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Case Study

Injectable Antibiotics for Treatment of Newborn Sepsis

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Photo 3: A newborn child sleeps next to his mother at the Tinh Gia District Health Center in Vietnam. © 2004 Philippe Blanc; courtesy of Photoshare.

Acronyms

BP	British Pharmacopoeia
DALY	disability-adjusted life years
E. coli	*Escherichia coli*
EMLc	Model List of Essential Medicines for Children
FCHV	Female Community Health Volunteers
GBS	Group B streptococci
IM	intramuscular
IMCI	Integrated Management of Childhood Illness
IV	intravenous
MIC	minimum inhibitory concentration
RCT	randomized controlled trials
S. *aureus*	*Staphyloccoccus aureus*
UNICEF	United Nations Children's Fund
USP	United States Pharmacopeia
WHO	World Health Organization

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Executive Summary

Neonatal mortality is responsible for 41% of the total under age five mortality, or approximately 3.1 million neonatal deaths per year. Approximately 99% of these deaths occur in developing countries, with 26% the result of severe infections.

The World Health Organization has listed three injectable antibiotics for the treatment of neonatal sepsis on the Essential Medicines List for Children: procaine benzylpenicillin, gentamicin, and ceftriaxone. The World Health Organization recommends antibiotic treatment with benzylpenicillin and gentamicin as first-line therapy for presumptive treatment in newborns at risk of bacterial infection. They also recommend ceftriaxone delivered alone for the treatment of neonatal sepsis as a second-line therapy.

Some countries have these medicines on their national essential medicines lists. However, little is known about national policies, availability and use of these drugs at various levels of the health care system. Similarly, few data are available about the supplier manufacturing base in low-resource settings. This presents a considerable barrier to determining actions and policies around these commodities at the global level.

These antibiotics are not readily available or are subject to stock-outs in weaker health systems, particularly in remote areas. Barriers to availability and use of procaine benzylpenicillin, gentamicin, and ceftriaxone at the country level are not clearly characterized.

In both Asia and sub-Saharan Africa, formulations at appropriate dosage may not be readily available from manufacturers. The supply of procaine benzylpenicillin, gentamicin, and ceftriaxone for neonatal sepsis treatment in the developing world has not been quantified or characterized.

Shaping the market for these medicines is extremely difficult without a clear understanding of market forces. Assessing the current supply and demand of procaine benzylpenicillin, gentamicin, and ceftriaxone is the first step toward ensuring access to affordable, high-quality injectable antibiotics that are listed on the World Health Organization Essential Medicines List for Children for neonatal sepsis treatment in low-resource settings. There is a clear and immediate need to:

1. Assess national policy and regulatory environment and financing strategies around the procurement and use of injectable antibiotics for the treatment of neonatal sepsis.
2. Undertake a rapid situational assessment to gather country-specific data on the status, availability, and related barriers to use of procaine benzylpenicillin, gentamicin, and ceftriaxone at various levels of health care delivery.
3. Conduct a landscape analysis of suppliers of available procaine benzylpenicillin, gentamicin, and ceftriaxone products in low-resource settings.
4. Engage in dialogue with distributors/manufacturers about security of future supply particularly in regard to procaine benzylpenicillin.
5. Engage with end-users to determine the most feasible and acceptable presentation of gentamicin for treatment of newborn sepsis.

6. Fund research to facilitate the development of a point-of-care, rapid, and effective diagnostic tool for the identification of serious bacterial infections in neonates that can be used in low-resource settings. This type of promising new technology could improve the specificity of diagnostic algorithms based on clinical signs alone.

1. Introduction

The United Nations Commission for Life-Saving Commodities for Women and Children aims to build consensus around priority actions for increasing the availability, affordability, accessibility, and rational use of selected commodities for women's and children's health. The purpose of this case study is to describe the global burden, availability, and need for three injectable antibiotics to treat neonatal sepsis: procaine benzylpenicillin, gentamicin, and ceftriaxone. This case study reviews available information about how these commodities are faring in low-resource settings beginning at the point of manufacture until they are in the hands of facility-based health workers. The purpose of this case study is to identify bottlenecks that might result in limited access to quality products for those that need them most.

1.1 Global burden

The most recent estimates suggest that neonatal mortality is responsible for 41% of the total under age five mortality, or approximately 3.1 million neonatal deaths per year.[1] Approximately 99% of these deaths occur in developing countries, and most are attributable to preterm birth (28%), severe infections (26%), and asphyxia (23%).[2,3] Three-quarters of neonatal deaths happen in the first week, and the highest risk of death is on the first day of life.[4,5,6,7,8] Case-fatality rates for severe bacterial infections in developing countries are high, in part due to late or inadequate administration of the necessary antibiotics.[9] The risk of death is great for newborns with serious infections, whether hospitalized or in the community, with mortality rates of early-onset sepsis (<7 days) between 3% and 40% and of late-onset sepsis (>7 days) between 2% and 20%.[10] Co-morbidities such as malnutrition or HIV can hasten early demise.

Newborn infection has a rapid onset, and urgent diagnosis and presumptive treatment is needed. Because sick newborns present with nonspecific signs and symptoms, diagnosing neonatal sepsis is difficult in even the most sophisticated settings and is particularly arduous in many low-resource settings. Deaths are often due to delays in the identification and treatment of newborns with infection, specifically, under-recognition of illness, lack of access to appropriate treatment and trained health workers to administer it, delay in initiation of treatment, and inability to pay for treatment by families, if warranted.

2. Global Policy

2.1 World Health Organization guidelines for antibiotic use and injection safety[11,12]

Current World Health Organization (WHO) guidelines recommend case management of newborn sepsis by identifying sick newborns at the community level and then referring them to treatment by professional health workers at the referral level.[13] Currently, WHO recommends that infants under the age of two with serious bacterial infections be referred to a hospital and given ten days of parenteral antibiotic treatment[14] although actual practice is to treat for seven days. If referral and treatment in a hospital is not possible, the infant should begin treatment immediately by appropriately trained health workers.[14]

The WHO Integrated Management of Childhood Illness (IMCI) guidelines provide specific guidelines for when referral is not possible.[15] Even if the baby is taken to the referral center, the first dose of

antibiotics should be given on site as the disease can progress very quickly. Specifically the IMCI guidelines state to give the first dose of intramuscular antibiotics (ampicillin and gentamicin) to the child at the health center. The guidelines then state:

> "Referral is best option for young infant classified as VERY SEVERE DISEASE. If referral is not possible, continue to give ampicillin and gentamicin for at least 5 days. Give ampicillin two times daily to infants less than one week of age and 3 times daily to infants one week or older. Give gentamicin once daily."[16]

WHO recommends antibiotic treatment with benzylpenicillin and gentamicin as first-line therapy for presumptive treatment in newborn at risk of bacterial infection. The recommendation is to use intramuscular injections of 50 mg/kg body weight of ampicillin (or a comparable penicillin such as procaine benzylpenicillin) every six to eight hours—depending on age—plus 7.5 mg/kg body weight of gentamicin (or another comparable aminoglycoside), divided twice daily for at least ten days—as the standard therapy.[9] It is important to note that gentamicin and benzylpenicillin cannot be mixed in the same syringe, meaning separate injections must be administered.

