Neonatal and Perinatal Infections

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KEYWORDS

• Neonatal sepsis • Neonatal morbidity • Neonatal mortality • Maternal health
• Maternal infection • Younger-than-5 mortality • Antimicrobial resistance

KEY POINTS

- Globally, 2.6 million neonates die each year, with preterm birth, infections, and intrapartum-related conditions being the leading causes.
- Maternal, environmental, and infant factors are closely linked to neonatal health and influence acquisition of infection in the perinatal and neonatal period.
- Evidence-based preventive and therapeutic interventions have been identified that address risk factors and underlying causes of neonatal infections.
- The emergence of new infections, such as Zika, and increasing antimicrobial resistance present challenges that must be addressed to achieve substantial reductions in neonatal mortality.

BURDEN AND EPIDEMIOLOGY

Significant progress has been made toward reducing child mortality in low- and middle-income countries (LMIC). Younger-than-5 deaths have decreased from 12.7 million in 1990 to 5.8 million in 2015, of which 2.6 million were neonates.[1] In spite of a notable reduction in younger-than-5 mortality, the decrease in neonatal mortality has been unsatisfactory. Forty-five percent of younger-than-5 mortality now occurs in the first month of life.[2] In addition to 2.6 million newborn deaths, there are an

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estimated additional 2.6 million still births, of which an estimated 12% are attributable to fetal infections.[3]

In 2015, the world transitioned from Millennium Development Goals to Sustainable Development Goals (SDGs). Along with intrapartum causes and preterm birth complications, infections are a major direct cause of neonatal deaths.[4] Preventing and managing neonatal infections are crucial to achieve subgoal 3.2 of SDGs, which aims to end preventable deaths of newborns and children younger than 5 years by 2030.

This article addresses neonatal infections that are primarily acquired in the perinatal period (late pregnancy, intrapartum, and postnatal period) (**Table 1**) and manifest clinically in the perinatal and neonatal period. Maternal infections acquired by the neonate early in pregnancy, such as rubella, syphilis, and toxoplasmosis, are not considered.

Conventionally, the perinatal period begins at 22 completed weeks of gestation and ends 7 days after birth. The neonatal period represents the first 28 days of life. The relative lack of structural barriers and an immature immune system put neonates at greater risk of infection and mortality. Preterm birth (36%), infections (23%), and intrapartum-related conditions, such as birth asphyxia (23%), are responsible for the greatest number of neonatal deaths[4] (**Fig. 1**). However, in the late neonatal period (>7 days), 48% of deaths are attributable to infections, the leading cause of death in this period[4] (see **Fig. 1**).

RISK FACTORS FOR NEONATAL AND PERINATAL INFECTIONS

Maternal Health and Infections

Poor maternal health and inadequate access to health care are determinants for neonatal outcomes.

Maternal infections

Infections during pregnancy are associated with spontaneous abortion, stillbirth, preterm delivery, and low birth weight (LBW).[5] Moreover, some infections are transmitted to the fetus, resulting in neonatal morbidity or fetal loss. Transmission can occur hematogenously from mother to baby or as an ascending infection via the uterine cervix. Early onset sepsis (EOS) and most infections in the perinatal period are associated with maternal factors. A neonate's immature immune system depends on maternal

Table 1
Key maternal infections acquired by neonates and period of transmission

	Early Pregnancy	Midpregnancy	Late Pregnancy	Intrapartum	Postnatal
Rubella	+	—	—	—	—
Toxoplasmosis	+	+	—	—	—
Syphilis	—	+	+	—	—
Cytomegalovirus	+	+	+	+	+
Zika virus	++	+	+	—	—
Chickenpox	—	—	+	+	+
Herpes simplex virus	—	—	—	+	—
HIV	—	—	+	++	+
Hepatitis B	—	—	—	+	—
Group B streptococcus	—	—	—	+	—

Abbreviation: HIV, human immunodeficiency virus.

