treatment.

Methods: This review employed a nonsystematic narrative approach. A comprehensive literature search was conducted using multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and ScienceDirect. The search prioritized peer-reviewed articles, clinical trials, and systematic reviews published within the past decade (2015–2025).

Results: Diagnosis is severely hampered by nonspecific symptoms and limitations of conventional methods like blood culture, especially in resource-constrained settings lacking advanced molecular diagnostics. This often necessitates empirical antibiotic treatment, which intensifies antimicrobial resistance (AMR), complicates therapy, and leads to adverse outcomes. Promising solutions include rapid diagnostic technologies, artificial intelligence (AI), clinical decision support systems (CDSS), novel antimicrobial agents, alternative therapies like maternal immunization, and robust public health strategies, such as antimicrobial stewardship and stringent infection prevention.

Conclusion: Addressing this complex issue requires concerted global efforts, substantial investment in local laboratory infrastructure, enhanced healthcare provider training, and the development of context-appropriate, affordable solutions to improve neonatal outcomes in LMICs.

1 | Introduction

Neonates or infants in their early days have an underdeveloped immune system, which predisposes them to infections due to

their compromised immune system [1, 2]. Due to their thin and incompletely developed epidermal and mucosal layers, neonates and preterm infants are more susceptible to infections as this allows for easier penetration of pathogens [3]. Newborns

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who are extremely premature and have an extremely low birth weight are at a 4- to 10-fold higher risk of developing blood stream infections caused by species like *Candida* spp [4, 5]. Among the infections, bloodstream infections (BSIs) are considered the most critical because of their connection with higher morbidity and mortality rates [2]. Neonatal BSIs are categorized into early (infections that occur within the first 48 h of life [6]) and late onset (infection that occurs in a newborn after the first 72 h of life) [7]. Early onset neonatal BSIs are most commonly caused by vertical transmission of pathogens from the mother to the newborn during delivery, and the frequent pathogens responsible are Group B *Streptococcus* (GBS) and *Escherichia coli* [7]. Late onset, on the other hand, is typically caused by nosocomial infections, often from the baby's microbiota or from environmental sources, such as coagulase-negative staphylococci and *Klebsiella pneumoniae* [7].

The global child mortality rate has decreased substantially, with an estimated 12.7 million deaths in 1990 to 5.9 million deaths in 2015 [8]. However, progress in reducing neonatal mortality has been slower, with an estimated 2.7 million deaths of newborns occurring in 2015. Lawn et al. [9] also added that more than one-third of the total burden of child mortality worldwide is attributed to neonatal deaths. Infection is an important cause of infant mortality in low- and middle-income contexts, and BSI is one of the common causes [8, 10]. BSIs are a significant health concern in developing countries, with an estimated incidence rate of approximately 5.5 cases per 1000 live births (LBs) [11]. Approximately 2.6 million neonates die each year, with three-quarters of these deaths occurring within the first week of life. Disproportionately, almost all of these deaths (99%) occur in low- and middle-income countries (LMICs) or developing countries [12, 13].

Moreover, studies on neonatal infections in developing countries have shown that early-onset (EO) infections occur more frequently than late-onset infections. For instance, a study by Acheampong et al. [14] at the Korle- Bu Teaching Hospital (a tertiary hospital in Ghana) found that early-onset sepsis (EOS) was responsible for 67.6% of cases, compared to late-onset sepsis (LOS) at 32.4%. A recent systematic review has indicated that EOS among infants in developing countries is predominantly caused by Gram-negative microorganisms, with *Klebsiella* spp. (31.7%) and *Staphylococcus aureus* (17.5%) being the most frequently identified pathogens [15]. The significant rates of neonatal infections in developing countries, particularly BSIs with gastroenteritis, *Staphylococcus aureus* infections, omphalitis, and gram-negative rods, suggest that poor hygiene practices during delivery and labor, feeding, and postnatal care are major factors that significantly contribute to severe infections and mortality in neonates [16].

The clinical presentation of neonatal BSIs can vary depending on the type of organism involved, the location of the infection, and the severity of the illness [17]. A variety of pathogens are associated with neonatal BSIs, including viruses and fungi, but bacterial infections are the most common cause of neonatal BSIs [18]. While sepsis is a common complication of neonatal BSIs, the infection can also lead to other conditions, such as pneumonia, meningitis, osteomyelitis, intraventricular hemorrhage, necrotizing enterocolitis, and omphalitis [18, 19]. Neonatal

infections caused by gram-negative organisms may be more prevalent in developing countries and are associated with a higher incidence of antimicrobial resistance (AMR) [1, 20].

Timely identification of the indications and symptoms of BSIs in neonates, along with immediate and intensive treatment, can help prevent their negative consequences [18]. However, in developing countries, timely identification via diagnosis of infections is challenging. This further encourages empirical treatment of neonatal BSI and prevents specific treatment [14]. Moreover, nonspecific treatments also result in numerous consequences, such as drug side effects and drug resistant organisms, as studied elsewhere [21]. Therefore, this review aims to provide insight into the diagnostic and therapeutic challenges in developing countries and further provides prospects for improving the diagnosis and treatment of BSIs in neonates in these settings.

2 | Methodology

2.1 | Literature Search Strategy and Eligibility Criteria

This review employed a nonsystematic narrative approach, consistent with the methodologies of previously published reviews [22, 23]. A comprehensive literature search was conducted to identify studies addressing the diagnostic and therapeutic complexities of neonatal BSIs in developing countries. While the primary focus remained on LMICs, select studies from developed countries were included to provide a critical comparative analysis of the synthesized evidence. The search encompassed multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and ScienceDirect. To identify relevant literature, a combination of Medical Subject Headings (MeSH) terms and keywords was used, including “neonate,” “bloodstream infection,” “sepsis,” “diagnostics,” “antimicrobial treatment,” and “developing countries.” To ensure the incorporation of the most current clinical data and technological innovations, the search prioritized peer-reviewed articles, clinical trials, and systematic reviews published within the past decade (2015–2025). However, highly relevant foundational and seminal studies published before 2015 were also included to provide critical historical and clinical context.