WHO also recommends ceftriaxone delivered alone for the treatment of neonatal sepsis as a second-line therapy.[17] In a randomized clinical trial in Pakistan, ceftriaxone has been shown to be as effective as once daily administration of procaine benzylpenicillin and gentamicin.[18,*] The recommended dose of ceftriaxone is 50 mg/kg once daily for all newborns except those older than one week and who weigh more than 2 kg. In these slightly older and heavier newborns, the dose is increased to 75 mg/kg once daily for ten days.[19]

Guidelines and best practices should be followed to ensure injection safety.[20] These guidelines cover hand hygiene, preparation of the injection site, precautions that the health care worker should take prior to the injection and following the injection, preparing the medication to obtain the correct dose, loading a syringe, giving a safe injection, safe storage of remaining product (neonates require small doses), safe disposal techniques (including the use of a sharps container with tamper-proof lid), and reconstitution.

2.2 The World Health Organization Model List of Essential Medicines for Children

All three of these antibiotics are listed on the WHO Model List of Essential Medicines for Children (EMLc)[21] under section 6, Anti-infectives, subsection 6.2 Antibiotics and 6.2.1 Beta Lactam Medicines (procaine benzylpenicillin and ceftriaxone) and 6.2.2 Other antibacterials (gentamicin). The listings are as follows:

> **Procaine Benzylpenicillin**
>
> Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial.

[*] Currently there is a study underway comparing ceftriaxone therapy to penicillin plus gentamicin for sepsis and meningitis in infants younger than two months in Malawi. Please see: http://clinicaltrials.gov/ct2/show/NCT01247909?term=malawi+AND+ceftriaxone&rank=1

Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.[†]

Gentamicin

Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial.

Ceftriaxone

Powder for injection: 250 mg; 1 g (as sodium salt in vial).

Do not administer with calcium and avoid in term infants less than 28 days with hyperbilirubinemia. It is contraindicated in infants less than 41 weeks corrected gestational age.[‡,§]

These three drugs are further characterized in Appendices A, B, and C.

3. Safety and Efficacy

3.1 Safety profile

Procaine benzylpenicillin is considered generally safe although there is very little reliable evidence on safety and efficacy in neonates. There is substantial experience using procaine benzylpenicillin intramuscularly to treat neonates with both sepsis and congenital syphilis. [19,22,23] A 2009 report by WHO on procaine benzylpenicillin noted that much of the data are outdated and not derived from randomized placebo-controlled clinical trials.[24] The WHO expert committee strongly recommended that further safety and efficacy studies be conducted in neonates in order to develop a body of evidence supporting its use in this population. It further suggested that studies be conducted to better assess the safety and efficacy of this medication when administered by community-based health workers[24], something that other experts have reiterated.

Gentamicin has been widely used to treat neonatal infections as a first-line therapy and is a commonly used antibiotic medication. It is a drug that should be monitored closely; risks related to toxicity include damage to patient hearing and kidney function. When given in facility settings, gentamicin is monitored by analyzing patient blood samples. This type of monitoring is difficult to carry out in low-resource settings and impossible in community-based care. This issue has been mitigated somewhat by the use of extended interval dosing[25] that uses relatively higher dosages than standard dosing regimens. While it is still advisable to monitor levels whenever possible, especially in preterm and asphyxiated babies, use of higher doses has helped alleviate the absolute necessity for those settings where it cannot be carried out.

[†]WHO recommendations note a preference for crystalline penicillin in neonates when penicillin is indicated. However, procaine benzylpenicillin is recommended as an alternative to crystalline penicillin, especially for infections like congenital syphilis and neonatal sepsis. It may be more practical for the community management of neonatal sepsis because of the once daily dosing schedule, cost, availability and ease of administration (WHO 2nd Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines).
[‡]Accurate gestational ages (like 41 weeks) may be difficult to assess by many frontline workers and health workers at lower-level facilities where antenatal care and follow-up may be poor.
[§]This will also limit its administration to many full-term babies between 38 weeks and 41 weeks of corrected gestational age.

Ceftriaxone has been widely used in treating neonatal infections in both developed and developing countries.[19,26] Ceftriaxone is a third-generation cephalosporin and has an excellent safety profile and can be used in a convenient once/twice daily administration.[14] It is also effective against the treatment of Gram-negative meningitis in neonates and young infants.[19,27,28,29] There is also a risk of hyperbilirubinemia (jaundice) and promotion of antimicrobial (specifically beta-lactamase) resistance.[14] Some researchers suggest that more information is needed about its use in the neonatal period.[30]

According to WHO, available evidence indicates no difference in cure rates and mortality between third-generation cephalosporin monotherapy (ceftriaxone) and benzylpenicillin-aminoglycoside combination therapy (penicillin-gentamicin). However, effects may vary in different settings depending on antibiotic resistance patterns.[14]

Development of resistance due to overuse of antibiotics is already occurring in some areas of the world. Resistance to ceftriaxone develops very rapidly, which has not been observed with gentamicin and procaine benzylpenicillin. This has led to concern that widespread, unregulated use of ceftriaxone may lead to a worsening pattern of antibiotic resistance amongst common pathogens, particularly extended spectrum beta lactamase (ESBL)-producing organisms. Of note, however, are recent study results from Bangladesh that indicate (1) antibiotic use is widespread in the community, and use of antibiotics for treatment of newborn infection is a very small fraction of overall antibiotic use in the community; and (2) the use of antibiotics in the community for treatment of newborn infections was not associated with higher antibiotic resistance.[31]

The potential for establishing antimicrobial resistance due to indiscriminate use of these antibiotics points toward the need for an accurate tool to diagnose neonatal sepsis. A rapid diagnostic test that can be used in both facility and community settings would be most appropriate. Experts have suggested that a diagnostic test with three or four inflammation markers to identity host response might be an ideal platform and promising new technology to improve specificity of diagnostic algorithms based on clinical signs alone.

3.2 Dosage

The dosage of injectable antibiotics is calculated based on patient weight to ensure the appropriate serum concentrations are obtained for safety and efficacy of the drug. Dosing protocols are defined in Appendix B. The recent WHO evidence for technical update (2012)[14] of the WHO Pocket Book of Hospital Care for Children (2005)[32] does not include ceftriaxone. This important resource for calculating treatment regimens use in developing countries could be updated with the most accurate and comprehensive data so that providers can make appropriate decisions regarding treatment administration in neonates.