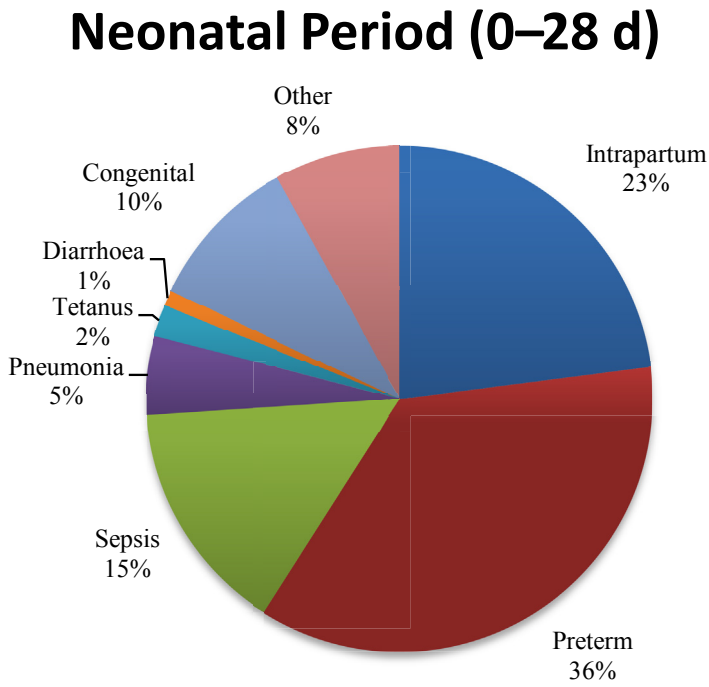

Fig. 1. Causes of death in the neonatal period globally. (*Adapted from* Lawn J, Blencowe H, Oza S, et al. Every newborn: progress, priorities, and potential beyond survival. Lancet 2014;384(9938):189–205.)

antibodies that cross transplacentally. However, maternal infections occurring close to term may not generate sufficient immune protection to pass to the fetus.

Cytomegalovirus (CMV), rubella virus, varicella-zoster virus, hepatitis B and C, and Zika virus can transmit to the fetus through the blood. Important organisms acquired by the ascending route are group B streptococcus (GBS), herpes simplex virus (HSV), and *Escherichia coli*.[6] Chances of acquiring certain infections intrapartum increase with vaginal deliveries, and clinicians may opt for cesarean deliveries in such cases.

Premature rupture of membranes

Premature rupture of membranes (PROM) is when the amniotic sac ruptures more than 1 hour before the onset of labor. Ruptured membranes increase the risk of maternal infection, preterm birth, and EOS. Some estimates show that nearly 10%[6] of neonates develop infection following PROM, whereas others report lower (4%) or higher (33%) rates.[7,8] Risk is directly proportional to the time membranes rupture before delivery: the earlier the membranes rupture, the higher the risk of infection.

Organisms most commonly associated with EOS secondary to PROM include GBS. Studies in low-income settings report predominantly gram-negative organisms.[7] Gram-positive species, such as GBS and *Staphylococcus aureus*, though detected, were not as common as in developed settings.

Intra-amniotic infection

Aside from other causes, a mother can develop fever during labor due to chorioamnionitis or intra-amniotic infection (IAI). IAI is associated with adverse pregnancy and

neonatal outcomes, including stillbirth, preterm birth, and infections. Risk of neonatal septicemia in these cases is estimated at 5% to 15%. Neonatal outcomes are influenced by not only causative organisms but also birth weight and timing of antibiotic therapy.[6]

OTHER RISK FACTORS FOR ACQUIRING INFECTION

Environmental Factors

Late-onset neonatal infections are commonly associated with nosocomial or community-related environment factors.

Hospital-acquired infections

Hospitals, especially nurseries and intensive care units, are high-risk environments for acquiring infections. Infants are in frequent contact with health care workers, leading to spread of pathogenic organisms, especially multidrug-resistant types. With increasing facility-based deliveries in LMIC, the risk of hospital-acquired infections has also increased. Some studies from high-income countries (HIC) report that more than 20% of critically ill newborns who survive greater than 2 days acquire a nosocomial infection.[6] Major pathways for nosocomial spread of organisms in neonate are summarized in **Box 1**.