2.2 | Study Selection and Synthesis

The literature search across PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar initially retrieved 579 records (Figure 1). After removing 277 duplicates, the remaining 302 unique studies were screened by title and abstract, resulting in the exclusion of 95 records. The full texts of the remaining 207 reports were then assessed for eligibility. At this stage, 59 papers were excluded because they focused solely on high-income settings ($n = 25$), lacked explicit diagnostic and/or therapeutic information ($n = 20$), or presented an ineligible document format ($n = 14$). Ultimately, 148 studies met all inclusion criteria and were selected for the final narrative synthesis. Data from these included articles were extracted to synthesize the diagnostic challenges, therapeutic hurdles, and

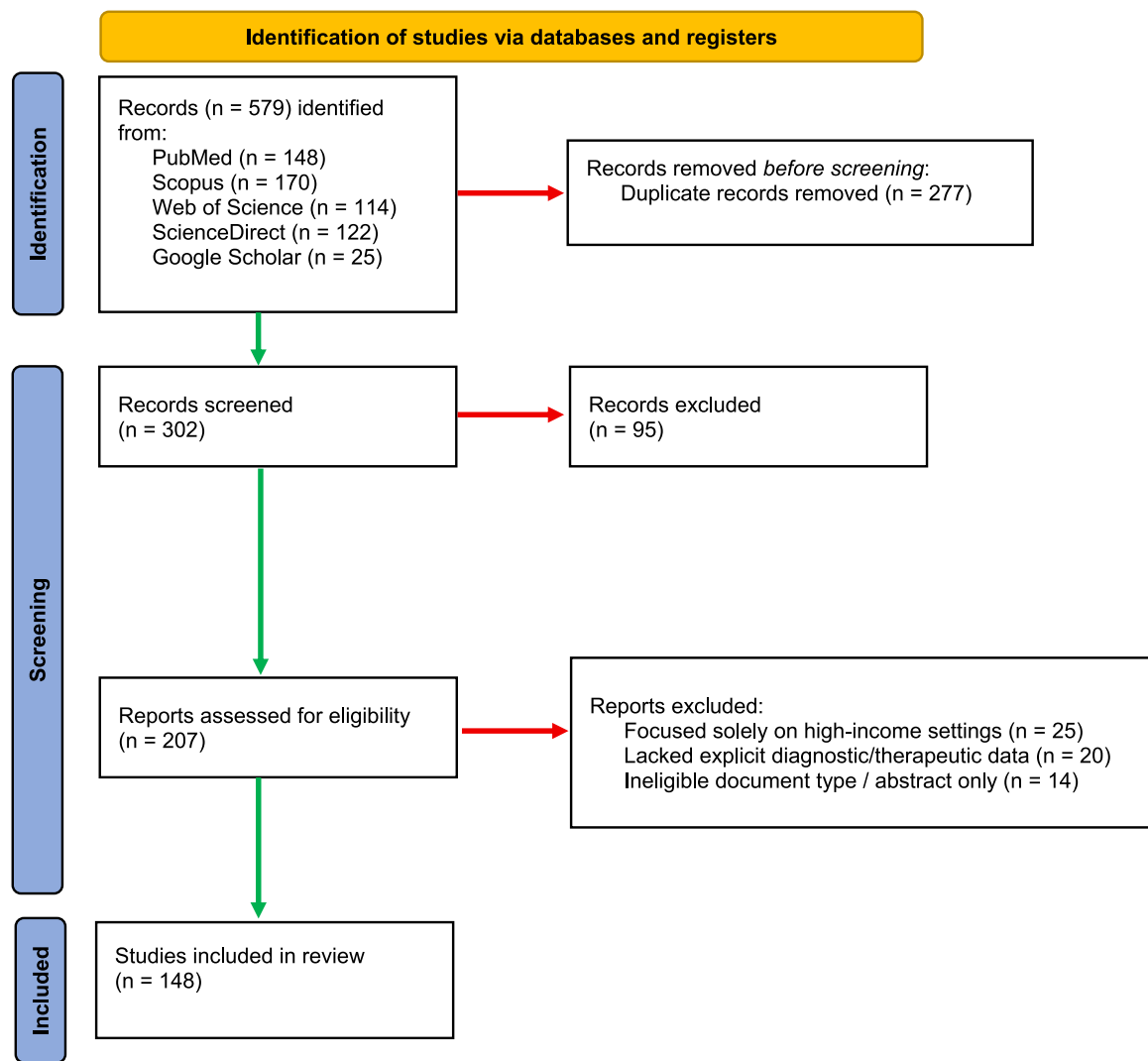


FIGURE 1 | The study selection process.

future prospects for managing neonatal BSIs, with the final findings organized and presented under thematic subsections to provide a clear overview of the current landscape in developing countries.

3 | Results and Discussion

3.1 | Clinical Significance of BSIs: The Neonatal Context

Neonatal BSIs are a significant clinical concern due to their potential to cause severe illness and death. There has been a reduction in the incidence of neonatal EO invasive infections in some developed countries due to the implementation of preventive measures such as universal screening of pregnant women for GBS colonization and administration of intrapartum antibiotics to GBS-positive women. For instance, in the United States, Puopolo et al. [24] saw a decrease in EO from 1.7 cases per 1000 LBs in 1990 to 0.23 cases per 1000 LBs in 2016. Similarly, in Sweden, Johansson Gudjónsdóttir et al. [25] saw a reduction in the incidence of neonatal EO invasive infections compared to a previous study in the same geographical location. Thus, from 1.4/1000 LB in 1997–2007 to 0.9/1000 LB in

2008–2017 [25]. However, developing countries still encounter higher neonatal deaths, which is of clinical significance.

Alongside the immunocompromised nature of neonates and the incompletely developed epidermal layer, procedures and equipment, such as catheters used in the hospital, disrupt epithelial barriers and promote infections [26]. Knowing the potential threat of these procedures limits the rate at which they are performed. However, these invasive procedures are performed on neonates as they are necessary to diagnose and treat medical conditions and improve medical outcomes [26]. Therefore, this limitation poses a major challenge to the clinical settings.

3.1.1 | Bacteria BSIs

To start with, BSI infections present a major challenge in the health sector as the discovery of bacteria that are not sensitive to most antibiotics keeps increasing. For instance, a study conducted by Turyasiima et al. [18] on neonatal omphalitis found that all bacterial isolates obtained from cord swabs demonstrated high levels of antibiotic resistance and low sensitivity to commonly used antibiotics for omphalitis treatment.

