EVALUATION OF NATIONAL PROTOCOLS FOR MANAGING SEVERE BACTERIAL INFECTIONS IN NEWBORNS: A REVIEW OF 90 ENAP COUNTRIES

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Abstract

Background: In 2020, the WHO released the Standards for improving the quality of care for small and sick newborns in health facilities (SSNC), which includes Standard 1.12, specifically focused on neonatal infection management. This standard supports the progress towards the 2023 Sustainable Development Goal 3.2, with the aim of reducing neonatal mortality to fewer than 12 deaths per 1,000 live births. The Every Newborn Action Plan (ENAP), developed and adopted by 90 countries in 2014, provides a framework for achieving this goal.

Method: A systematic literature search was conducted to identify published research on neonatal infection management in the 90 ENAP countries using keywords derived from SSNC Quality statement 1.12. In addition, publicly available national protocols were compiled. Key components were evaluated against WHO standard 1.12, including national availability, antibiotics mentioned, dosages, first- and second-line antibiotics, signs of sepsis, and blood cultures.

Results: Out of 622 publications, 53 were selected for in-depth analysis, focusing on 23 of the 90 ENAP countries. This study provides a comprehensive review of neonatal infection research from these 23 countries, 18 of which have publicly available national protocols. National protocols were accessible for 30 out of 90 countries (33.3%). Among these, 28 (93.3%) addressed clinical symptom assessment at admission, and 29 (96.7%) specified antibiotic use, with 22 (73.3%) detailing dosages. Blood culture collection was mentioned in 19 (63.3%) protocols. However, only 13 (43.3%) countries fully incorporated all components of WHO standard 1.12, revealing significant gaps in neonatal infection management protocols across ENAP countries.

Conclusion: Addressing the identified gaps and improving the availability of publicly accessible national protocols can enhance healthcare delivery, transparency, and accountability. However, significant gaps remain in their implementation across ENAP countries

Introduction

Worldwide neonatal mortality data of 2021 shows that neonatal mortality rate stood at an approximate figure of 18 fatalities for every 1,000 live births. Translated into raw numbers, this statistic indicates that around 2.3 million infants lost their lives within their initial 28 days of existence annually (1). It's crucial to note that this rate is not consistent across the globe. Significant disparities can be observed when comparing regions and even between individual countries. The greatest mortality burden is predominantly observed in regions such as sub-Saharan Africa and South Asia. There are several leading factors attributed to neonatal mortality. The primary factors contributing to most neonatal

fatalities include preterm delivery, complications during birth such as asphyxia or respiratory difficulties, infections, and congenital anomalies (2). Addressing this pressing issue has been at the forefront of many health agendas. A multitude of efforts have been put in place with the objective of curtailing neonatal mortality. The primary focus of these initiatives is on enhancing the standard of maternal and child healthcare. Moreover, emphasis has also been placed on ensuring that individuals have unobstructed access to high quality medical services. Parallel to that, there's an understanding of the importance of addressing the foundational social and economic elements that play a significant role in the occurrence of newborn deaths.

The Sustainable Development Goals (SDGs) 3.2 were formulated by collaboration between the World Health Organization and various United Nations bodies, with the intention of providing a comprehensive framework for global progress. Within this array of objectives, there is a distinct emphasis on neonates, which refers to infants during their initial 28 days of life, as outlined in SDGs 3.2(3). This specific goal is oriented towards the reduction of neonatal mortality rates, achieved through the assurance of access to high-quality healthcare services for newborns, the promotion of skilled attendance during childbirth, and the targeted mitigation of preventable factors contributing to neonatal fatalities. By prioritising the well-being of neonates, the SDGs highlight the critical significance of nurturing a world in which every newborn has the prospect to not only survive but also flourish, thus actively contributing to a future that is both sustainable and just.

Neonatal Infections pose a serious dilemma in healthcare, frequently resulting in critical health issues for newborns. This issue is particularly pronounced in low- and middle-income countries, where the rate of severe community-acquired bacterial infections among newborns is markedly elevated compared to more affluent nations (4). Bacterial agents are usually the primary culprits behind these rapidly worsening infections, affecting an already at-risk demographic. A study conducted in Madagascar revealed a high occurrence of lab-confirmed severe neonatal infections, reporting 17.7 cases for every 1,000 live births (5).

Factors such as premature birth, low birth weight, and weakened immune systems make newborns particularly prone to severe bacterial infections(2). Addressing immediate health risks and preventing loss of life are critical and time sensitive. Current medical guidelines advocate for the hospitalization of young infants exhibiting symptoms of severe infections. Standard treatment usually involves a 7–10-day course of intravenous broad-spectrum antibiotics, commonly a combination of ampicillin and gentamicin (6). Tackling this involves a comprehensive strategy that encompasses standardized treatment guidelines, stringent sanitation measures, and ongoing medical training. Developing and implementing effective treatment protocols for handling severe bacterial infections in newborns have the potential to empower healthcare providers in delivering prompt and appropriate care. This could contribute to better health outcomes and reduced rates of morbidity and mortality. By pinpointing deficiencies in current healthcare systems and suggesting measures, the study aims to across participating nations to enhance their practices, thereby uplifting the general health and welfare of their communities.

Every Newborn Action Plan (ENAP) was introduced in 2014, ENAP is a collaborative initiative with the goal of reducing preventable deaths among newborns and stillbirths (6). By the year 2030, the plan aims to achieve national targets of fewer than 12 neonatal deaths per 1000 live births and fewer than 12 stillbirths per 1000 total births. Achieving these targets involves enhancing care assessment during childbirth and improving the monitoring of care quality, inclusivity, and coverage for small and sick newborns around the time of birth (7). On September 3, 2020, the World Health Organization (WHO) introduced the key aims of the "All Newborn" Action Plan for 2025 in a webinar. The strategy sets forth four primary ambitions to put an end to avoidable deaths of newborns and stillbirths by 2025: 1) achieving 90% antenatal attendance by mothers for at least four sessions, 2) ensuring 90% of deliveries are overseen by qualified medical professionals, 3) securing 80% of mothers acquire postnatal check-ups within two days following delivery, and 4) making certain that 80% of countries are equipped with

both a detailed plan and the necessary facilities to cater to and defend fragile and unwell infants (8). Since its endorsement by 194-member states in 2014, the global ENAP has gained prominence as a significant initiative rooted in evidence-based strategies. It goes beyond reducing preventable newborn and stillbirth deaths, also contributing to the reduction of maternal morbidity and mortality. Developed as a comprehensive plan of action within the 'Every Woman Every Child framework,' ENAP's recommendations are actively adopted and monitored by 90 countries, as highlighted by the UNICEF progress report in 2019 (9).