3.3 Efficacy of injectable antibiotics for neonatal sepsis treatment in developing countries

A review of evidence of home-based and first-level facility treatment of neonatal bacterial infections[33] found substantial reductions in neonatal mortality in a nonrandomized controlled study in rural India (62% reduction, P 0.001) and in a cluster randomized trial in rural Bangladesh (34% reduction, 95% CI: 7%–53%). Reduced case fatalities (0%–3%) with community-based management of neonatal sepsis were observed in two small uncontrolled studies from India and Guatemala, as well as a recent

randomized trial from Pakistan.[34] These data suggest substantial benefit of case management approaches using antibiotics for neonatal sepsis in such settings.

A review of available data about injectable antibiotics for treatment of neonatal infections in developing-country communities[30] found that penicillins and cephalosporins have relatively favorable efficacy and safety profiles. Although the aminoglycosides (e.g., gentamicin) have narrow therapeutic indices, when used appropriately they are safe and effective. Although inexpensive and effective, chloramphenicol is the least preferred due to its potential association with significant life-threatening toxicity among neonates. The authors concluded that the preferred injectable antibiotic regimens for community and first-level facility use are procaine benzylpenicillin with gentamicin, or ceftriaxone alone. They are safe and retain efficacy when dosed at extended intervals (24 hours) by intramuscular administration.

A review of evidence for treatment of neonatal infections in developing countries with oral antibiotics[35] found that case management of pneumonia in developing countries has resulted in a 27% reduction in total neonatal mortality and 42% reduction in pneumonia-specific neonatal mortality. However, limited available data indicate that injectable antibiotic therapy is superior to oral regimens. The authors conclude that injections should be used for treatment of serious neonatal infections whenever possible. In settings in which this is not possible, however, oral antibiotic therapy is superior to no antibiotic therapy.

A review of community-based studies to describe the burden of disease from neonatal infections and infection-associated neonatal mortality in developing countries found that infections may be responsible for 8% to 80% of all neonatal deaths (this broad range reflects very different contexts and/or differences in definitions/classifications) and as many as 42% of deaths in the first week of life. Rates of neonatal sepsis were as high as 170 per 1,000 live births (clinically diagnosed) and 5.5 per 1,000 live births (blood culture confirmed).[9] The authors conclude that current recommendations of hospitalization and injections for managing neonatal infections are inadequately followed in developing countries. Approaches for detecting and managing serious infections within the community, at home, or first-level health facilities may be more effective in some cases.

A summary of available data on antimicrobial resistance among common pathogens causing infections in neonates and young infants in community settings in developing countries[36] showed that resistance is a concern. Among the three major pathogens studied (*Escherichia coli* [*E. coli*], *Staphyloccoccus aureus* [*S. aureus*], and Klebsiella species), a high proportion of *E. coli* were ampicillin (72%) and cotrimoxazole (78%) resistant; 19% were resistant to third-generation cephalosporins. Among Klebsiella species, almost all were resistant to ampicillin, 45% to cotrimoxazole, and 66% to third-generation cephalosporins. Resistance to gentamicin was low among *E. coli* (13%) but much higher among Klebsiella species (60%). Methicillin-resistance *S. aureus* (MRSA) was rare (1 of 33 isolates) but 46% were resistant to cotrimoxazole. Significant resistance, in particular to cotrimoxazole among all pathogens, and to gentamicin and third-generation cephalosporins among Klebsiella and emerging resistance in *E. coli* is cause for concern. Further studies from different developing-country regions are needed to determine prevalence of resistant strains as well as assess regional and time trends.

According to a review of 63 studies that were mainly facility based (only 13 focused on community-acquired infections) in developing countries, the major pathogens for neonatal sepsis within the first week of life are Klebsiella species (25%), *E. coli* (15%), and *Staphylococcus aureus* (18%).[37] Group B streptococci (GBS) were relatively uncommon (7%), although regional differences existed. After the first week of life, *S. aureus* (14%), GBS (12%), *Streptococcus pneumoniae* (12%), and nontyphoidal *Salmonella* species (13%) were most frequent. Gram-negatives predominated (77%) among home-delivered babies. Most infections in the first week of life are due to Gram-negative pathogens, and many may be environmentally rather than maternally acquired owing to unhygienic delivery practices. Such practices may also explain the predominance of Gram-negative infections among home-born infants, although data from home settings are limited.

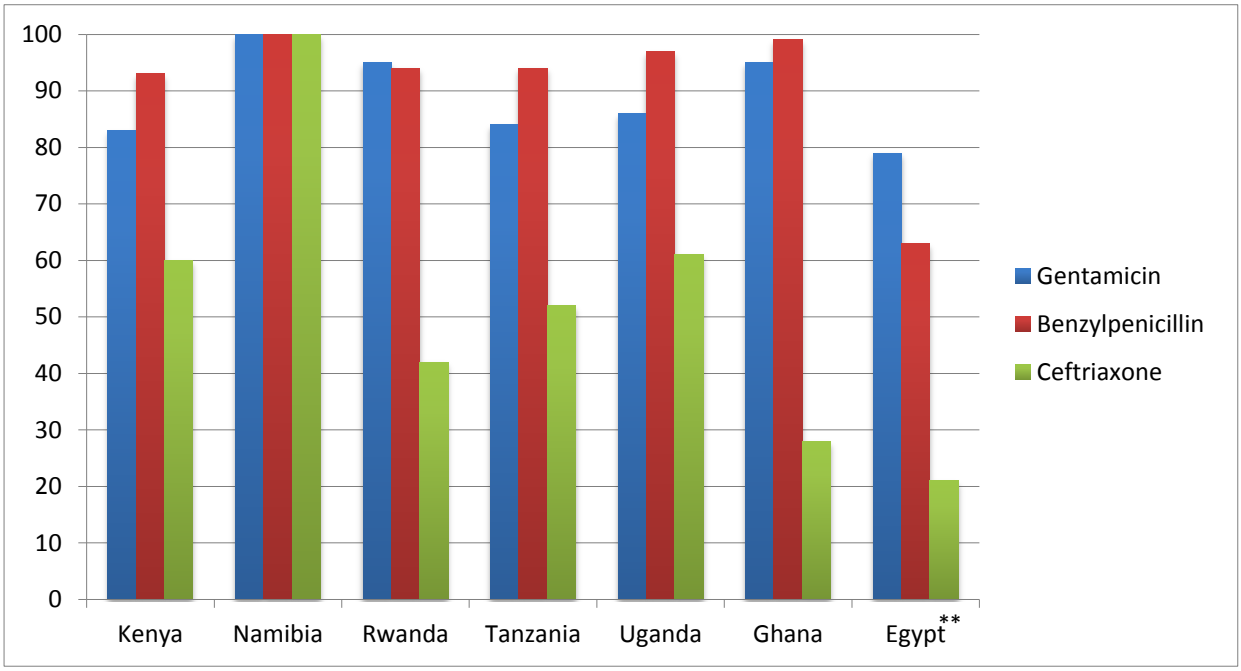
4. National Regulatory Policy

All drug imports are subject to the approval of the government through a foods and drugs board or similar organization in each country. Generally, only medicines included on the national essential medicines list are included in public-sector formularies, national procurement budgets, and addressed through cost-recovery schemes. The WHO EMLc is often used as a base document for national health authorities to create their essential medicine lists. While some countries have procaine benzylpenicillin, gentamicin, and ceftriaxone on their national essential medicines lists[38] little information is available about national policy.