S. aureus, the most frequently identified bacteria, showed high resistance rates to ampicillin (87.5%), gentamicin (54.4%), and cloxacillin (34.4%). However, just half a decade ago, UNAS et al. [27] estimated that the resistance of *S. aureus* to ampicillin ranged from 40% to 100%, and the resistance to gentamicin was up to just 30%. This poses a significant threat as bacteria can use few years to optimize their resistance activities.

Moreover, the study of Turyasiima et al. [18] further showed that cefotaxime and imipenem had a low incidence of resistance, at 34.4% and 25%, respectively, indicating that these antibiotics could be used as an alternative to cloxacillin and gentamicin in the treatment of staphylococcal omphalitis [18]. However, with the rapid increase in the resistance profile of the bacteria, it is just a matter of time before these limited arsenals are also overcome by pathogens.

Furthermore, BSIs result in increased healthcare costs and may also result in long-term health consequences: Infants who survive neonatal BSIs may be at increased risk of long-term health consequences, such as developmental delays, cognitive deficits, chronic lung disease, and other organ damages [28, 29]. These infections can lead to chronic organ damage that may require ongoing medical management [29]. BSIs can further inflict neurological damage when bacteria enter the central nervous system (CNS), increasing the risk of later cognitive and physical disability [30].

3.1.2 | Fungal BSIs

The underdeveloped immune system of neonates exposes them to fungal BSIs, such as candidemia, aspergillosis, cryptococcosis, histoplasmosis, and pneumocystis pneumonia [26, 31]. Fungal infections, particularly invasive candidiasis, pose a challenge for definitive diagnosis, and even with appropriate treatment, there is a high risk of death or significant neurodevelopmental impairment [31]. Recent reports have shown a decrease in the prevalence of candidemia in developed countries, but the same cannot be said in developing countries due to the unavailability of effective surveillance data and large, multicentre studies [31, 32]. Fungal infections in neonates are alarming in the clinical settings. This is further supported by Warris et al. [33], as their study reported that, among 1395 reported episodes of candidemia across 23 hospitals in 10 European countries, 36.4% were reported in neonates, which is higher than in adults and children.

In the United States, as of 2005, a propensity analysis found that candidemia is linked to an average increase in hospitalization of 21 days and a 10% increase in mortality [34]. Furthermore, neonatal candidiasis has a mortality rate of 20%, and half of the infants who survive the infection experience severe neurodevelopmental impairment [35, 36]. These alarming data from developed countries that possess sophisticated tools further suggest the devastating effect neonatal BSIs have on developing countries that barely have similar clinical equipment. However, other invasive fungal infections, such as aspergillosis, histoplasmosis, pneumocystis pneumonia, and cryptococcosis, are uncommon in neonates [26], but are serious infections when they occur. For instance, invasive aspergillosis in neonates typically manifests as pulmonary or disseminated disease. However, it can also present in the CNS and gastrointestinal

(GI) tract. The symptoms and severity of invasive aspergillosis depend on the location and extent of the infection. Treatment may involve antifungal medications and, in some cases, surgery. Early diagnosis and treatment are crucial for improving outcomes in neonates with invasive aspergillosis [26]. Although fungal BSIs are more common in immunocompromised individuals, they can still affect healthy people without compromised immune systems, thus putting neonates in more danger.

3.1.3 | Viral Systemic Infections

Although this review primarily focuses on BSIs, viral systemic infections are retained here because they provide valuable clinical insights into the diagnostic workup of the febrile infant and account for significant neonatal morbidity. Neonatal viral infections may result from vertical transfer from the parent or from environmental sources. In addition to the risk factors responsible for neonatal BSIs, the innate cytokine response to viral infections in neonates can be insufficient or, on the other hand, excessive, which is linked to increased disease severity [37]. These viral infections include congenital cytomegalovirus (CMV) infection, congenital herpes simplex virus (HSV) infection, neonatal hepatitis B virus (HBV) infection, neonatal human immunodeficiency virus (HIV) infection, and neonatal enterovirus infection [38–42].

While more attention is drawn to bacteremia, systemic viral infection in neonates is significantly noteworthy. For instance, one-third of all cases of sensorineural hearing loss in early childhood in the United States are attributed to CMV [43]. Further, a survey conducted in the United States by Cannon [44] estimated that around 0.7% of all newborns, or roughly 30,000 infants, are born with CMV infection each year. Out of these, there are about 150 infant deaths, and over 5500 infants experience substantial neurodevelopmental deficits [45]. Further, Bennett and his team also found that 52% of all tested infants had a positive virus screen at least once during their birth hospitalization, identifying infants with a positive virus screen who had no or only minimal clinical symptoms [46].

Neonates are often affected differently and more severely by enteroviruses than older children [38]. Although the clinical symptoms of enterovirus infection are similar to those of bacterial sepsis, such as fever, poor feeding, lethargy, respiratory distress, and cardiovascular collapse, it can be difficult to differentiate between the two. Nevertheless, enterovirus infection can have severe, life-threatening complications, including hepatic necrosis with coagulopathy, meningoencephalitis, and myocarditis, which typically present during the first week of life [38].

Although rare, neonatal HSV is a devastating infection in newborns that can result in significant morbidity and mortality [47]. As of 2003, it was estimated that the rate of neonatal HSV disease occurrence in the United States is approximately 1 in 3200 deliveries, representing an estimated 1500 cases of neonatal HSV infection per year [48]. HSV can cause serious health problems, including brain damage, seizures, and developmental delays [42, 47].

Neonatal hepatitis B/C virus (HBV, HCV) infection and HIV infection are both viral infections that can be transmitted from

the mother to the baby. Despite the devastating effect of neonatal viral infections, only a few antiretroviral drugs are available in formulations that are appropriate for neonates, and there is limited safety and pharmacokinetic information available for most of these drugs in this population [39]. Unfortunately, there is currently no approved treatment for neonates or infants infected with HCV, although clinical trials evaluating treatment options for younger children are underway. However, direct-acting antiviral (DAA) therapy is now FDA-approved for HCV-infected children who are 12 years of age or older [40].