A study which looks at persistent barriers to achieving quality neonatal care in low-resource settings, the experts agreed that there was a lack of locally relevant standardised guidelines and a need to introduce concise, accessible, easy to follow clinical guidelines and frameworks (10). To tackle this issue, the WHO released SSNC standards in Health Facilities in 2020 (11). These guidelines aim to elevate the standard of care for these vulnerable newborns. They set new benchmarks for how to treat these infants, how to monitor their condition, and how to train healthcare staff to manage these critical cases effectively.

The SSNC in Health Facilities is a carefully crafted set of guidelines aimed at creating a consistent and standardised approach to caring for newborns needing hospital treatment. These guidelines build on essential practices for newborn care and are designed to ensure that the care provided follows the high-quality standards set by the WHO for newborns admitted to hospital. The main goal of SSNC is to offer practical advice to countries on how to effectively meet the needs of these vulnerable infants, while also improving the overall quality of care for all newborns within the framework of universal health coverage. The SSNC standards are purposefully crafted to serve as a comprehensive resource for all parties involved in the care of vulnerable newborns. This encompasses decision-makers, medical staff, healthcare service planners, program overseers, regulating authorities, professional organizations, and technical collaborators. These standards are essential for effective planning, ensuring quality execution, and ultimately delivering high quality healthcare. Quality Statement 1.12 focuses on carefully checking all newborns for signs of infection or things that could lead to an infection. If needed, additional tests are done, and if necessary, the right antibiotics are given according to WHO guidelines, all to avoid using antibiotics when they're not needed. The present study is targeted to assess the national protocols for the management of neonatal infections for 90 countries tracking ENAP, against the WHO standards for the inpatient management of newborns who are suspected of, or at risk for, infection.

Literature Survey

Literature survey for this study was done through two-stages.

Stage1

Information sources and search strategy for reviewing the literature in this stage was executed through the utilization of databases like OVID, EMBASE, and African Journals Online (AJOL). The search strategy comprised English-language keywords and medical subject headings, targeting four primary domains: 1) Severe bacterial infections, 2) Health of mothers, newborns, and children, 3) Established guidelines and practices, and 4) The 90 countries in alignment with ENAP. Relevant keywords are enumerated in Table 1.

COMPONENT	KEYWORDS
Serious Bacterial Infections	"severe," "serious," or "critical," combined with terms like "bacterial" or "microbial," and "infections" or "diseases."
Health of Mothers, Newborns, and Children	"maternal," "motherly," or "pregnancy," along with "newborn," "neonatal," or "infant," and "pediatric" or "child."
Guidelines and Practices	"national," "country-specific," or "state," combined with "guidelines," "recommendations," or "protocols," along with

	"management," "treatment," or "care," and "intervention," "action," or "measures," as well as "clinical practice" or "best practices."
List of 90 Countries committed to ENAP	Montenegro, Kazakhstan, China, Azerbaijan, Georgia, Uzbekistan, Democratic People's Republic of Korea, Maldives, Bangladesh, Mongolia, Armenia, Rwanda, Morocco, Sri Lanka, Serbia, India, Libya, Lebanon, Indonesia, Nepal, Egypt, Bhutan, Iran (Islamic Republic of), Tajikistan, Zimbabwe, Ethiopia, Malawi, Solomon Islands, Senegal, Iraq, Burundi, Cabo Verde, Afghanistan, Kyrgyzstan, Angola, Jordan, Uganda, Sierra Leone, Ghana, South Africa, Guinea-Bissau, Burkina Faso, Myanmar, Niger, Timor-Leste, Liberia, Slovakia, Argentina, Mali, Gambia, Djibouti, Samoa, Mozambique, Eritrea, Turkmenistan, United Republic of Tanzania, Comoros, Pakistan, Cote d'Ivoire, Equatorial Guinea, Kenya, Mauritania, Democratic Republic of the Congo, Togo, Eswatini, Madagascar, Papua New Guinea, Somalia, Cameroon, Kiribati, Sudan, Central African Republic, Guinea, Chad, Congo, Philippines, Vietnam, Benin, Lesotho, Zambia, Namibia, South Sudan, Nigeria, Tunisia, Nicaragua, Yemen, Syrian Arab Republic, Seychelles, Malaysia, Venezuela.

Table 1: Search Strategy Components and Keywords

Eligibility Criteria for selecting studies is aligned with the parameters based on SSNC quality Statement 1.12 as set forth in Table 2.

No.	COMPONENT	DESCRIPTION
1	Health Facility Guidelines	Up-to-date guidelines, protocols, and standard operating procedures consistent with WHO guidelines for preventing, diagnosing, and managing neonatal infection in all relevant areas.
2	Antibiotic and Medication guidelines	Written guidelines, protocols, and standard operating procedures for the safe and rational use of antibiotics and medications for small and sick newborns, based on weight or age.
3	Supplies of first-line antibiotics	Adequate quantities of first-line injectable antibiotics maintained at the health facility to cover the expected case-load.
4	Supplies of injectable antibiotics for referral facilities	Sufficient quantities of injectable antibiotics (including first- and second-line options for neonatal sepsis and meningitis) maintained at the referral health facility.
5	Knowledgeable staff	Health care staff possess knowledge about signs of newborn sepsis, accurate diagnostic tests, and appropriate treatments.
6	Trainer and Refresher sessions	Health care staff receive in-service training and regular refresher sessions, occurring at least once every 12 months, to enhance recognition and management of suspected newborn infections

Table 2: Expected quality measures within healthcare facilities regarding SSNC quality statement 1.12.

Research methods of all types were considered eligible for inclusion. Studies were ruled out if they did not focus on newborn care units or included infants older than 28 days. Publications such as conference summaries, editorials, reviews, research protocols, and opinion articles were also excluded, as were any studies for which the full text could not be accessed. Instances of duplicate records were detected and removed.