5. Access and Use of Injectable Antibiotics

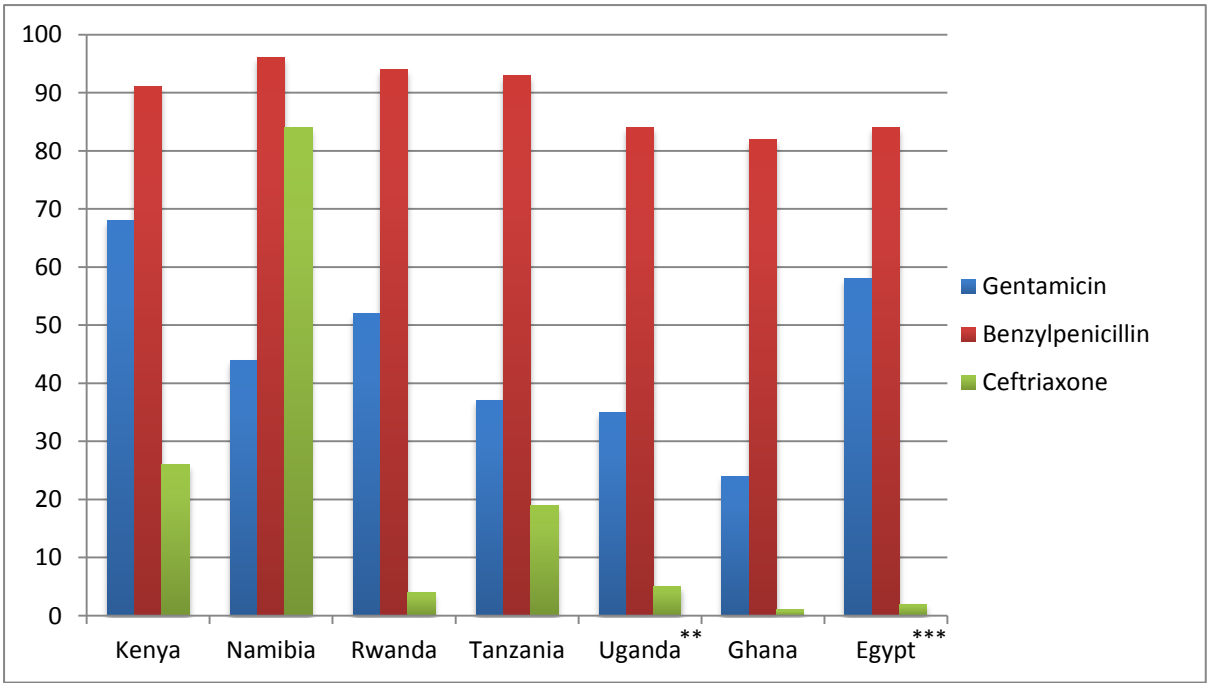
Country-specific data on the availability and use of procaine benzylpenicillin, gentamicin, and ceftriaxone appear to be lacking. Data on the availability of two of the three drugs and benzylpenicillin (not the long-acting procaine benzylpenicillin) at the hospital, health center, and clinic levels are available from the Demographic and Health Surveys Service Provision Assessments (Tables 1 to 3).

Table 1. Percent of hospitals with injectable gentamicin, benzylpenicillin, and ceftriaxone available.*



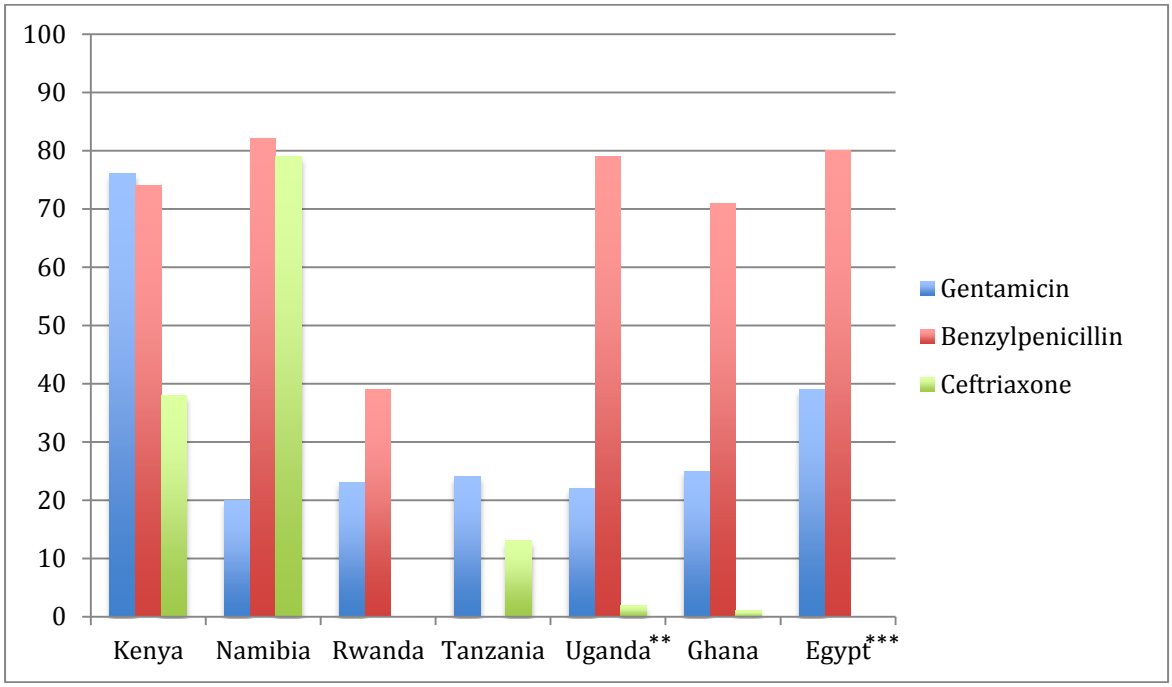
*Data obtained from the Demographic Health Surveys: Maternal and Child Health Service Provision Assessment. Kenya 2010, Namibia 2005, Rwanda 2007, Tanzania 2006, Uganda 2007, Ghana 2002, Egypt 2004.
**Hospital data for Egypt is based on "fever hospitals" whose main purpose is to provide curative services.

Table 2. Percent of health centers and primary facilities with injectable gentamicin, benzylpenicillin, and ceftriaxone available.*



*Data obtained from the Demographic Health Surveys: Maternal and Child Health Service Provision Assessment. Kenya 2010, Namibia 2005, Rwanda 2007, Tanzania 2006, Uganda 2007, Ghana 2002, Egypt 2004.
**Health center/primary facility data for Uganda is based on health center-III data.
***Health center/primary facility data for Egypt is based on maternal child health/urban health units.