Community-acquired infections

Because of social and economic factors, many births, especially in rural areas of LMIC, take place at home. Risk of community-acquired infections in such home-delivered infants is higher. Other factors, such as lack of skilled birth attendants, unhygienic delivery practices, and unsterile cord cutting, further increase the risk of

Box 1
Common pathways for the nosocomial spread of sepsis in a neonate

- Excessive vaginal examinations of mother
- Lack of aseptic delivery
- Inadequate hand hygiene and glove use
- Failures in sterilization/disinfection or handling/storage of multiuser equipment, instruments, and supplies leading to contamination
- Inadequate environmental cleaning and disinfection
- Overuse of invasive devices
- Reuse of disposable supplies without safe disinfection/sterilization procedures
- Failures in isolation procedures/inadequate isolation facilities for babies infected with antibiotic-resistant or highly transmissible pathogens
- Unhygienic bathing and skin care
- Absence of mother-baby cohorting
- Inappropriate and prolonged use of antibiotics
- Lack of knowledge, training, and competency regarding infection control practice
- Overcrowded and understaffed labor and delivery rooms

Adapted from Khan AM, Bhutta ZA. Childhood infectious diseases: overview. In: Quah SR, Cockerham WC, editors. The international encyclopedia of public health. 2nd edition. vol. 1. Oxford (United Kingdom): Academic Press; 2017. p. 517–38.

infections. In other settings, newborns discharged from the hospital can also acquire infections from household or community contact.

Infant Factors

Compared with other infants, those who have bacterial sepsis frequently possess distinctive risk factors, such as preterm birth, LBW, PROM, maternal IAI, and birth asphyxia.

The 20 million LBW babies born globally each year[9] are either preterm or small for gestational age (or both). Vulnerability to hypothermia, immature immune systems, and an underdeveloped skin barrier predispose them to infections.[10] Preterm birth is considered the chief risk factor for acquiring neonatal infections immediately before, during, or after delivery.[6] Preterm birth complications are now the number one killer of children younger than 5 years.[4]

Evidence indicates a low Apgar score at birth is associated with increased risk of infection-attributable neonatal mortality.[11] Fetal hypoxia and hypothermia can impair immune mechanisms as well as predispose to birth asphyxia, a risk factor for infections.[6]

PERINATAL VIRAL INFECTIONS

These viral infections are largely acquired from the mother in the perinatal period and manifest soon after birth.

Cytomegalovirus

CMV is the most common perinatal viral infection. Primary CMV infection in pregnant women can cause fetal infection in 40% of the cases. Ten percent to 15% are symptomatic, whereas the rest have subclinical congenital infection.[12] Moreover, perinatal infection can also occur by exposure to the virus in the maternal genital tract during delivery, through breastfeeding, or blood transfusions.

Symptomatic congenital CMV at birth occurs in 10% of infected infants and can present with jaundice, hepatosplenomegaly, and microcephaly. Complications in infants include sensorineural hearing loss (35%), neurologic deficits (66%), and death (4%).[13] Twenty-five percent of neonates with asymptomatic congenital CMV will have sequelae in the first 2 years of life.[6] Infants with perinatal CMV can develop a sepsis-like syndrome accompanied with hepatosplenomegaly.

Diagnosis of maternal CMV is through serologic tests for CMV antibodies. Amniocentesis is the best option for prenatal diagnosis of fetal congenital CMV infection.[12] Postnatal diagnosis of congenital CMV is recommended through virus isolation.

Antenatal treatment of maternal CMV with antiviral agents is not recommended except for research purposes. However, antiviral drugs can be used in symptomatic congenital CMV and have been shown to improve long-term hearing and neurologic outcomes.[13] Vaccine development remains a research priority.

Zika Virus

Zika virus generally causes a mild disease and can even be asymptomatic in pregnant women and adults. However, it can also cause a dengue-like constellation of symptoms, including rash, myalgias, fever, and conjunctivitis. In 2015, reports of association of Zika with increased incidence of Guillain-Barre syndrome and other neurologic conditions led to worldwide alarm. Further evidence suggested that infants born to Zika-infected women can have microcephaly and central nervous system abnormalities. In September 2016, the World Health Organization (WHO)

concluded that Zika infection during pregnancy increases risk of congenital brain abnormalities, particularly with infection acquired in the first trimester.[14] Termed *congenital Zika syndrome* (CZS), it manifests with brain defects, craniofacial disproportion, limb contractures, and ocular and hearing abnormalities.[15] Infections in the third trimester are mostly associated with brain malformations but with normal-sized heads.[16]

Zika is transmitted by bite of the *Aedes aegypti* mosquito and less commonly through sexual contact and blood transfusion. Prevention includes control of mosquito breeding sites and protection against bites. Public health officials in pandemic regions continue to advise women to delay pregnancies until the virus is controlled. There is currently no vaccine for Zika. Treatment is supportive based on symptomatic and fluid management. Similarly, there is no specific treatment of infants with CZS other than supportive care.