Essential data attributes like the author, year of publication, and the country where the research was conducted were also collected and encompassed in the study. The Endnote citation management software was used for methodical organization of the data amassed. To access complete articles, specific online searches were executed for chosen references. After securing full-text versions, they were assessed for their relevance to the research goals. The information obtained at this stage was crucial in identifying relevant studies and uncovering potential areas for further research.

The dataset was structured to associate individual publications with their respective countries of origin. This allowed evaluation of the scope of the research landscape by contrasting these countries against those committed to ENAP but lacking in published research. The published studies were plotted per country, all of which was visualized on a global map. In addition, the data was arranged to quantify the number of publications originating from each country, providing insight into their level of focus on the subject matter.

Stage 2

This phase entailed a search for the most up to date national protocols available through public sources using online search engines. These protocols are crucial in managing severe bacterial infections under ENAP framework. To efficiently manage this data, a structured approach was adopted by creating an Excel document. Furthermore, this phase included developing a visual representation of the research by organising the identified studies into a framework. This was inspired from the structure of the 3+I Classification Framework (8), in which the researcher devised a novel framework tailored for their study.

In this study, SSNC standard 1.12 (Table 2) was adapted into a framework which encompasses three main categories—Type 1, Type 2, and Type 3. A fourth component, Type 4, was formulated by integrating elements from Type 2 and Type 3 to create a Grading system. This fourth component serves to evaluate national guidelines against the quality statements outlined in Table 2. All categories are summarized in Table 3 as below.

CATEGORY	COMPONENTS OF SSNC STANDARDS QUALITY STATEMENT 1.12
TYPE 1: Protocol Details	a) Author's name and publication year b) The corresponding country of study
TYPE 2: Protocol Specifications	c) Accessibility of national, regional, or local protocols within the public domain d) Mention of antibiotic usage in the protocols e) Indication of recommended antibiotic dosages f) Identification of first-line antibiotics recommended g) Specification of second-line antibiotics advised.
TYPE 3: Clinical Indicators and Procedures	h) Highlighting of notable sepsis indicators within the protocols i) Inclusion of discussions related to blood culture procedures in the protocols.

TYPE 4: Grading (out of 7)	1 point is awarded to each Component from TYPE 1 and TYPE 2. Each country can achieve a maximum grade of 7.

Table 1: Framework categories and details of components of SSNC Standard Quality Statement 1.12

Inclusion Criteria with only publications in English were included for this stage. Original standardised guidelines which were published either by well-regarded organisations or in platforms known for their peer-review processes or recognised professional societies were included. Furthermore, to ensure specificity and relevance, these guidelines concentrate on the specific nations committed to ENAP.

A variety of data was collected which was then subjected to a thorough and comprehensive examination. This in-depth analysis was specifically designed to facilitate the extraction of meaningful and actionable conclusions from the vast pool of information that had been gathered. Using this data, a tally sheet was compiled which served as a comparative framework, putting various country-specific infection control protocols side by side with the SSNC Standards quality statement 1.12 recommendations (Table 2) . Once this comparative evaluation was completed, the total tallies were used as the foundational data for the construction of a detailed bar chart. The purpose of this visual representation was to clearly highlight any existing gaps, inconsistencies, or variations between the implemented infection control protocols across different countries and the established standards.

Methodology

Stage1

A total of 622 publications were identified (Figure 2). After duplicate removal, 594 records remained for screening. After screening these records by title and abstract, 69 publications were selected for full-text screening. 17 of these publications were excluded according to the eligibility criteria, and the remaining 53 articles were selected for inclusion. Overall, 53 studies were included to provide a robust background into the topic. The subsequent PRISMA flow chart illustrates the incorporation of studies (13).

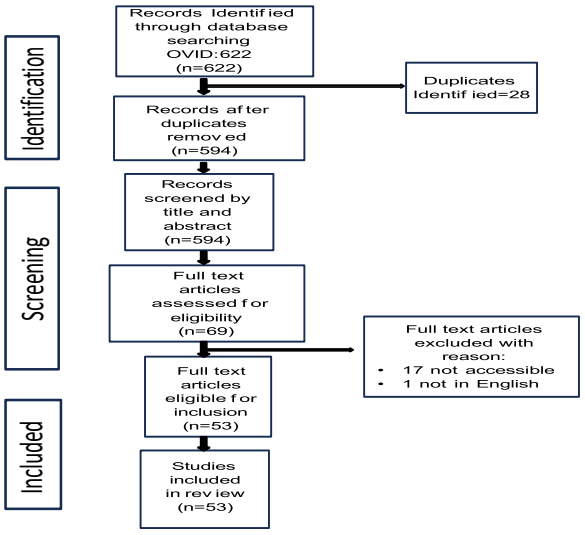

Figure 1: PRISMA Flow Diagram of study selection

Figure 2: Distribution of published research from ENAP countries on protocols for severe bacterial infections in neonates

Out of the 90 countries participating in ENAP, research on severe bacterial infections in newborns is concentrated in just 23 nations, making up 25.5% of the total. A significant portion of these studies come from Sub-Saharan Africa and South Asia, regions that also have the highest rates of neonatal mortality. Specifically, in 2018, Sub-Saharan Africa recorded the highest neonatal mortality rate with 28 deaths per 1000 live births, while Central and Southern Asia followed with 25 deaths per 1000 live births(14). Notable contributors to this body of research include India, Bangladesh, and Ethiopia, each accounting for 8.8% of the studies as shown in Figure 3. These countries are particularly interesting because of their large populations and evident focus on research in this crucial health issue. Conversely, a distinct group of 14 countries has a noticeably smaller number of published studies on the subject.