Table 3. Percent of clinics with injectable gentamicin, benzylpenicillin, and ceftriaxone available.*



*Data obtained from the Demographic Health Surveys: Maternal and Child Health Service Provision Assessment. Kenya 2010, Namibia 2005, Rwanda 2007, Tanzania 2006, Uganda 2007, Ghana 2002, Egypt 2004.
**Clinic data for Uganda is based on health center-II data.
***Clinic data for Egypt is based on rural health units.

Evidence noted above suggests that the currently recommended antibiotics are not readily available or are subject to stock-outs in weaker health systems and particularly in remote areas. In particular, the availability of procaine benzylpenicillin (which is long acting and used specifically for newborn sepsis treatment) is not included in the survey indicators. Additionally, in a recent assessment of 20 health centers in one district in Nigeria, ceftriaxone and procaine benzylpenicillin were the least available of the three antibiotics (available in 5 of 20 and 6 of 20 centers respectively) while gentamicin was available in slightly over half (11 of 20) of the centers.[39] A forthcoming study in the Dominican Republic will assess the practices of diagnosing and treating neonatal infections of about 700 infants in three referral hospitals and will include correct use of antibiotics listed on the WHO EMLc for treatment of neonatal sepsis. Data from this assessment of quality of treatment of newborn sepsis in three referral centers in the Dominican Republic will be available in 2012.[40] Overall barriers to availability and use of procaine benzylpenicillin, gentamicin, and ceftriaxone at the country level are not clearly characterized.

6. Innovation

Current IMCI guidelines[15] recommend referral but also note need for treatment at the community level if referral is not possible. Currently lower-level government health facilities in some country contexts lack trained staff to manage neonatal infection. Thus there is a need for governments within country health system contexts and regulations to increase access to antibiotics as close to home as is feasible and safe. To achieve this goal, consideration of different strategies including task shifting and emergency transport must be undertaken.

6.1 Task shifting to community-based treatment of neonatal infection

Criteria for country-level decision-making on how to operationalize a neonatal infection treatment program is needed. There is considerable divergence in policy, practice, and need for a community-based treatment strategy and case management of neonatal sepsis in many countries.[41] Because national policies and levels of implementation vary dramatically from country to country as do cultural beliefs and expectations around childbirth and neonatal care, it is likely that one policy for community-based care and management will not meet the needs of all countries and that a country-by-country approach may be more appropriate. Oral treatment alternatives exist and are under consideration for communities where injectable antibiotics are not feasible. Additionally, in many countries, policies permitting community health workers to administer antimalarials were much more lenient than those for antibiotics; only one-third of all Millennium Development Goal countries included in the survey allowed oral antibiotic use at the community level, and antibiotic injections were prohibited in three-quarters of the countries surveyed.[41]

There is no clear cohesion among policymakers on the optimal antibiotic treatment for community scenarios. Several studies are currently under way to evaluate simplified antibiotic regimens with the goal to provide guidance as to the most appropriate choice of antibiotic and dosing regimen at the community level. Study details are outlined in Table 4.

Table 4: Ongoing studies about community-based treatment of neonatal sepsis.

Study Title	Study Objective	Study Design	Location(s)
Simplified Antibiotic Therapy for Sepsis in Young Infants (SATT)	To understand if 7 days of therapy or less is effective and to determine the efficacy of simplified antibiotic regimens	• Injectable benzylpenicillin and gentamicin given for 7 days. • Injectable benzylpenicillin and gentamicin given for 2 days, followed by 5 days of oral amoxicillin.* • Injectable gentamicin (1x daily) along with oral amoxicillin (2x daily) for 7 days.	Pakistan, Bangladesh
AFRINEST	To understand if 7 days of therapy or less is effective and to determine the efficacy of simplified antibiotic regimens (Sister to SATT study.)	• Injectable benzylpenicillin and gentamicin given for 7 days. • Injectable benzylpenicillin and gentamicin given for 2 days, followed by 5 days of oral amoxicillin. • Injectable gentamicin (1x daily) along with oral amoxicillin (2x daily) for 7 days. • Gentamicin (1x daily) for 2 days, followed by 7 days amoxicillin.	Kenya, Democratic Republic of the Congo, and three sites in Nigeria

*Oral amoxicillin is essentially the syrup equivalent of ampicillin. Ampicillin is recommended in cases where referral fails (see section 2.1 above on WHO guidelines).

6.2 Innovation in antibiotic delivery systems for neonatal care

Because procaine benzylpenicillin and ceftriaxone powders must be reconstituted with sterile water before use, it is difficult to develop alternative delivery mechanisms for them. Therefore, much of the innovation in this space has focused on gentamicin.

6.2.1 Gentamicin in the Uniject® prefilled injection system

In 2011, PATH conducted a landscape analysis[42] to review the range of drug packaging and intramuscular delivery devices that might be suitable for injectable gentamicin with a focus on

devices that could offer benefits to improve the safety, ease of delivery, and reduce training requirements and the possibility of health care worker error. Packaging and delivery options were compared based on ease of use, safety, technology development status, and cost. The most promising alternatives included fixed-dose presentations for basic needles and syringes and prefilled delivery devices such as the Uniject® device.

Two different doses of gentamicin in Uniject® prefilled injection system (gentamicin in Uniject®) have been produced—a 10-mg dose and a 13.5-mg dose—based on pharmacokinetic studies that were undertaken to determine safe and effective dosing regimens of gentamicin for use in the Uniject® device.[25,43] Results from these dosing verification studies led to the revised extended-interval dosing guidelines for gentamicin use in newborns as follow:

Less than 2,000 grams: 10 mg every 48 hours.

2,000 to 2,499 grams: 10 mg every 24 hours.

Greater than 2,500 grams: 13.5 mg every 24 hours.

One study has explored the feasibility and acceptability of this innovative delivery system in Nepal. Results from that study indicate that gentamicin in Uniject® in combination with cotrimoxazole-p and an appropriate newborn weighing scale is a feasible and acceptable option for treatment of neonates with possible severe bacterial infection in the community by Female Community Health Volunteers (FCHV).[44]

6.2.2 Microneedle patch

Microneedle technology allows for drugs to be delivered via the skin (transdermally), requiring less medication to be used and thereby reducing the costs to national health programs. Microneedles are being developed as safe, pain-free alternatives to needles and syringes[45] that can be efficient and easily applied.[46] Silk fibroin microneedles show considerable promise for controlled release of sensitive drugs like antibiotics with the added benefit of inhibiting pathogens and helping to prevent local infections when used with antibiotics.[46]

A second effort places small microneedles in a patch to target delivery of antibacterial drugs[47] directly to dentritic cells, the body's first line of defense against infection. As a first step in this product development effort, researchers are using human blood and skin cells to map the immune response. This technology has the potential to ease some of the delivery issues associated with injectable antibiotics for neonatal sepsis treatment such as easy application and fixed dosage presentations (i.e., they will not require dose calculation and drawing into a needle and syringe), which could facilitate use by community health workers. Still in early upstream development, it remains to be seen whether the cost of this kind of technology will be out of reach of national health programs.