Varicella

The 3 main forms of varicella associated with the perinatal and neonatal period are summarized in **Table 2**.

Varicella zoster immunoglobulin is indicated in infants whose mothers manifest the infection between 5 days before and 2 days after delivery. These neonates would not be protected by maternal antibodies.[6]

Introduction of the varicella vaccine has reduced the incidence of varicella zoster virus (VZV) infection among pregnant women, especially in HIC. Coverage of vaccine in LMIC remains low, however incidence of VZV is also low for unclear reasons.

Table 2
Varicella in the neonate in perinatal and neonatal period

	Transplacentally Acquired[a]		Postnatally Acquired
Acquisition by Infant	**Maternal Rash in Early or Midpregnancy**	**Maternal Rash, 5 d Before Delivery to 2 d After Birth**	**Postnatal Infant Chickenpox**
Clinical form in infant	Congenital varicella syndrome	Congenital/neonatal chickenpox	Chickenpox
Signs and symptoms in infant	Rare form with congenital lesions such as • Cicatricial skin lesions • Ophthalmic defects (chorioretinitis, microphthalmia) • Neurologic abnormalities • Hypoplastic limbs *Prematurity, LBW, and death are also possible complications of the syndrome*	Most severe form with • Signs of infection • Rash • Complications, such as hepatitis, pneumonia, or encephalitis *Can be associated with significant mortality*	Generally mild form with signs of infection and rash
Manifestation	First 10 d of life	First 10 d of life	10–28 d after birth

[a] Mother infected during pregnancy.

Herpes Simplex Virus

Eighty-five percent of cases of neonatal herpes are acquired by intrapartum virus exposure in the maternal genital tract. Five percent of neonates acquire disease in utero, whereas 10% acquire postnatally.[17] Disseminated herpes is the most severe form, with multisystem involvement.

Viral culture and polymerase chain reaction (PCR) for HSV DNA are used to diagnose neonatal herpes. Parenteral therapy with antiviral agents and long-term antiviral suppressive therapy are part of the treatment regimen.[18]

Human Immunodeficiency Virus

Mother-to-child perinatal transmission of human immunodeficiency virus (HIV) can occur in utero, most commonly intrapartum or postnatally through breastfeeding. Although a public health challenge, intensified services and global use of efficacious drugs has resulted in decreased rates of transmission. An estimated 1.4 million children were prevented from being infected between 2000 and 2014.[19]

HIV-positive infants could remain asymptomatic during the neonatal period or present with nonspecific symptoms. Suggested average age for onset of clinical signs of perinatally acquired HIV has been between 5 and 6 months.[20] Growth delay, oral thrush, lymphadenopathy, and hepatosplenomegaly are frequent, early findings. Importantly, these children are more susceptible to bacterial and opportunistic infections.

All HIV-exposed infants should receive antiretroviral (ARV) drugs to reduce the chance of perinatal transmission. If possible, prophylaxis should be initiated within 6 to 12 hours of delivery.

Children infected perinatally could present for the first time in adolescence. Conversely, some may have had multiple treatment regimens by adolescence and have a resistant strain, presenting a management challenge.[19]

Hepatitis B

Globally, hepatitis B virus (HBV) chronically infects more than 240 million individuals[21] and causes nearly 1 million deaths annually.[22] Most cases are a consequence of maternal-to-fetal transmission with the most frequent route being intrapartum. Early detection of HBV in mothers can inform prophylactic interventions postnatally.