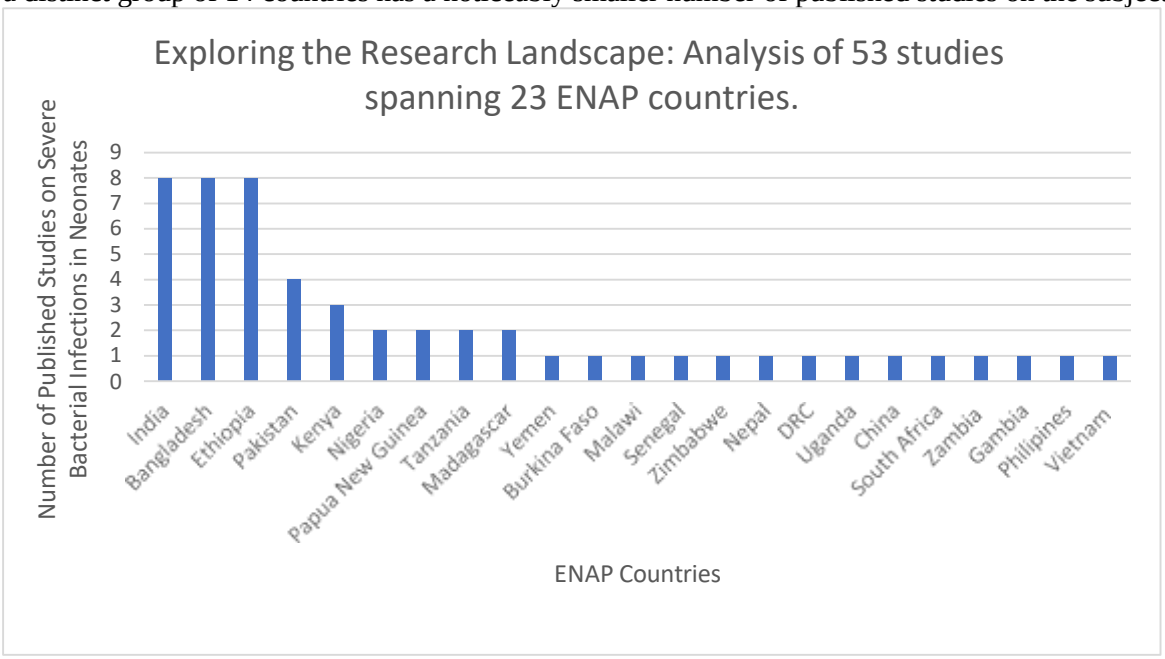

Figure 3: Exploring the Research Landscape: Analysis of 53 studies spanning 23 ENAP countries.

All of the studies focus on the topic of neonatal health, specifically addressing the challenges and interventions related to neonatal infections and mortality. They discuss various aspects such as community perceptions and beliefs (15), quality of care (16, 17), and the use of integrated management

strategies (18). They also highlight the importance of continuous monitoring and supervision (17, 19) and the role of community-based management (15) in improving neonatal health outcomes. Furthermore, they all emphasize the need for a comprehensive approach that includes prevention, protection, and treatment to improve neonatal mortality. Upon conducting an exhaustive analysis of the 53 studies, it becomes strikingly evident that enhancing neonatal survival is contingent upon a comprehensive and multifaceted approach. The results of these studies highlight the significant challenges and potential interventions in addressing neonatal mortality, particularly in low-resource settings. The following methodological strategies mentioned in the included studies emerged as particularly significant:

Preventing Infections is essential since, a substantial proportion of neonatal deaths stem from preventable causes, most notably infections (20). A study by Bhutta et al. (21) indicates that 95% of such neonatal and infant deaths occur in developing countries, where many births take place at home in unsterile conditions. These statistics not only highlight the disparities in infant mortality rates between developed and underdeveloped nations but also underscore the urgent need for initiatives aimed at improving sanitation and prenatal education. Consequently, policy interventions should focus on either promoting institutional deliveries or ensuring a sanitary environment for home births at the very least. To effectively achieve this, a multi-pronged approach is necessary, encompassing the promotion of cleanliness, timely immunization schedules, and the delivery of prenatal services to expecting mothers. These efforts are geared towards staving off infections that may jeopardize the health of newborns (17).

Appropriate Antibiotic usage is worth to mention. The importance of optimal antibiotic usage is emphasised by the African Neonatal Sepsis Trial (AFRINEST) group, as it can significantly decrease infection-related fatalities and is considered a crucial intervention for child survival. Ensuring access to high-quality care is essential to guarantee timely and effective antibiotic treatment for neonates (22). In contexts with limited resources, inpatient care may not always be feasible or culturally acceptable for many families due to financial, cultural, or logistical reasons. Therefore, interventions aimed at enhancing the prevention, early diagnosis, and management of bacterial infections in neonates should be given high priority. Nevertheless, it is important to recognise that the inappropriate use of antibiotics could contribute to the emergence of multi-drug-resistant bacteria, posing a substantial concern in low-income nations (5).

Enhancing quality of care at birth and in the initial days is a key. A significant contributor to neonatal mortality is the lack of access to quality care during labour and the critical initial days of life. Notably, substantial reductions in neonatal deaths can be achieved by elevating the quality of care provided during this crucial period. This encompasses ensuring the presence of skilled attendants during childbirth, delivering appropriate care to preterm infants, and promptly addressing complications in newborns (17). In addition, research throws light on the acute prevalence of severe neonatal infections in Madagascar (5), with 17.7 cases per 1,000 live births. These numbers suggest that besides improving birth conditions, immediate attention should also be paid to postnatal care. This could involve rapid diagnostic tests, more widespread availability of antibiotics, and urgent medical attention for newborns showing signs of infection.

Community-Based management of pneumonia is a noteworthy example from a study conducted in Nepal highlights the effectiveness of managing pneumonia within communities, leading to a considerable 27% reduction in all-cause neonatal mortality (23). Proactively focusing on the prevalent sources of infections and implementing evidence-based practices can substantially diminish the overall mortality rate. Especially in remote or underserved areas, training local health workers can serve as an effective stopgap measure, providing timely medical intervention that could be lifesaving.

Integrated Management of Neonatal and Childhood Illnesses (IMNCI) strategy is designed with three primary pillars in mind: enhancing the skills of healthcare practitioners in diagnosing and treating illnesses, strengthening health systems to ensure the effective delivery of child healthcare services

(including adequate supplies of medications, supervision, and thorough monitoring and evaluation), and implementing interventions at the community and household level to address factors that contribute to childhood illnesses. By implementing these strategies, the aim of significantly reducing neonatal mortality and achieving the Sustainable Development Goal (SDG) target of 12 deaths per 1000 live births becomes a realistic goal (14).