7. Manufacturing

7.1 Global antibiotic industry

Injectable procaine benzylpenicillin, gentamicin, and ceftriaxone are available throughout the world for use in both health care and veterinary applications. Over 50 different companies throughout Asia

and South Asia, Europe, the Middle East, and North America manufacture these drugs for use in humans, with the majority of manufacturers located in China, India, and the United States.

7.2 Antibiotic supply in developing countries

Formulations of procaine benzylpenicillin, gentamicin, and ceftriaxone are standardized per United States Pharmacopeial Convention (USP) and British Pharmacopoeia (BP) and are governed by good manufacturing practices. The supply of procaine benzylpenicillin, gentamicin, and ceftriaxone for neonatal sepsis treatment in the developing world has not been quantified or characterized.

Experts have indicated that procaine benzylpenicillin was difficult to procure for the ongoing randomized controlled trials in sub-Saharan Africa, and there is one report in Bangladesh of insufficient demand for manufacturers to produce any procaine benzylpenicillin product. Insufficient demand may stem from the shift from a traditional treatment of illnesses such as congenital syphilis, rheumatic fever, and streptococcal pharyngitis with procaine benzylpenicillin to other drugs, thereby reducing overall demand particularly in developed countries.[48] New strategies for congenital syphilis elimination (i.e., WHO Global Elimination of Congenital Syphilis: Rationale & Strategy for Action) as well as strategies to eliminate pediatric HIV and improve maternal survival by linking syphilis treatment with penicillin highlight a potentially newfound demand and renewed importance of procaine benzylpenicillin in developing countries. These programs have yet to be operationalized, however, so impact on demand and subsequent supply of procaine benzylpenicillin has yet to be demonstrated.

In both Asia and sub-Saharan Africa formulations at appropriate dosage may not be readily available from manufacturers. For example, in some Indonesian health centers, gentamicin is available only as 80 mg/ml and not the recommended neonatal presentation of 20 mg/ml. In addition, problems with filling the small dose needed for newborns in a prefilled syringe and issues of possible overdosing given these small doses have been identified. Specifically, the dose for gentamicin is very small and must be accurate. It is preferable to use pediatric syringes for administration of this drug, not larger syringes that might compromise the dose. Anecdotal reports of health systems not having pediatric syringes available for dosing may be contributing to lack of willingness to use gentamicin.

The relatively low levels of injectable antibiotics procured through the United Nations Children's Fund (UNICEF) between 2007 and 2011 (Table 5) indicate that these drugs are most likely being procured locally.

Table 5: Procurement of selected injectable antibiotics (UNICEF Supply Division).

Medication and Presentation	Year				
	2007	2008	2009	2010	2011
Procaine benzylpeni.pdr/inj 1-g vl/BOX-50	18,500	0	4,000	6,000	4,000
Procaine benzylpeni.pdr/inj 3-g vl/BOX-50	22,500	1,163	NA	17,000	4,000
Gentamicin inj 40 mg/ml 2-ml amp/BOX-50	57,890	95,428	27,200	131,000	38,745
Ceftriaxone pdr/inj 1-g vial/BOX-10	24,000	102,016	50,900	75,828	31,000
Ceftriaxone pdr/inj 250-mg vial/BOX-50	1,041	8,700	2,000	21,000	0

7.3 Shipping and storage considerations

Product requirements[49] are noted in Table 6. Procaine benzylpenicillin and ceftriaxone do not require refrigeration when stored as dry powder for reconstitution. Once reconstituted however, they must be refrigerated and used within a very short time. Gentamicin, which is a ready-for-injection liquid, does not require refrigerated storage.

Table 6. Product requirements.

Antibiotic	Storage Condition	Shelf Life	Packaging
Procaine benzylpenicillin	Dry powder prior to reconstitution should be stored at 20°C to 25°C (68°F to 77°F).	Sterile reconstituted solution can keep in refrigerator (2°C to 8°C) for 3 days.	Colorless glass vial closed with a bromobutyl rubber stopper and sealed with an aluminum cap; keep from bright light and in airtight containers away from moisture.
Gentamicin	2°C to 30°C (some is labeled for storage at 20°C to 25°C). Should be kept from freezing.	36 months is typical.	Glass ampoules.
Ceftriaxone	Dry powder prior to reconstitution should not be stored above 25°C. Immediate use required if opened.	Shelf life for powder is 36 months unopened. Sterile reconstituted solution can keep in refrigerator (2°C to 8°C) for 24 hours.	Colorless glass vial closed with a bromobutyl rubber stopper and sealed with an aluminum cap; keep from bright light and in airtight containers away from moisture.

8. Financing

8.1 Product cost

Information on probable product cost from the International Drug Price Indicator Guide[50] is displayed in Table 7.

Table 7. Probable product cost information.

Antibiotic	Product Presentation	Price (US$)	Average Price per ml (US$)
Procaine benzylpenicillin	1-mu and 3-mu vials	1-mu vial = $0.08 3-mu vial = $0.18	$0.09
Gentamicin	2-ml volume, either 10-mg/ml vials or 40-mg/ml vials.	10 mg/ml = $0.06 to $0.30 40 mg/ml = $0.01 to $0.12	10 mg/ml = $0.15 40 mg/ml = $0.04
Ceftriaxone	250-mg or 1-g vials	250-mg vial = $0.44 to $1.59 1-g vial = $0.27 to $1.00	250-mg vial = $0.69 1-g vial = $0.48

Based on the average cost of each drug as listed in the above table and product dosages listed in Appendix B the estimated price for treating a 2-kg and 2.5-kg baby with seven-day and ten-day treatment courses of each drug is listed in Table 8 below.

Table 8. Estimated prices for 7-day and 10-day courses.

Course	2 kg baby (US$)	2.5 kg baby (US$)
7 days, procaine benzylpenicillin	$0.13*	$0.16
10 days, procaine benzylpenicillin	$0.18	$0.23
7 days, gentamicin**	$0.17 to $0.63	$0.38 to $1.42
10 days, gentamicin	$0.24 to $0.90	$0.0.54 to $2.03
7 days, ceftriaxone***	$0.50	$0.63
10 days, ceftriaxone	$0.72	$0.90

*All prices are rounded to the nearest cent.

**Prices for courses of gentamicin treatment for a 2-kg baby are based on treatment guidelines for infants in the first week of life. The prices for courses of gentamicin for a 2.5-kg baby are based on those for babies born at normal birth weight per the WHO Pocket Book of Hospital Care for Children (2005). The cost of treating a 2-kg baby in weeks 2–4 of life with a 7-day course of gentamicin is between $0.42–$1.58; a 10-day course would cost between $0.60 and $2.25. The cost of treating a 2.5-kg baby in weeks 2–4 of life with seven days of treatment is between $0.50 and $1.89; ten days would cost between $0.72 and $2.70.
***Data for ceftriaxone is based on a 1-g vial.