3.2 | Neonatal Sepsis

As described across the various types of infections, all three categories of systemic pathogens can lead to neonatal sepsis. Neonatal sepsis is a clinical condition characterized by non-specific symptoms and signs resulting from invasion of the body by various pathogens [49]. The recommended and standard treatment approach for neonatal sepsis is empiric antibiotic therapy [15]. Usually, when selecting an empiric antibiotic for infection treatment, it is typically necessary to consider the commonly isolated microorganisms associated with the infection and their antibiotic susceptibility patterns [50], though other multiple conditions resemble sepsis [51].

In developing countries, pathogens isolated in hospital settings within the first 72 h of life are often similar to those isolated later. This suggests that poor hygiene practices during delivery may contribute to early-life infections caused by nosocomial pathogens [16]. In addition, it is important to note that a significant proportion of neonates are born at home, and therefore remain at risk of contracting community-acquired pathogens even beyond the first 72 h of life [52]. Due to the high prevalence of community-acquired infections among neonates in developing countries, some authors have categorized neonatal sepsis in these regions as community- and hospital-acquired rather than early- and late-onset [53].

Neonatal sepsis is the third most common cause of neonatal mortality, following prematurity and intrapartum-related complications [54]. It accounts for 13% of all neonatal deaths and is responsible for 42% of deaths that occur during the first week of life [12]. Developing countries often lack a surveillance system, and a significant proportion of newborns in these countries die at home before being registered. As a result, cases of neonatal sepsis are probably underreported in these countries, indicating that its impact on mortality may be even greater than currently estimated [55].

Wang et al. documented in their long survey that accelerated decreases in neonatal deaths have been observed in India, as well as in almost all countries in sub-Saharan Africa and Eastern Europe. However, the rate of decline in child mortality has slowed down in several Latin American countries despite overall progress in reducing mortality rates [13]. Only 27 developing countries are expected to achieve MDG 4. Furthermore, 17 nations, of which many are developing countries, exhibited slower rates of change in under-five mortality than anticipated [13]. They further suggested that, unless there is

further accelerated progress, many countries in West and Central Africa will continue to experience high levels of under-five mortality in 2030.

Traditionally, blood culture is the gold standard for diagnosing neonatal sepsis. However, its positivity rate is relatively low and can be influenced by factors such as the volume of blood inoculated, use of prenatal antibiotics, level of bacteremia, and laboratory capabilities [55, 56]. In a study that investigated common pathogens associated with neonatal sepsis, it was found that 68% of infants with sepsis had low-level bacteremia (≤ 10 colony-forming units [CFU]/mL), and 42% had counts of ≤ 1 CFU/mL [57].

In recent times, Pyrosequencing, real-time polymerase chain reaction (PCR), microfluidic technologies (such as the TaqMan Array Card), and other “lab-on-a-chip” devices have been implanted in diagnosis but still have their respective shortcomings [58]. Other technological advancements have aided in diagnosis. For example, Peptide Nucleic Acid Fluorescent In-Situ Hybridization Molecular Stains (PNA-FISH) is a validated method for species identification. With the advent of the QuickFISH system, the turnaround time has been reduced to just 20 min, allowing for rapid reporting of species identification results similar to Gram staining [49]. Since these technologies are novel, we suggest that they are yet to be prevalent in developing countries, and further surveillance needs to be conducted to validate them. According to a meta-analysis of 23 studies on the molecular diagnosis of neonatal sepsis, real-time PCR assays demonstrated the highest performance, with a sensitivity and specificity of 96% [58]. Following the immense negative significance of sepsis in clinical settings, further studies need to be conducted to reduce the burden in developing countries.

3.3 | Challenges In Diagnosing Infections in Neonates

Early signs and symptoms of infections in neonates are often subtle and nonspecific, which can make diagnosis challenging. Symptoms include fever, lethargy, poor feeding, respiratory distress, and apnea. However, these signs may also be present in other conditions, and some neonates may not exhibit any clear signs of infection [7]. However, administering antibiotics non-specifically or empirically to newborns can lead to microbiome manipulation, exposure to drug toxicity, increased risk of nosocomial infections, and development of antibiotic-resistant bacterial strains [59]. Therefore, it is crucial to accurately identify infected newborns while minimizing the unnecessary use of antibiotics in healthy infants to mitigate these negative effects [60].

Some diagnostic techniques only verify the presence of infection but not the specific organism. For instance, physical examination of the umbilicus is an acceptable standard of diagnosis of omphalitis according to the World Health Organization (WHO) [18]. However, this method does not identify specific causative organisms, which can lead to imprecise antibiotic treatment [14]. Consequently, many clinicians resort to empirical antibiotics for neonates with suspected umbilical sepsis, contributing to the

global problem of antibiotic resistance [18]. Since neonates are vulnerable to drug side effects, and there are limited drug options for them, it is crucial to optimize culture and sensitivity testing to identify the specific causative organisms involved in omphalitis and ensure appropriate antibiotic treatment.

Difficulty in prescribing for neonatal infection is further influenced by the fact that viral, fungal, and bacterial infections can present with similar symptoms [56, 61]. All types of infections can cause fever, lethargy, poor feeding, respiratory distress, and cardiovascular collapse. This can make it difficult to distinguish between the three types of infections based on clinical symptoms alone [61]. However, there may be differences in the severity and progression of symptoms, as well as other clinical and laboratory findings, that can help differentiate between viral and bacterial infections. Therefore, laboratory testing and other diagnostic methods are often necessary to accurately diagnose and treat BSIs in neonates [49, 62]. Blood culture, which is the golden diagnostic method, especially in developing countries, has its own shortfalls [56, 63]. The volume of blood collected for cultures is the most critical factor that influences the likelihood of recovering and identifying pathogens in the blood culture [56]. However, collecting an optimal blood volume for cultures can be challenging in neonates and extremely preterm infants [56], especially in developing countries where the ratio of medical practitioners to patients is alarmingly low.

3.3.1 | Challenges With Diagnosing Fungal BSIs in Neonates

Generally, the diagnosis of neonatal fungal infections is challenging as there is no single reliable diagnostic test for fungal BSIs in neonates. Blood cultures, which are commonly used to diagnose bacterial infections, have a low sensitivity for detecting fungal infections [64]. Despite the capability of blood cultures to detect *Candida*, the required time in detecting the organism can be challenging. It usually takes about 36 h as the median time to detect *Candida* species from blood cultures, but this time may increase to 42 h when infants are on antifungal therapy prior to blood collection [65]. Other diagnostic tests, such as fungal antigen tests and PCR, have limited sensitivity and specificity [58]. Further, obtaining a definitive diagnosis of fungal infection may require invasive procedures such as lumbar puncture or tissue biopsy. These procedures are associated with risks and may not be feasible in critically ill neonates. In developing countries, such as Ghana, there is limited surveillance on general fungal infections, and only a few medical centers diagnose fungal infections.