Empowering healthcare providers through capacity building and tailored training programs for healthcare providers and program managers working in delivery facilities can significantly enhance their proficiency in adopting new interventions and improve the quality of care provided (17). Capacity building refers to the development of knowledge, skills, and abilities in individuals, organizations, and communities to competently drive and sustain the interventions. The results of a study by Nelson et al. (24), which shows significant knowledge improvement in South Sudan's frontline healthcare workers post-training, affirms the impact of educational initiatives. This serves as an encouragement for further investments in capacity-building programs, not just in South Sudan but in similar contexts where healthcare providers may lack essential knowledge about neonatal care.

Continuous Monitoring and Oversight means that every stage, from planning and implementation to evaluation, needs careful attention to detail and regular assessment. The capacity building of all stakeholders involved plays a pivotal role in this process. A study (19) found that facilities with functional Quality Improvement Teams (QITs) had improved client flow, classification, and documentation of Sick Young Infants (SYIs) and had reduced the number of commodity stock-out days.

Stage2

The appropriate methodologies employed for the studies are outlined in the below table with the specifics of protocols that are accessible on a public domain.

		TYPE 1: PROTOCOL DETAILS	
Country	**Year**	**Protocol Title**	**Author**
Malaysia	2014	Rational Antibiotic Utilization in Selected Pediatric Conditions (25)	Ministry of Health Malaysia and Academy of Medicine Malaysia
	2020	Neonatal Antibiotic Guideline [updated](26)	University of Malaya Medical Centre: Neonatal Intensive Care Unit
Kazakhstan	2009	Pediatric Care Standard in the Republic of Kazakhstan (27)	Joint Commission on the Quality of Medical Services of the Ministry of Healthcare of the Republic of Kazakhstan.
China	2013	Early essential newborn care: clinical practice pocket guide(28)	Western Pacific Regional Office of the WHO
Uganda	2021	Essential Maternal and Newborn Clinical Care Guidelines for Uganda(29)	The Republic of Uganda Ministry of Health: Reproductive and Child Health Department
Sierra Leone	2018	National Protocols and Guidelines for Emergency Obstetric and newborn care(30)	Government of Sierra Leone Ministry of Health and Sanitation: Directorate of Reproductive and Child Health

South Africa	2017	Standard clinical guidelines and EDL for Paediatric Care (31)	National Department of Health
	2014	LINC guidelines for district hospitals (Limpopo) and LINC Charts on routine care and the care of the sick and small newborn(32)	National Department of Health and Limpopo Initiative for Newborn Care
Rwanda	2019	National Neonatal Care Protocol(33)	Republic of Rwanda, Ministry of health
Bangladesh	2009	National Neonatal Health Strategy and Guidelines for Bangladesh(34)	Ministry of Health and Family Welfare
	2021	Newborn Health Standard Operating Procedures (SOP)(35)	
Sri Lanka	2014	National Guidelines for Newborn Care - Volume I-III(36)	Family Health Bureau: Ministry of Health: Antenatal and Newborn care Unit
	2020	National Guidelines for Newborn Care - Volume I-III (Revised)(37)	
India	2009	Facility Based Integrated Management of Neonatal and Childhood Illness (F-IMNCI) Chart Booklet.(38)	Ministry of Health & Family Welfare, Government of India
	2014	Operational Guidelines: Use of Gentamicin by ANMs for management of sepsis in young infants under specific situations(39)	
Nepal	2016	National Neonatal Clinical Protocol (40)	Ministry of Health, Department of Health Services, Child Health Services
Egypt	2010	Neonatal Care Protocol for Hospital Physicians (41)	Egyptian Ministry of Health
Zimbabwe	2017	Reproductive, Maternal, Newborn, Child, Adolescent Health & Nutrition Quality Improvement Guidelines(42)	Ministry of Health and Child Care Family Health Department
Ethiopia	2014	Neonatal Intensive Care Unit (NICU) Training Participants' Manual(43)	Ministry of Health Ethiopia
	2021	Neonatal Intensive Care Unit (NICU) Management Protocol(44)	
Malawi	2015	Neonatal Operational and Clinical Guidelines (45)	Ministry of Health Malawi: Reproductive Health Directorate
	2016	Care of the infant and newborn in Malawi: The COIN Course Participants Manual(46)	Research Repository St. Andrews
Solomon Islands	2017	Standard Treatment Manual for Children- 4th Edition(47)	Ministry of Health and Medical Services
Burkina Faso	2018	Emergency Obstetric and Neonatal Care(48)	Department of Health Burkina Faso

Liberia	2015	Newborn Protocols and Guidelines (49)	Ministry of Health Liberia
Eritrea	2018	Reproductive, Maternal, Newborn, Child, Adolescent Health, Nutrition and Healthy Aging Programs in Eritrea(50)	Division of Family and Community Health of Eritrea
Tanzania	2019	National Guideline for Neonatal Care and Establishment of Neonatal Care Unit(51)	Ministry of Health Tanzania: Community Development, Gender, Elderly and Children
Kenya	2017	Integrated Management of Newborn and Childhood Illness (IMNCI): A guide for healthcare workers(52)	Ministry of Health: Newborn Child and Adolescent Health Unit (NCAHU)
Eswatini	2018	Kingdom of Eswatini Neonatal Care Clinical Guidelines(53)	Ministry of Health, UNICEF, WHO
Papua New Guinea	2016	Standard Treatment for Common Illnesses of Children in Papua New Guinea: 9th Edition(54)	Paediatric Society of Papua New Guinea
Somalia	2015	Somali Treatment Guidelines in line with Essential Package of Health Services(55)	Somali Health Authorities & World Health Organization
Philippines	2019	Clinical Practice Guidelines for the Screening, Diagnosis, Treatment and Prevention of Neonatal Sepsis(56)	Philippine Society of Newborn Medicine (PSNbM) and the Pediatric Infectious Disease Society of the Philippines (PIDSP)
Zambia	2011	Essential Newborn Care Guidelines (57)	Ministry of Community Development: Mother and Child Health
Namibia	2011	Namibia Standard Treatment Guidelines(58)	Republic of Namibia: Ministry of Health and Social Services
Nigeria	2021	National Guidelines for Comprehensive Newborn Care(59)	Federal Ministry of Health
Nicaragua	2009	Algorithm for diagnosis and treatment of neonatal sepsis(60).	Ministry of Health of Nicaragua (MINSA) & USAID
Iran	2020	Clinical Guideline Adaptation for Treatment of Neonatal Sepsis Based on Frequency of Microbial Agents(61)	Tabriz University of Health Sciences