8.2 Cost-effectiveness

Data on cost-effectiveness of the use of injectable antibiotics for newborn sepsis treatment are sparse. In one cost-effectiveness analysis, the management of severe neonatal infections through inpatient care including treatment with intravenous or intramuscular antibiotic resulted in 1.8 million disability-adjusted life years (DALY) averted annually with an estimated average cost-effectiveness ratio of Int$77 per DALY averted for the Africa region, assuming a 95% coverage rate.[51] Additionally, an economic analysis to determine the benefit of injectable antibiotics in terms of lives saved as compared to oral antibiotics is presented in Appendix D.

8.3 Potential for public procurement

Both procaine benzylpenicillin and gentamicin are relatively low-cost antibiotics, making them excellent options for public procurement. This is especially true in those countries with high neonatal mortality due to sepsis that are looking for a cost-effective way to save newborn lives. The relative expense of ceftriaxone may make it less affordable for public procurement although it is a necessary drug for second-line therapy. Further investigation into the most common supply sources and their regulatory status as well as financing, procurement and tendering processes used to procure procaine benzylpenicillin, gentamicin, and ceftriaxone at the national level is needed. Most drugs procured by the national public sector are imported by private importers and then resold to private- and public-sector health systems. The importers and the manufacturers they represent are significant levers in availability.

8.4 Potential for private-sector user purchases

Given the apparent unavailability of procaine benzylpenicillin, gentamicin, and ceftriaxone in some public-sector facilities, it is likely that users are purchasing these drugs in the private sector or not using them at all. There is increasing evidence of the private sector providing care for newborn infection in Asia and some reluctance of families to seek care outside of their home environment.[52,53,54,55] Ongoing research studies are evaluating simplified antibiotic regimens, some of which are currently in use in private-sector and emergency settings.

9. Cultivating Demand from Caregivers

Facility-based health workers at referral centers are primary caregivers of newborn sepsis treatment. In instances where referral fails, first-level and community workers may also be providing treatment. In pilot projects, some lower-level workers such as village health workers, midwives, and other unskilled nonclinical workers have also provided treatment. This is because many births and neonatal deaths occur in the home, and community-based management may be one of the most effective ways to reach children at risk of dying from sepsis in the first few days of life.

Recent efforts to assess community-based management of newborn sepsis include the Morang Innovative Neonatal Intervention (known as MINI) in Nepal. This project found that FCHVs were able to successfully identify, treat, and refer infants suspected of having bacterial infection for care.[56]

The Gadchiroli study in India showed that home visits by village health workers and the mobilization of community activities to improve newborn health can improve detection rates and outcomes, including the cause-specific neonatal morality rate which decreased by 90%.[57] The ANKUR project in India (a scale-up study based on the results from the Gadchiroli study) assessed diagnosis and antibiotic treatment of sepsis by village workers in urban areas. It showed a large 79% reduction in the sepsis-specific neonatal mortality rate when the algorithm approach along with treatment by village health workers was used.[41] Results from one study in Mirzapur, Bangladesh, showed that community health workers were able to successfully use a clinical algorithm to identify infants needing immediate referral.[58] In a related study in Sylhet, Bangladesh, community health workers were able to use an algorithm to assess, identify, and manage neonates with potentially serious illnesses.[59] It also showed that they were able to treat infants safely and effectively with antibiotics for 10 days in cases where parents refused referral.[59]

Several studies evaluating community management of newborn sepsis are currently underway. The Naushero Feroze[60] study in Pakistan will determine the effectiveness of a package of community-based interventions to reduce neonatal deaths due to birth asphyxia, low birth weight, and neonatal sepsis. In this study, Lady Health Workers in selected intervention areas will receive additional training on essential newborn care for identification, management, and referral for birth asphyxia, low birth weight, and neonatal sepsis using oral treatment with amoxicillin for suspected infection. In Nepal, the Dhanusha study is examining the impact of sepsis management by community volunteers and use of a community group mobilization model on newborn survival.[61] Results from this study are currently being analyzed. In Ethiopia, a study known as COMBINE will evaluate effectiveness of Health Extension Worker treatment at health post of possible severe bacterial infection in newborns if caregiver is unwilling or unable to accept referral to health center/hospital. The treatment regimen used by Health Extension Workers is gentamicin once daily for seven days plus oral amoxicillin for seven days.[62]

Policy dialogue around this issue will continue for some time. The main discussion revolves around the need for evidence from representative settings that could assist in formulating guidance about which antibiotics to use by what type of health worker at which level of care.

10. Monitoring and Evaluation

Illustrative indicators for monitoring and evaluating injectable antibiotics for newborn sepsis treatment are presented in Table 9.

Table 9: Illustrative metrics for injectable antibiotics supply and demand.

Supply Metrics	• Global monthly production volume of the three antibiotics. • Geographic and demographic reach of manufacturers.
Demand Metrics	• Number of countries whose regulatory policies reflect recommendations to use these antibiotics for neonatal sepsis. • Volume of public tenders for these antibiotics. • Percent of public and private facilities with these antibiotics in stock. • Percent of community health care workers referring patients to health facilities for care and treatment with antibiotics. • Percent of parents bringing children to health clinics for treatment.
Correct Use Metrics	• Percent of babies receiving injectable antibiotics. • Percent of babies receiving complete antibiotic regimen being used in country. • Levels of antimicrobial resistance in the community.
Impact Metrics	• Neonatal mortality rate. • Neonatal mortality from newborn sepsis.

Additional measures are needed to ensure quality of the injectable antibiotics and of the health workers performing the injections. This needs to be built into an ongoing process of quality assurance that buttresses current oversight including supervision.

11. Recommendations

Shaping of the market for these medicines is extremely difficult without a clear understanding of market forces. Assessing the current supply and demand of procaine benzylpenicillin, gentamicin, and ceftriaxone is the first step toward ensuring access to affordable, high-quality injectable antibiotics that are listed on the WHO EMLc for neonatal sepsis treatment in low-resource settings. There is a clear and immediate need to:

1. Assess national policy and regulatory environment and financing strategies around the procurement and use of injectable antibiotics for the treatment of neonatal sepsis. Cost-recovery schemes, national procurement budget allocations, and the impact of diverse financing strategies must be understood more thoroughly.

2. Undertake a rapid situational assessment to gather country-specific data on the status, availability, use, and related barriers to use of procaine benzylpenicillin, gentamicin, and ceftriaxone at various levels of health care delivery.

3. Conduct a landscape analysis of suppliers of available procaine benzylpenicillin, gentamicin, and ceftriaxone products in low-resource settings.

4. Engage in dialogue with distributors/manufacturers about the security of future supply, particularly in regard to procaine benzylpenicillin. A forum for larger-country procurers might yield a solution as they are likely to have reliable information about their sources of drug supply.