3.3.2 | Challenges With Diagnosing Bacterial BSIs in Neonates

Diagnosing bacterial BSIs in neonates is challenging due to non-specific symptoms, limited diagnostic tools, and contamination of blood cultures, among others. Diagnosis and identification of this condition can be challenging due to its subtle clinical manifestations, which can overlap with those of noninfectious conditions. Consequently, clinicians often prescribe empirical antibiotics to symptomatic or “at-risk” infants while waiting for culture results, which are currently considered the gold standard for identifying BSIs [63]. Moreover, recent studies evaluated the use of molecular kits, which were found to be very effective. For instance, for EOS, the results obtained from the

molecular kit were consistent with those from blood culture, but the former had a faster turnaround time of 3 h, which is a significant advantage over blood culture [66]. However, these molecular kits may not commonly be found in developing countries. However, this hypothetical statement would require thorough surveillance of molecular kits in developing countries to be deemed accurate.

3.3.3 | Challenges In Diagnosing Viral Infections in Neonates

Similar to clinical management, tracking, and isolating viral agents poses a unique diagnostic dilemma in the febrile infant. Previously, viral diagnostics were based on serology, antigen detection, or virus culture from urine, stool, mucocutaneous lesions, or other sites such as the mouth and nasopharynx [43, 67]. These laborious and time-consuming diagnostic methods have been replaced with PCR tests [67]. The rapid advancement of high-throughput molecular techniques has led to the identification of several new viruses that cause respiratory diseases, including bocavirus-1, metapneumovirus, and coronavirus. This has significantly expanded our understanding of virus infections [67].

PCR tests are considerably more sensitive than other methods, resulting in higher rates of viral detection. In the last decade, multiplexed PCR tests have become available, enabling the screening of up to 16–20 respiratory viruses simultaneously from a single mucus sample using a flocked nasal swab [68]. However, it is important to note that the sensitivity of multiplex PCR tests is not as high as that of PCR tests designed to detect a single virus [67]. Furthermore, it is essential to emphasize that unlike a positive virus culture, a positive PCR test does not always indicate active virus replication [67]. For instance, a PCR test for rhinovirus may yield a positive result during and after symptomatic infection, in cases of subclinical infection, or even in instances of innocent contamination [69]. But transcriptional profiling can be a valuable tool for differentiating between active infection and incidental virus detection [70]. Given that early recognition of neonatal bacterial infection and prompt administration of appropriate antimicrobial agents can significantly improve outcomes, it is possible that viral diseases in neonates are frequently treated with broad-spectrum antibiotics [71]. However, it is important to always consider the possibility of concomitant bacterial co-infection [67]. For instance, respiratory syncytial virus infection in neonates has been linked with severe bacterial complications, such as the development of a pulmonary abscess [72]. Compared to bacterial infections, nosocomial viral infections tended to occur later during the birth hospitalization period [62].

3.4 | Challenges In Treating BSIs in Neonates

3.4.1 | AMR

The development of antibiotic resistance is a major public health concern in both developed and developing countries, and the use of antibiotics is a contributing factor to this issue. The high rates of antibiotic resistance in developing countries have led to the use of broad-spectrum antibiotics as first-line therapy, which can be more expensive and may not be affordable for many families in low-resource communities [73]. The inappropriate use

of antibiotics and the use of leftover medications can also lead to contamination and outbreaks of resistant bacteria, further compounding the issue of antibiotic resistance [74]. Antibiotic resistance in developing countries has reached alarming levels, particularly in neonatal sepsis cases, where *Klebsiella* sp. has exhibited resistance rates of 60%–72% to gentamicin and 57%–66% to third-generation cephalosporins. *E. coli* has also shown high resistance rates to gentamicin (13%–48%), amikacin (15%), and third-generation cephalosporins (19%–64%). *S. aureus* resistance to methicillin is at 4% [75]. Despite these high resistance rates, current recommendations suggest that newborns with suspected sepsis should be treated with ampicillin plus gentamicin, but physicians must consider local resistance patterns when deciding on empiric therapy [76].

Hospital-acquired infections in developing countries also exhibit high resistance rates, with *Klebsiella* spp. and *E. coli* showing high resistance levels to commonly used antibiotics against gram-negative bacteria, ranging from 30% to 90% [77]. *S. aureus* resistance to methicillin is also high, reaching 38% on average and up to 56% in South Asia [78]. These high resistance rates have forced healthcare providers to use broad-spectrum antibiotics, such as carbapenems and vancomycin, as first-line regimens, which are more expensive and may not be affordable for many families in low-resource communities [73]. In addition, the inappropriate use of antibiotics and the use of leftover medications can lead to contamination and outbreaks of resistant bacteria [74]. Therefore, it is imperative for healthcare workers and policymakers to implement effective strategies to address the issue of antibiotic resistance in developing countries.

3.4.2 | Limited Availability of Appropriate Antibiotics

Antibiotic use is common in neonatal intensive care units (NICUs), with almost all neonates receiving antibiotics, despite only a small percentage having positive blood cultures [79]. However, empirical antibiotic courses are often prolonged, and inappropriate courses are prevalent, affecting up to 35% of neonates [80–82]. The current WHO recommendation for treating Staphylococci infections in neonatal sepsis involves specific antibiotics, but recent studies indicate that the current guidelines for empirical treatment may not be as effective as they once were. Early, prolonged, or inappropriate use of antibiotics can increase neonates' risk of infection, hospitalization, and microbiome disruption [83]. Inappropriate antibiotic administration in NICUs is linked to the development and spread of antibiotic-resistant pathogens [84]. Studies have shown that some antibiotic combinations used for suspected EOS can significantly increase the risk of colonization with resistant pathogens. Newborns who were administered cefotaxime were found to be at a significantly higher risk of developing an extended-spectrum beta-lactamase infection compared to those who were administered tobramycin. In fact, the risk was 33 times higher with the use of cefotaxime [53]. Studies have also shown that using amoxicillin plus cefotaxime can increase the risk of colonization with resistant pathogens by 18-fold compared to using penicillin plus tobramycin [85, 86]. Therefore, appropriate antibiotic use in NICUs is crucial to prevent the development and spread of resistant pathogens and to avoid intensifying the issue of antibiotic resistance in neonatal sepsis.