Table 2: Framework of components: Type 1: Protocol Details

	TYPE 2: PROTOCOL SPECIFICATIONS					TYPE 3: CLINICAL INDICATORS AND PROCEDURES		TYPE 4: PROTOCOL GRADING (Out of 7)
Country	National Availability	Antibiotics Mentioned	Doses Mentioned	First Line Antibiotics Recommended	Second line Antibiotics Recommended	Signs of Sepsis	Blood Cultures	
Malaysia	✓	✓	✓	✓	✓	✓	✓	7
Kazakhstan	✓	✓	✓	✓	✓	✓	✓	7
China	✓	✓	✓	✓	✓	✓	✓	7
Uganda	✓	✓	✓	✓	✓	✓	✓	7
Sierra Leone	✓	✓	✓	✓	✓	✓	✓	7
South Africa	✓	✓	✓	✓	✓	✓	✓	7
Rwanda	✓	✓	✓	✓	✓	✓	✓	7
Bangladesh	✓	✓	✓	✓	✓	✓	✓	7
Sri Lanka	✓	✓	✓	✓	✓	✓	✓	7
India	✓	✓	✓	✓	✓	✓	✓	7
Nepal	✓	✓	✓	✓	✓	✓	✓	7
Egypt	✓	✓	✓	✓	✓	✓	✓	7
Zimbabwe	✓	✓	✓	✓	✓	✓	X	6
Ethiopia	✓	✓	✓	✓	✓	✓	X	6
Malawi	✓	✓	✓	✓	✓	✓	X	6
Solomon Islands	✓	✓	✓	✓	✓	✓	X	6
Burkina Faso	✓	✓	X	✓	✓	✓	✓	6
Liberia	✓	✓	✓	✓	X	✓	✓	6
Eritrea	✓	✓	✓	✓	✓	✓	X	6
Tanzania	✓	✓	✓	✓	✓	✓	X	6
Kenya	✓	✓	✓	✓	X	✓	✓	6
Iran	X	✓	✓	✓	✓	✓	✓	6
Eswatini	✓	✓	X	✓	✓	✓	✓	6
Papua New Guin	✓	✓	✓	✓	X	✓	X	5
Somalia	✓	✓	X	✓	X	✓	✓	5
Philippines	✓	✓	X	X	X	✓	X	3
Zambia	✓	✓	X	✓	X	X	X	3
Namibia	✓	✓	X	✓	X	X	X	3
Nigeria	✓	✓	X	X	X	✓	X	3
Nicaragua	✓	X	X	X	X	✓	✓	3

Table 3: Analysis of Framework Components Type 2 and Type 3 for Type 4 (Grading of Protocols)

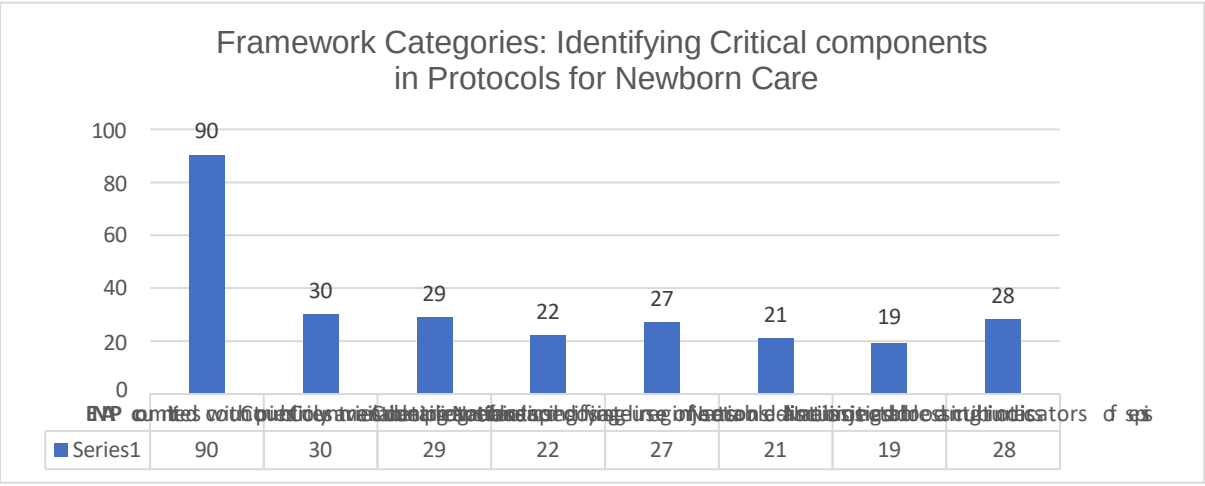

Figure 4: Framework Categories: Identifying Critical components in Protocols for Newborn Care

Each Framework Category in the above context is methodologically investigated as below.

Type 1: Protocol Details, it becomes evident that out of the 90 countries that have committed to ENAP, a relatively small proportion of only 30(33.3%) countries have taken the step to make their protocols publicly accessible. Furthermore, among these 30 countries, a specific subset of 23(25.5%) nations has gone above and beyond by publishing guidelines from the year 2014 onwards, coinciding with the initiation of their commitment to ENAP.

Type 2: Protocol Specifications offers a unique lens through which to view the situation. Among the 90 nations involved, a mere 29(32.2%) nations have officially acknowledged the critical role that antibiotics play within the realm of sepsis care. Delving deeper, it becomes apparent that within this group of 90 countries, 22(24.4%) nations have diligently outlined precise and standardised dosing regimens for the administration of antibiotics. Within the subset of protocols, a noteworthy number of 27(30%) protocols explicitly refer to the usage of first-line injectable antibiotics. A further breakdown reveals that 22 (24.4%) countries have tried to combine detailed dosing regimens with explicit mentions of first-line antibiotics. This is where a noticeable gap in comprehension and implementation comes into focus. As for second-line injectable antibiotics, 21 (23.3%) countries have taken the initiative to lay down guidelines, with 20 (22.2%) of these countries also taking care to specify the dosing. Interestingly, among the entire pool of 90 countries, 20 (22.2%) countries have succeeded in issuing guidelines that encompass both lines of antibiotics, complete with the necessary dosing information.