An infant who has acquired HBV perinatally has a 90% risk of becoming a chronic carrier and a subsequent 15% to 20% chance of dying of chronic liver conditions in adulthood.[23] However, intervening postnatally with hepatitis B immunoglobulin and birth-dose vaccination provides the susceptible infant an 85% to 95% chance of being protected. Conversely, researchers have noted that mothers with a high viral load may pass on HBV to infants, underscoring the importance of peripartum use of antiviral drugs. Further studies are needed to assess appropriate timing of these drugs and their long-term safety in pregnancy.[21] Breastfeeding is not considered a risk factor for transmission and is recommended with accompanying prophylaxis.

Most infected newborns will remain asymptomatic until the first or second decade of life. Rarely, infants will manifest acute hepatitis with associated symptoms.[6] Diagnosis of HBV in neonates is generally made by detecting HBsAg or through PCR. Management is supportive, and treatment regimens available are for children older than 2 years.

BACTERIAL INFECTIONS

Neonatal Sepsis

Sepsis is a significant cause of newborn morbidity and mortality, particularly in preterm and LBW infants. Neonatal sepsis and meningitis are responsible for an estimated 420,000 deaths annually, accounting for 16% of neonatal mortality.[24]

Traditionally, neonatal sepsis is defined by systemic signs and blood stream infection identified in the first 4 weeks of life. Sepsis is classified as EOS or late-onset sepsis (LOS). There is a lack of consensus in the literature as to what age limits define both, though the most commonly used cutoff is less than 7 days (EOS) versus more than 7 days (LOS).

Neonates usually have nonspecific signs of infection, such as lethargy and irritability. Sepsis can be diagnosed both clinically and microbiologically. Some possible signs and symptoms of serious infection in newborns are shown in **Box 2**.

The organisms most commonly causing sepsis in developing and developed countries are given in **Table 3**.

Promptly identifying and treating neonates with infections is critical. Integrated management of childhood illness (IMCI) has been widely implemented, especially in LMIC. Modifications of IMCI to include the neonatal period and expansion to community settings have now been prioritized as a public health strategy.

Box 2
Possible symptoms and signs of sepsis in a neonate

Sepsis

Grunting

Not feeding well

Drowsiness or unconscious

Lethargy

Reduced movements

Fast breathing (60 breaths per minute or more)

Severe chest in-drawing

Increased body temperature (>38°C)

Hypothermia (<35.5°C)

Cyanosis

Convulsions

Signs of bacterial infection (in addition to the aforementioned signs)

Severe jaundice

Severe abdominal distension

Many or severe skin pustules

Umbilical redness

Pus draining from umbilicus

Bulging fontanelle

Joint swelling and tenderness

Adapted from Pocket book of hospital care for children. 2nd edition. Geneva (Switzerland): World Health Organization; 2013.

Table 3
Organisms most commonly causing sepsis in developing and developed countries

Neonatal Sepsis	
Developing Countries	**Developed Countries**
Gram-negative organisms (more common) *Klebsiella* *E coli* *Pseudomonas* *Salmonella*	Gram-negative organisms *E coli* (more common)
Gram-positive organisms (less common) *Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes*	Gram-positive organisms GBS (more common) CONS (NICU settings mostly) *Staphylococcus aureus*

Abbreviations: CONS, coagulase-negative staphylococci; NICU, neonatal intensive care unit.
Adapted from Khan AM, Bhutta ZA. Childhood infectious diseases: overview. In: Quah SR, Cockerham WC, editors. The International encyclopedia of public health. 2nd edition, vol. 1. Oxford (United Kingdom): Academic Press; 2017. p. 517–38.

Recent studies have established effectiveness of simpler treatment regimens that have achieved reductions in neonatal mortality with the use of oral cotrimoxazole and injectable gentamicin by community health workers. The African Neonatal Sepsis Trial (AFRINEST) demonstrated that simplified antibiotic regimens using combinations of injectable gentamicin, oral amoxicillin, and in some cases injectable procaine benzylpenicillin (given at home or at primary health care level) in possible serious bacterial infections (PSBI) were as effective as parenteral WHO-recommended regimens.[25] These strategies could be valuable where referral is a challenge.[26]

Facility-based treatment regimens for neonatal sepsis often use a combination of ampicillin and gentamicin with or without vancomycin. If at risk of *Staphylococcus aureus* infection, cloxacillin with gentamicin is recommended as an option, although rates of methicillin-resistant *Staphylococcus aureus* are rapidly increasing in many settings. The WHO recommends treating neonatal meningitis with ampicillin or a third-generation cephalosporin in combination with gentamicin, for at least 3 weeks.[27] (However, in some settings gentamicin is limited to 2 weeks because of ototoxicity.) **Table 4** shows the commonly used antibiotic treatment options for sepsis in neonates.