3.4.3 | Adverse Effects of Antimicrobial Agents

Neonatal sepsis is a rapidly fulminating clinical disease, and practitioners often administer parenteral antibiotics without waiting for diagnostic test results, prioritizing the health of the individual patient over the potential risks associated with the emergence of antibiotic resistance [87]. However, antibiotics are not without risks and have been linked to adverse outcomes in neonates, such as a higher risk of candida-invasive disease, necrotizing enterocolitis, and mortality [88, 89]. Prolonged antibiotic treatment may also lead to negative consequences that persist beyond the neonatal phase, such as an increased likelihood of experiencing wheezing during childhood [90]. Therefore, healthcare workers and policymakers must implement effective strategies to address the issue of antibiotic resistance in neonates and prevent the development and spread of resistant pathogens. Such strategies may include improving access to affordable antibiotics, promoting appropriate antibiotic use, and implementing infection control measures to prevent the spread of resistant bacteria.

3.4.4 | Difficulty in Monitoring Therapeutic Drug Levels

In LMICs, community management of neonatal sepsis may be a life-saving option, but providing adequate management and treatment can be an economic challenge, highlighting the importance of investing in strategies for diagnosis, prevention, and management in these regions [11, 91]. Studies on local antibiotic resistance rates should consider the availability of antibiotics at the national or regional level to have a substantial impact on treatment options [92]. Investigations that acquire clinical data on antibiotic usage should incorporate details on treatment duration and the frequency of modifications in antibiotic regimens [93]. The choice of antibiotics is influenced by cost, and healthcare providers may opt for more cost-effective treatment options to minimize expenses [94–96]. Discrepancies in antibiotic dosing guidelines can result in inconsistent dosing, which can impact the effectiveness of the treatment [97]. Extended-interval dosing may be advantageous for gentamicin and amikacin, but a single dose may be more practical for community use due to its logistical and cost benefits [98, 99]. It is crucial to invest in strategies for characterizing, diagnosing, preventing, and managing neonatal sepsis in LMICs, given the economic burden associated with its management and treatment [11, 91].

3.5 | Prospects for Improving the Diagnosis and Treatment of Neonatal BSIs in Developing Countries

The diagnosis of neonatal sepsis is challenging, and conventional microbiologic culture techniques are time-consuming and not entirely reliable, especially in LMICs due to limited resources and practical limitations [49, 100]. Overdiagnosis of “culture-negative” sepsis has led to increased antibiotic use and associated effects, such as fungal infections and necrotizing enterocolitis [49]. The use of rapid culture techniques, antibiotic stewardship, and bundled approaches has reduced morbidity and mortality from neonatal sepsis [101]. Although serum assays and biomarkers have been suggested as potential diagnostic tools for sepsis, their accessibility, training requirements,

and prognostic accuracy are still matters of debate [102, 103]. The current biomarkers and assays for neonatal sepsis have limited value and are challenging to interpret due to low sensitivity and dependence on normal ranges that vary during the neonatal period [87]. However, new molecular and non-culture-based methods are needed to facilitate timely detection and accurate diagnosis of sepsis [104]. Researchers are exploring innovative diagnostic modalities, such as using PCR and molecular biology and gene expression profiling techniques, to tackle these challenges [105]. However, logistical challenges may make implementing these diagnostic techniques difficult in developing countries [91]. The need for accurate and timely diagnosis of neonatal sepsis remains critical, highlighting the importance of continued research and investment in diagnostic strategies [91]. Clinicians may use laboratory tests in addition to blood culture to facilitate timely diagnosis of EOS [106].

3.5.1 | Development of Rapid Diagnostic Tests

Alternative diagnostic methods are needed to improve the diagnosis of neonatal sepsis, particularly in LMICs, to improve neonatal health outcomes. Rapid diagnostic systems that identify organisms in positive blood cultures have revolutionized the identification of microbial pathogens in whole blood samples, providing faster turnaround times than conventional methods. PCR-based molecular techniques are the primary method for detecting bacterial and fungal genes in sepsis diagnosis, and several diagnostic systems, such as Sep-tiFast, SepsitTest, and T2 MR, have been reported to accurately detect PCR-amplified pathogen DNA from blood hybridized to capture probe-decorated nanoparticles [107–110]. Point-of-care devices have the potential to revolutionize the diagnosis and treatment of neonatal sepsis, leading to faster and more precise diagnoses, better patient outcomes, and reduced healthcare costs [111, 112]. Researchers are exploring the effectiveness of biomarkers, such as blood plasma protein quantification and leukocyte monitoring, in diagnosing sepsis using point-of-care (POC) devices [103]. Furthermore, novel techniques, including the analysis of volatile organic compounds in breath, have been promising in distinguishing sepsis from inflammation in rat models, although additional validation studies in humans are required [113]. The development of rapid diagnostic assays has led to significant improvements in clinical outcomes, reduced hospital stays, and considerably lower healthcare costs, making them an essential tool for sepsis management [114].

3.5.2 | Improving Access to Appropriate Antibiotics

Community management of neonatal sepsis includes several interventions, but home antibiotics alone have been estimated to reduce case fatalities by 35% [115, 116]. Simplified antibiotic regimens are needed for the home management of neonatal sepsis [117]. Intramuscular gentamicin, procaine penicillin, and ceftriaxone can be given once daily, while oral antibiotics like cotrimoxazole, cefuroxime, and amoxicillin are potential options for community settings [118, 119]. Resistance to antibiotics, particularly among *E. coli*, is a growing concern [120]. Trials are underway to evaluate new regimens for home-based treatment [121]. Chloramphenicol is not recommended due to its potential for toxicity [122]. The recommended parenteral

regimens include penicillin/ampicillin and gentamicin or third-generation cephalosporins for 10–14 days [76, 97]. Oral therapy is recommended when referral is not possible [123]. Researchers are exploring new oral antibiotics like second-generation cephalosporins [124, 125]. Ongoing research is necessary to improve neonatal health outcomes [126–128].