Type 3: Clinical Indicators and Procedures bring another dimension to the analysis. Within this category, 28(31.1%) countries have thoughtfully included a mention of the tell-tale signs of sepsis, along with the associated warning signs that healthcare providers should remain attentive to. Within a more specific context, 19(21.2%) countries have made it a point to emphasise the importance of obtaining blood cultures in situations involving severe neonatal bacterial infections. Perhaps the most striking discovery is the fact that a mere 19(21.1%) out of the 90 countries have managed to achieve a comprehensive integration of all the essential elements of Clinical Indicators and Procedures. These encompass various vital aspects, with blood cultures standing out as a pivotal component.

Expanding the scope of analysis, the additional insights reveal a decision to incorporate elements from two components (Type 2 and Type 3), resulting in the creation of a grading system (Table 5). This system encompasses national availability, Antibiotics Mentioned, Doses Mentioned, First-Line Antibiotics Recommended, Second-line Antibiotics Recommended, Signs of Sepsis, and Blood Cultures. Each of these categories is allocated one point. Among the 90 countries in consideration, a relatively small subset of 13(14.4%) countries has emerged as exemplars by successfully embracing and seamlessly integrating all these diverse elements into their respective national protocols.

These findings draw attention to substantial gaps that persist in both the availability and the effectiveness of sepsis protocols across the nations participating in ENAP. It is apparent that the number of countries with openly accessible protocols remains restricted, and an even more limited subset has managed to adeptly incorporate all the indispensable components of sepsis care, thus aligning with the established SSNC standard 1.12 (as showcased in Table 2).

Results and Discussion:

Initially, out of 622 publications, 53 were selected for in-depth analysis, largely emanating from 23 of the 90 countries involved in the Every Newborn Action Plan (ENAP). These are concentrated in regions like Sub-Saharan Africa and South Asia, known for high neonatal mortality. The studies collectively advocate for a multifaceted approach to reduce neonatal mortality, emphasizing aspects such as healthcare quality, community perceptions, and integrated strategies. Notably, India, Bangladesh, and

Ethiopia are key contributors to this research. The findings underscore the need for comprehensive, globally-distributed efforts to address neonatal health.

Second, out of 90 countries, only 30 (33.3%) have made their neonatal management protocols accessible to the public. Within this subset, 28 countries (93.3%) recognize the need for assessing clinical symptoms upon admission. Nearly all, 29 countries (96.7%), advocate the use of antibiotics for neonatal infections, and 22 among them (73.3%) provide specific dosage guidelines. A total of 19 countries (63.3%) highlight the role of blood cultures in managing neonatal infections. Overall, 13 countries (43.3%) have protocols that comprehensively integrate all the elements outlined in the standard 1.12.

Stage 1

Contextual factors are important since, in some countries, political, social, and economic factors could pose significant barriers to implementing national protocols for inpatient management of severe bacterial infections in newborns. There may be limited access to published data due to publications in different languages. This could include a lack of baseline data or inadequate monitoring and evaluation systems, which could make it difficult to determine whether the interventions are having the desired impact. It may be challenging to determine the effectiveness of the guidelines. Possible reasons for this could be constraints in research funding or underdeveloped research infrastructure.

Early-Stage research has its own merits. The observation that the count of studies per country is relatively modest implies that the research efforts in this field are still in their early stages of development. This suggests that the exploration of neonatal and maternal health, as guided by the ENAP framework, is a growing area of interest and attention among these nations. As these countries further invest in research and gather data, the insights gained are likely to contribute to the advancement of knowledge and the refinement of healthcare practices, ultimately aiding in the improvement of neonatal and maternal outcomes.

A varied level of research activity is observed because the substantial range in the number of studies conducted by different countries points to the diversity in the extent of global research engagement. Some nations might be more proactive in allocating resources and establishing research infrastructure, leading to a higher volume of studies. On the other hand, countries with a lower count of studies could be facing challenges such as limited funding, lack of research institutions, or competing healthcare priorities. This variation highlights the need for collaborative efforts, where countries with greater research capacity can potentially provide support and resources to help bridge the research gap in regions with fewer resources.

Absence of quality assessment is a barrier because the data presented does not include an evaluation of the quality of the studies conducted. While the quantity of research output is an important metric, the absence of quality assessment prevents making definitive conclusions about the efficacy and reliability of the findings. High-quality research involves rigorous methodologies, robust data collection, and thorough analysis. Without assessing the quality, it's challenging to determine which countries are generating the most trustworthy and impactful research outcomes. Including a measure of research quality would provide a more comprehensive view of the contributions made by different nations to the field of neonatal and maternal health.

Stage 2

Strategic insights from a Graphical Analysis (Figure 4) are observed in Advancing Sepsis Protocols in place for Improved Neonatal Care. The utilisation of this study as a tool unveils distinct opportunities for countries to enhance their sepsis protocols. These findings warrant an immediate call to action, prompting nations to embark on the refinement or development of protocols.

Evident discrepancy is observed due to a notable difference between nations with publicly available protocols and those that fully cover all aspects of sepsis care. This gap indicates that many countries may have protocols that are either obsolete or lacking in some areas. Protocols for medication dosing are crucial for the safe treatment of newborns, yet only 22 countries, or 24.4%, include this in their guidelines. This omission creates potential for mistakes and inconsistent medication administration. Aligning these protocols with WHO guidelines could benefit healthcare systems universally.

The Importance of Antimicrobial Stewardship is one of the most crucial requirements. The absence of robust guidelines not only leaves room for error but also amplifies the global challenge of antimicrobial resistance (62). This is an urgent concern in today's healthcare landscape, especially given the rise of multi-drug-resistant bacteria, as highlighted in a study from Madagascar (5) which reported a high rate of severe neonatal infections with resistant pathogens. Implementing antibiotic stewardship strategies in neonatal intensive care units (NICU) could significantly minimize the risk of drug resistance (63). Reduced usage of antibiotics in such settings has been shown to lower the prevalence of Methicillin-resistant Staphylococcus aureus (MRSA) and multi-drug-resistant bacteria, further underscoring the need for comprehensive and up-to-date neonatal sepsis protocols.