Possible Serious Bacterial Infection

As per the WHO's recommendations, serious bacterial infections[28] in neonates should be referred for hospital treatment with a 7-day course of benzylpenicillin with

Table 4
Commonly used antimicrobials for neonatal sepsis

	Antimicrobial Choice	
Likely Cause	**Developed Countries**	**Developing Countries**
Developed countries *Streptococcus* (group B) *E coli* Developing countries *Klebsiella* *Pseudomonas* *Salmonella*	Ampicillin or penicillin plus gentamicin Or Third-generation cephalosporin	Ampicillin or penicillin plus aminoglycoside Or Cotrimoxazole plus gentamicin

gentamicin or ampicillin with gentamicin. However, considering the lack of access and compliance in many low-resource settings, the WHO now recommends that PSBI in neonates be treated at first-level care facilities by a trained health worker.[29] For this purpose, the diagnosis of PSBI is recommended based on the presence of one or more easily identifiable clinical signs.[29] Recommended treatment regimens include intramuscular gentamicin with oral amoxicillin.

GROUP B STREPTOCOCCAL INFECTIONS

GBS is the leading organism causing neonatal sepsis and meningitis and is well-documented in high-income regions. GBS burden in LMIC is poorly recognized. However, certain reviews have associated Africa with a GBS incidence 3 times higher than the Americas.[30] Current global incidence is estimated at 0.53 per 1000 livebirths, which is most likely an underestimate, as many cases in LMIC are fatal before diagnosis.[30]

Risk of infection with GBS is greatest in the first 90 days of life.[31] Colonization of the maternal genital tract, especially in the intrapartum phase, puts the neonate at risk of infection. Based on the age of onset, GBS infection can be early onset (0–6 days) or late onset (7–89 days). Early-onset disease (EOD) is largely a result of vertical transmission from the mother, whereas late-onset disease (LOD) can be from the mother or horizontal transmission from environmental sources. EOD usually manifests with nonspecific signs of bacteremia (80%–85%), pneumonia, or meningitis. LOD, with a lower fatality rate than EOD, can present with similar clinical features. More recently, the terminology *late-late-onset infection* has been applied to GBS disease occurring in infants older than 89 days, most of whom are preterm, which contributes to this late manifestation of GBS.[6]

GBS can be isolated from blood, cerebrospinal fluid, or focal site of infection. Penicillin G is the treatment of choice. However, in most scenarios, before confirmatory microbiology and transition to definitive therapy, initial therapy is started with ampicillin and an aminoglycoside. Fourteen- to 21-day parenteral therapy is advised for both meningitis and septic arthritis.

Most HICs implement universal GBS screening of women at 35 to 37 weeks of gestation through a rectovaginal swab followed by intrapartum antibiotic prophylaxis (IAP) in those with positive cultures. GBS bacteriuria or previous delivery of an infant with invasive GBS always requires IAP. Reliable prophylaxis consists of penicillin G or ampicillin given at least 4 hours before delivery. Widespread application of IAP has been instrumental in decreasing GBS burden in HIC. However, applying IAP in LMIC might prove to be challenging. GBS vaccine development trials are at various stages.[30]

NEONATAL TETANUS

Neonatal tetanus is usually acquired through the umbilical stump following unclean cutting of the cord. Approximately 85% untreated neonates die of the disease. It is completely preventable by immunization of mothers with at least 2 doses of tetanus toxoid. Although the disease cannot be eradicated, widespread maternal vaccination efforts for its elimination have led to a significant decrease in disease incidence and consequent fatalities.

EVIDENCE-BASED INTERVENTIONS FOR PREVENTION OF NEONATAL INFECTIONS

Well recognized in literature, out of all causes of death, severe infections are likely simplest to intervene, prevent, and treat.[32] The 2014 *Lancet* Every Newborn series

concluded that scaling up of available interventions across the continuum of care (preconception to the postnatal period and beyond) could reduce neonatal infections by 84%[33] and prevent nearly 2 million deaths by 2025.