3.5.3 | Development of Novel Antimicrobial Agents

Neonatal sepsis is a serious condition, and there is a need for better antibiotic treatment options [73]. Recent research has shown that combining fosfomycin with other agents, such as amikacin, may enhance current empirical guidelines for treating neonatal sepsis caused by multidrug-resistant bacteria [91]. However, there are concerns about the lasting efficacy of fosfomycin due to induced resistance reported in vitro [129]. Moreover, the cost and accessibility of fosfomycin may restrict its use in LMICs [130]. Research has shown promise for Lata-moxef in treating EOS, and ongoing research is evaluating the potential of oxacephems [131]. Therefore, ongoing research efforts are necessary to develop effective and accessible alternative antibiotics to fosfomycin and improve neonatal health outcomes [132, 133].

3.5.4 | Use of Alternative Therapies (Immunotherapy)

Maternal immunization is a promising strategy for providing neonates with appropriate antibodies immediately upon birth. Studies on maternal tetanus toxoid and influenza immunizations have demonstrated success in several studies [134, 135]. Similarly, studies on maternal immunization with *S. agalactiae* type III conjugate vaccine and pneumococcal polysaccharide and conjugate vaccines have also shown promising results [136]. Effective treatment of neonatal sepsis is crucial, and recent research indicates that community health workers can safely and effectively deliver antibiotic treatment to neonates with severe infections at home when hospitalization is not an option [137]. Effective treatment must be safe for the newborn, feasible to deliver in a hospital or community setting, and effective against the pathogen causing the infection [138]. Implementing maternal immunization programs can be an effective strategy for reducing neonatal sepsis-related morbidity and mortality, particularly in LMICs [139, 140]. However, barriers to maternal immunization include liability issues for vaccine manufacturers in developed countries, public and healthcare provider education regarding the benefits of maternal immunization, and poor ascertainment of data from low-income countries [141, 142]. Recent research also identified inadequate staff training and retention, high cost, and referral difficulties due to a lack of ambulances and poor institutional links as barriers to the widespread implementation of effective neonatal sepsis treatment. In summary, the passage highlights the potential of maternal immunization as a strategy for reducing neonatal sepsis-related morbidity and mortality while also identifying barriers to its implementation and the need for effective and accessible treatment options [143, 144]. Overcoming the barriers to implementing community-based antibiotic treatment and maternal immunization programs will require concerted efforts from policy-makers, healthcare providers, vaccine manufacturers, and other stakeholders [145].

3.5.5 | Integration of Artificial Intelligence (AI) and Clinical Decision Support Systems (CDSS)

The integration of AI and CDSS represents a transformative opportunity for improving the diagnosis and management of neonatal BSIs, particularly in resource-constrained settings. Due to the prolonged turnaround time of blood cultures (24–48 h), the definitive diagnosis of neonatal sepsis is often delayed, contributing to increased morbidity and mortality [146]. AI-powered predictive models offer the potential to identify at-risk neonates hours before clinical recognition, enabling earlier intervention and improved outcomes [147].

3.5.5.1 | Machine Learning (ML) for Early Sepsis Prediction

Recent advancements in ML have significantly enhanced the ability to distinguish neonatal sepsis from other conditions, aiding early diagnosis and intervention [148]. ML models can simultaneously analyze multiple clinical parameters, including vital signs, laboratory measurements, and clinical observations, to predict sepsis onset with high accuracy [149]. Studies have demonstrated that ML algorithms can identify infants with sepsis in the NICU several hours before clinical recognition by healthcare providers [147]. A ML-based model developed for low-resource settings in Zimbabwe successfully used routine clinical data to predict EOS risk, demonstrating feasibility in LMIC contexts [150]. Similarly, a ML model specifically designed for EO neonatal sepsis prediction in LMICs has been developed and validated, showing promise for deployment in resource-limited settings [151].

3.5.5.2 | CDSS in Neonatal Care

CDSS are computer-based tools that integrate medical knowledge and patient-specific information to assist healthcare providers in making clinical decisions [152]. CDSS can help reduce diagnostic uncertainty by providing evidence-based recommendations for antibiotic selection, dosing, and duration based on local resistance patterns and patient characteristics [153]. A systematic review assessing clinical decision support algorithms (CDSAs) for sepsis prediction in neonates found that non-invasive parameters could be effectively utilized for early detection, though implementation in LMICs remains limited [154]. The development of AI-based software systems for predicting LOS and necrotizing enterocolitis has shown promising results in improving neonatal care outcomes [155].

3.5.5.3 | AI-Enhanced Diagnostic Tools

Novel AI-enhanced diagnostic technologies are emerging as potential game-changers for neonatal sepsis diagnosis. A ML-based electronic nose (cNose) system has been developed for neonatal sepsis detection, achieving accuracy, sensitivity, and specificity of over 88% [156]. Gene expression biomarkers combined with AI algorithms represent an exciting new field of diagnostics with potentially increased sensitivity and specificity compared to conventional methods [157]. AI-powered analysis of volatile organic compounds in breath samples has shown promise in distinguishing sepsis from inflammation, though further validation in human neonates is required. These technologies could be particularly valuable in settings where conventional laboratory infrastructure is limited.

3.5.5.4 | Applications for Antimicrobial Stewardship

ML is a potential tool to help clinicians determine the most appropriate empiric antibiotic treatment based on local resistance patterns and patient risk factors [153]. AI-driven antimicrobial stewardship programs (ASPs) can help optimize antibiotic use by predicting which neonates are at low risk for bacterial infection, thereby reducing unnecessary antibiotic exposure and its associated complications [153]. This is particularly important given that prolonged or inappropriate antibiotic therapy increases the risk of necrotizing enterocolitis, invasive candidiasis, and mortality in neonates. CDSS can also support de-escalation strategies by alerting clinicians when culture results become available or when clinical improvement suggests antibiotics can be safely discontinued.