Limited mention of Second-Line Injectable Antibiotics is a concerning revelation emerges in the minimal count of countries explicitly specifying the utilisation of second-line injectable antibiotics. Given their crucial role in treating severe sepsis, this deficiency poses a potential risk to effective sepsis management. In the realm of neonatal infections, ciprofloxacin, a second-generation fluoroquinolone, occasionally serves as an alternative treatment option (18). However, reports indicate growing resistance to this antibiotic (5). Similarly, co-amoxiclav, a form of penicillin, is another option when intravenous administration isn't feasible. Yet, misuse of these antibiotics can exacerbate pathogen resistance (63). Consequently, it's essential to exercise caution when utilizing second-line antibiotics, ideally guided by culture and sensitivity tests when available (7).
Missed emphasis on Sepsis Indicators has revealed another significant observation among numerous countries with reference to the use of antibiotics, while neglecting to incorporate vital sepsis indicators. This oversight is deeply troubling, as the timely recognition of sepsis indicators is pivotal for improving survival rates. Diagnosing sepsis in neonates and young infants is often a complex task, even for seasoned healthcare professionals, due to its nonspecific clinical indicators (1). The WHO has outlined various symptoms to identify possible serious bacterial infection (pSBI), which is commonly linked with sepsis (64). These symptoms encompass issues such as inadequate feeding, seizures, rapid respiration, pronounced chest retractions, either fever or hypothermia, and limited movement or complete lack of it unless stimulated.

Grading (Type 4) of protocols against SSNC Standard 1.12 was a necessary indicator because within the cohort of 30 countries with accessible protocols, a noteworthy subset of 13 countries has demonstrated exemplary commitment by satisfying all seven criteria (Table 3). These high-performing countries include Malaysia, Kazakhstan, China, Uganda, Sierra Leone, South Africa, Rwanda, Sri Lanka, Bangladesh, Egypt, Nepal, India, and Iran. Their dedicated approach places them at an advantageous standing.

Strengthening neonatal healthcare through resource management is a novel concept to highlight as observation. The concept of implementing efficient national protocols for the management of severe bacterial infections in newborns, particularly within the framework of ENAP, presents a compelling avenue for enhancing healthcare outcomes. It holds the potential to result in better health outcomes, improved access to high-quality healthcare, and enhanced skills of healthcare workers, greater community involvement, and better healthcare systems.

The presence of antibiotics significantly influences the effective treatment of severe bacterial infections in newborns, which is a key factor in neonatal mortality, especially in areas with limited resources. Low-income countries bear a substantial burden of neonatal deaths due to these infections. A

comprehensive study conducted in low-level private health facilities in Western Uganda sheds light on the availability of antibiotics. The findings highlight that many healthcare facilities have the necessary antibiotics for treating pneumonia and severe bacterial infections in children (16). However, an interesting perspective emerges on the ongoing challenge of having suitable antibiotic formulations for neonates. Their research, which focuses on simplified antibiotic regimens for treating serious infections in infants across South Asia and sub-Saharan Africa, identifies regions where suitable antibiotic formulations remain a concern (65). This perspective calls for urgent attention and action to address the disparities in antibiotic availability and formulation, which can have profound implications for neonatal health outcomes. The issue of antibiotic stock-outs, prevalent in resource-limited settings, arises from various challenges. Problems in distribution, often linked to transportation issues, and fluctuations in antibiotic supply chains have been documented (66). The shortage of essential antibiotics can hinder the timely and effective management of severe neonatal infections.

A notable example from Kenya, the Ponya Mtoto project, offers promise. This initiative has improved predicting and quantifying essential supplies for managing severe infections in young infants. By monitoring antibiotic stock-outs and other crucial resources, and using data for strategic planning, significant improvements have been achieved. This resulted in a substantial reduction in the average duration of unavailability of amoxicillin dispersible tablets, a critical antibiotic for managing severe neonatal infections (19). Strategies to ensure consistent access to suitable antibiotic formulations, robust distribution mechanisms, and resilient antibiotic supply chains are imperative. The findings from this review underscore the significance of not only having antibiotics available but also ensuring their accessibility and appropriateness for neonatal care.

Conclusion

The strength of this study lies in its comprehensive analysis of 23 countries with accessible published research on severe bacterial infections in neonates, 18 of which have established publicly available national protocols for their management as well. These nations are making unified efforts to tackle neonatal survival challenges. However, a critical limitation is the presence of gaps in these protocols compared to WHO global standards. Furthermore, 66% of ENAP countries have not made their protocols publicly available, which restrict collaborative efforts and inhibit accountability. While many protocols acknowledge the use of antibiotics for sepsis treatment, few provide specific dosage guidelines, illustrating a concerning fragmentation of knowledge.

The limited public availability of guidelines hinders the development of a global community focused on newborn health. To foster a collaborative learning environment, nations must make their protocols public and ensure they are comprehensive and practical. Moreover, only 14% of countries achieve the highest score in the grading system (Type 4), indicating a pressing need for robust protocol implementation. To truly advance under the ENAP framework, nations should align their protocols with best practices. This will require global teamwork, open sharing of knowledge, and a firm commitment to protecting newborn lives.

While significant contributions in research are coming from regions like sub-Saharan Africa and South Asia, there is an evident gap due to varying resource capabilities. Resource-rich nations have the opportunity and responsibility to partner with those facing limitations, thereby boosting collective research effectiveness. The research landscape must prioritize both the volume and value of studies to make meaningful progress in maternal and neonatal outcomes. Additionally, there's a need for more nuanced research to develop comprehensive strategies that go beyond mere symptom identification, such as including diagnostic measures like blood tests in sepsis treatment protocols.

This study highlights are not just the need for public accessibility of neonatal care protocols, but more importantly, on bridging the significant discrepancies between national protocols and World Health Organization guidelines. The current limited public availability hampers both accountability and the

growth of a global, collaborative network committed to enhancing newborn health. Making these protocols publicly accessible would catalyse a shared learning environment, thereby better positioning nations to meet the aims of the Every Newborn Action Plan (ENAP) and Sustainable Development Goal 3.2. To attain the targeted fewer than 12 neonatal deaths per 100 live births by 2023, as outlined in Sustainable Development Goal 3.2, an unwavering focus on quality care is paramount. Therefore, advancing neonatal health outcomes globally necessitates a multifaceted strategy that includes transparent sharing of aligned protocols and sustained international collaboration focused on delivering high-quality care.

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