Antenatal Interventions

- Improved maternal nutrition, balanced protein energy and micronutrient supplementation in pregnancy, and early detection and management of intrauterine growth restriction have all been shown to reduce LBW and, indirectly, the risk of neonatal infections.
- Screening and management of maternal infections during pregnancy, such as HIV, syphilis, herpes, and hepatitis B, are central to preventing prenatal transmission.
- It is well established that tetanus toxoid vaccination of pregnant mothers (or women of childbearing age) has led to a significant reduction in neonatal tetanus and consequent mortality.[34] Rubella and varicella vaccination have reduced the incidence of the diseases in pregnant women. Influenza vaccine is recommended in pregnant women to reduce the incidence of disease and its complications in mothers and neonates. However, there is less consistent evidence to demonstrate positive effects of pneumococcal and *Haemophilus influenzae* type B.[33]

Intrapartum Interventions

- Optimal handwashing, clean birth practices, and sterile cord cutting can reduce the risk of neonatal sepsis and mortality. According to the *Lancet* Every Newborn series, handwashing with soap and water by birth attendants and caregivers could reduce the risk of neonatal tetanus by 42% and omphalitis by 31%.[33] Use of clean delivery kits has been proposed to promote safe delivery and reduce neonatal morbidity and mortality.[35]
- IAP against known GBS colonization can reduce the incidence of early infection in neonates.[33]
- Women with a history of PROM should be given prophylactic antibiotics. Evidence from LMIC indicates antibiotics for preterm PROM can help avert 4% of neonatal deaths due to prematurity and 8% of deaths due to postnatal infections.[36]

Postnatal Interventions

- Immediate postdelivery drying, thermal protection, delayed bathing, and kangaroo mother care for LBW infants help avert hypothermia. Systematic reviews have concluded that thermal care practices can prevent up to 10% of neonatal deaths caused by infections.[33]
- Percutaneous entry of organisms through the umbilical cord is an underlying cause of omphalitis and sepsis. The WHO currently recommends dry cord care for newborns in health facilities (lower neonatal mortality settings) and the application of chlorhexidine (CHX), a broad-spectrum topical antiseptic, to the cord stump for neonates born at home in high neonatal mortality settings. Evidence from Asia has supported the effectiveness of CHX[37,38]; however, recent studies from Africa[39,40] have indicated the role of CHX in moderate neonatal mortality settings is limited and further research is recommended.
- Innovations in neonatal skin care include topical emollient therapy, which has been shown to reduce risk of hospital-acquired infections and mortality by 50% and 27%, respectively.[41]

- Optimal feeding practices, that is, early initiation of breastfeeding, exclusive breastfeeding until 6 months of age, and continued breastfeeding until 2 years of age, contribute to prevention of infections. Breast milk possesses a variety of immune and nonimmune components that provide resistance to infection. Estimates indicate scaling up breastfeeding to a global level could prevent nearly 823,000 younger-than-5 deaths.[42]
- The WHO also recommends prophylactic antibiotics for neonates if certain risk factors exist, such as PROM (>18 hours before delivery), maternal fever (>38°C during labor), and/or foul-smelling amniotic fluid (usual recommended duration would be 48 hours until cultures are negative).

NEONATAL INFECTION AND ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) is a global health challenge. Annually, an estimated 214,000 neonatal sepsis deaths are attributable to resistant organisms.[43] Most of these occur in LMIC where data on etiologic organisms is scarce and indiscriminate use of antimicrobials is high. Resistance to first-line antibiotic regimens (ampicillin/penicillin and gentamicin) is increasing globally.[32]

A recent prospective cohort study on neonatal sepsis from India[44] reported an 'alarming degree' of AMR with nearly 82% of *Acinetobacter* spp and 54% of *Klebsiella* spp demonstrating multidrug resistance. With increasing AMR and a growing number of facility-based births in LMICs, recognition of causative organisms, infection control measures, and appropriate use of antibiotics in community and health care facilities have never been more critical. The Etiology of Neonatal Infection in South Asia study (ANISA) initiated in 2010 and a proposed identical study in sub-Saharan Africa should provide crucial data on AMR patterns in organisms causing neonatal infections.[32]

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