3.6 | Strategies to Overcome Challenges of Neonatal BSI in Developing Countries

Excessive, prolonged, and inappropriate use of antibiotics can lead to an increased risk of infection, hospitalization, and negative effects on the microbiome of neonates. The administration of antibiotics to uninfected neonates increases the chances of complications, emphasizing the importance of appropriate antibiotic use [158]. The WHO recommends β -lactam antibiotics, primarily ampicillin or cloxacillin, for Staphylococci infections, and gentamicin, with a third-generation cephalosporin, for second-line treatment in neonatal sepsis. However, recent data suggest that these guidelines may no longer be effective, and a study has reported low coverage for ampicillin in combination with gentamicin, suggesting that “Ampicillin is now redundant” [159]. To optimize neonatal health outcomes and mitigate the risks associated with antibiotic treatment, healthcare providers must weigh the potential benefits of antibiotics against the risks of overuse and inappropriate use. Promoting appropriate antibiotic use requires education and training for healthcare providers, ASPs, and improved diagnostic techniques to guide the appropriate use of antibiotics. Implementing these measures can reduce the risk of antibiotic resistance and improve neonatal health outcomes [159, 160].

3.6.1 | Antimicrobial Stewardship Programs (ASPs)

Neonates are at high risk of bacterial infection, and LMICs often rely on empirical antibiotic prescription due to diagnostic uncertainty and concerns for infection-related deaths. However, the negative long-term effects of neonatal antibiotic exposure, such as changes in the microbiome and selection of resistance genes, are increasingly recognized. ASPs are essential to address this issue in neonatal units, but there is limited data on program implementation in LMICs. Effective ASPs in these settings should consider local context, resources, and healthcare provider capacity and include education and training for healthcare providers, monitoring and feedback mechanisms, and protocols for antibiotic use in specific clinical situations. Implementing ASPs can improve antibiotic use, reduce antibiotic resistance, and minimize adverse long-term effects. However, stakeholders need to collaborate to promote ASPs and address the underlying causes of inappropriate antibiotic use [161, 162].

3.6.2 | Implementation of Infection Prevention and Control Measures

Neonatal sepsis is a leading cause of child mortality worldwide, but there are low-cost interventions and promising approaches that can significantly reduce the burden of neonatal sepsis globally [163–165]. Implementing care bundles in LMICs can prevent neonatal sepsis and reduce sepsis-related mortality, but concerted efforts from policymakers, healthcare providers, and other stakeholders are required to promote their implementation in neonatal units and address the underlying causes of neonatal sepsis [163–165]. To prevent healthcare-associated infections (HAIs) in neonatal units in LMICs, low-cost and highly cost-effective interventions that are easy to implement, measure, evaluate, and scalable are needed [161]. Neonatal sepsis prevention in LMICs requires the practicability of interventions such as skilled attendance at delivery, risk-based antibiotic prophylaxis, improved hand washing during delivery, and innovative approaches involving healthcare providers, policy makers, and governmental bodies [166, 167].

3.6.3 | Collaborative Multidisciplinary Approach

A collaborative multidisciplinary approach is essential to effectively combat neonatal sepsis. Herbert et al. [168] emphasize the importance of home visiting programs in identifying sick newborns early in life, especially in low-income settings where care-seeking for neonatal illnesses can be challenging. To combat neonatal sepsis, frontline health workers and families must be partners in all research and evaluation planning [169, 170]. Programs to reduce morbidity and mortality from neonatal sepsis should include a detailed assessment of end-user attitudes and preferences using formative and qualitative research methods [166]. Advocacy for equitable resource allocation across and within countries is a priority, and modeling techniques to assess the public health impact of neonatal sepsis interventions should be developed and used more widely [171]. By addressing these challenges and involving front-line health workers and families in research and evaluation planning, LMICs can make progress in reducing the burden of neonatal sepsis and sepsis-related mortality [168]. Home visiting programs, rapid diagnostic tests, and appropriate antibiotic use are just a few of the strategies that can be used to reduce neonatal morbidity and mortality in LMICs [87, 170]. It is critical that policymakers and healthcare providers work together to implement these interventions and address the underlying causes of neonatal sepsis [166, 169, 171].

4 | Conclusion and Future Perspectives

Neonatal BSIs remain a significant cause of morbidity and mortality in developing countries. Their diagnosis and treatment are often challenging due to limited resources, the non-specific nature of symptoms, and alarmingly high rates of AMR. The inherent vulnerability of neonates is compounded by systemic deficiencies in healthcare infrastructure and practices in LMICs, creating a complex and persistent public health crisis. The underreporting of neonatal deaths further obscures the true magnitude of this problem, hindering effective resource allocation and policy development.

However, early and accurate diagnosis, appropriate treatment, and robust infection prevention measures are crucial to reduce the burden of neonatal BSIs and improve neonatal outcomes. Developing countries must prioritize investment in improving laboratory infrastructure, increasing access to appropriate and affordable antibiotics, and improving infection control practices to address the issue of neonatal BSIs and mitigate the burden of antibiotic resistance. The development and widespread adoption of rapid diagnostic tests, including point-of-care devices, alongside the integration of AI and CDSS, hold immense promise for timely and precise pathogen identification and risk prediction.

Furthermore, healthcare providers must receive comprehensive training in proper diagnostic techniques, appropriate antibiotic use, and effective infection prevention measures. The implementation of ASPs is vital to preserve the efficacy of existing antibiotics and combat the rise of resistance. Finally, a collaborative multidisciplinary approach, involving policymakers, healthcare providers, community health workers, and families, is essential to implement and scale up effective interventions, ensuring that the most vulnerable newborns receive the care they desperately need. Continued research into novel antimicrobial agents and alternative therapies, such as maternal immunization, is also critical for a sustainable long-term strategy. Addressing these multifaceted challenges requires sustained global commitment and targeted investment to achieve a significant reduction in neonatal BSI-related morbidity and mortality worldwide.

Author Contributions

Alex Odoom: conceptualization, methodology, software, data curation, investigation, validation, formal analysis, visualization, resources, writing – original draft, writing – review and editing, project administration. **Abdul-Halim Osman:** conceptualization, methodology, software, data curation, validation, formal analysis, resources, project administration, visualization, writing – original draft, writing – review and editing, investigation. **Onyansaniba K. Ntim:** methodology, software, data curation, validation, writing – review and editing, formal analysis. **Fleischer C. N. Kotey:** conceptualization, methodology, software, data curation, writing – review and editing, validation, formal analysis. **Eric S. Donkor:** conceptualization, methodology, software, data curation, investigation, validation, formal analysis, supervision, funding acquisition, visualization, writing – review and editing.

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Ethics Statement

The authors have nothing to report.

Consent

All authors approved the manuscript for publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. All authors have read and approved the final version of the manuscript. Eric S. Donkor had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency Statement

Eric S. Donkor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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