5. Engage with end-users to determine the most feasible and acceptable presentation of gentamicin for treatment of newborn sepsis.

6. Fund research to facilitate the development of a point-of-care, rapid, and effective diagnostic tool for the identification of serious bacterial infections in neonates that can be used in low-resource settings.

Appendix A: Drug Characteristics

Procaine Benzylpenicillin

Intramuscular administration of procaine benzylpenicillin has been extensively used in neonates to treat both sepsis and congenital syphilis in neonates.[19,22,23] It provides excellent coverage against Group B streptococcus, Group A streptococci, meningococci, *Treponemapallidum, L. monocytogenes,* and most strains of *Steptococcuspneumoniae.*[30] Doses of 50,000 units/kg delivered intramuscular produce peak levels 4 to 6 hours following administration with mean serum levels of seven to 9 µg/mL for up to 12 hours and 1.5 g/mL at 24 hours after the dose in infants less than 7 days of age, demonstrating that once-daily dosing of infants is possible.[30,63] It has been shown that serum levels decrease more rapidly—0.4 g/ml at 24 hours—in older neonates due to renal system maturity,[63] but this is above the MIC for streptococci and most pneumococci, whose MICs for penicillin are between 0.005 and 0.1 µg/ml.[19,**] The cerebral spinal fluid penetration has been shown to be variable.[22,63,64] In addition to its uncertain cerebral spinal fluid penetration, other major concerns around the use of procaine benzylpenicillin in the treatment of neonatal sepsis include its lack of coverage against staphylococci, lack of activity against Gram-negative rods, and rising resistance among pneumococci.[30]

Gentamicin

Gentamicin has an excellent spectrum of activity against Gram-negative rods, and combined with penicillin it works well against GBS, *S. aureus,* enterococci. and *Listeria.*[30] By itself, it has very little activity against staphylococci. While *S. aureus* exhibits in vitro susceptibility, break-through colonies appear within 24 to 48 hours and therefore gentamicin has to be paired with a synergist beta-lactam agent to ensure protection against stapholococci.[30] Limited hospital data from developing countries indicate that Gram-negative rods are increasingly resistant to gentamicin,[65] but this needs to be confirmed in community settings, and improved facility-based monitoring of drug resistance is also required.

Gentamicin pharmacokinetics are essentially identical whether administered by intramuscular or intravenous routes.[30] The drug exhibits a concentration-dependent bactericidal effect in which a linear relationship exists between higher peaks, minimum inhibitory concentration (MIC) ratio, and improved clinical response.[30] Moreover, the post-antibiotic effect of gentamicin, or the ability of the drug to continue to suppress bacterial growth even after antibiotic concentrations have fallen below the MIC for the organism, is also concentration dependent.[19,66] These two features (concentration-dependent killing and post-antibiotic effect) mean that gentamicin exerts a significant antibacterial effect even with extended-interval dosing such as once-daily administration. Multiple studies have shown that once-daily dosing of gentamicin produces higher peak drug concentrations than more frequent dosing intervals, and several studies in neonates have confirmed these findings. Doses in these studies used have ranged from four to five mg/kg given once daily.[67,68,69,70,71, 72,73,74,75,76,77,78,79] However, WHO recommends that for a newborn of normal gestation/weight at birth, treatment after seven days of life should be a calculated dose of 7.5 mg/kg/day.[32]

** There is, however, a growing threat from reduced streptococci sensitivity to penicillin such that the WHO is now recommending a high dose of oral amoxicillin in combination with penicillin for infants and children.

Ceftriaxone

Ceftriaxone is a third-generation cephalosporin, which provides excellent coverage against Gram-negative organisms, Group B streptococcus, pneumococci, and H. influenzae, as well as some activity against methicillin-susceptible *S. aureus*.[30] They do not exhibit activity against L. monocytogenes and enterococci, however.[30]

The administration of a 50-mg/kg intravenous dose of ceftriaxone to newborns of various birth weights and postnatal ages resulted in mean peak serum concentrations of from 136 to 173 µg/ml.[80] Concentrations 6 hours later were from 66 to 74 µg/ml. The mean plasma half-life values were longer in those weighing less than 1500 g. Repeated drug administration at 12-hour intervals resulted in drug accumulation in the serum.[19]

Subsequent pharmacokinetic studies of ceftriaxone during the neonatal period have suggested that the drug's plasma half-life is actually longer than initially estimated.[81,82,83,84, 85] Elimination half-life ranged from 8 to 34 hours (mean, 19 hours) in 20 sick neonates receiving single 50-mg/kg intravenous doses of ceftriaxone. In another study, neonates treated with single daily intravenous or intramuscular 50-mg/kg doses had mean peak serum concentrations after the first dose of about 149 µg/ml, and the mean elimination half-life was 15.5 hours.[82,83] After three or four days of treatment, however both the mean peak serum concentration and elimination half-life decreased to 141 µg/ml and 9.4 hours, respectively. The observed decrease was believed to be a result of increasing postnatal age, which was associated with increased plasma clearance of ceftriaxone.

Appendix B: Dosing Protocols

			Dosage by Weight of Infant						
Drug	**Dosage**	**Form**	**1<1.5 kg**	**1.5-<2 kg**	**2-<2.5 kg**	**2.5<3 kg**	**3-<3.5 kg**	**3.5-<4 kg**	**4-<4.5 kg**
Procaine Benzylpenicillin *	Intramuscular (IM): 50,000 units/kg once a day	3-g vial (3,000,000 units) mixed w/ 4 ml sterile water	0.1 ml	0.15 ml	0.2 ml	0.25 ml	0.3 ml	0.3 ml	0.35 ml
Gentamicin*	Preferably calculate EXACT dose based on the infant's weight								
	1st week of life: Low birth weight babies: IM/intravenous (IV): 3-mg/kg/dose once daily.	Vial 20 mg/2 ml Vial 80 mg/2 ml dilute to 8 ml with sterile water to give 10 mg/ml	0.3-0.5 ml	0.5-0.6 ml	0.6-0.75 ml				
	Normal birth weight: IM/IV: 5-mg/kg/dose					1.35-1.5 ml	1.5-1.75 ml	1.75-2 ml	2-2.25 ml
	Weeks 2-4 of life: IM/IV: 7.5-mg/kg/dose once daily		.75-1.1 ml	1.1-1.5 ml	1.5-1.8 ml	1.8-2.2 ml	2.2-2.6 ml	2.6-3.0 ml	3.0-3.3 ml
Ceftriaxone**	50-mg/kg/dose once daily in infants younger than 1 week old and < or equal to 2,000 g	1-g vial mix with 9.6 ml sterile water to give 1 g/10 ml	.5-.75 ml	.75-1.5 ml					
	In infants older than 1 week and greater than 2 kg: 75-mg/kg/dose once daily				1.5-1.88 ml	1.88-2.25 ml	2.25-2.63 ml	2.63-3.0 ml	3.0-3.4 ml

*Data for procaine benzylpenicillin and gentamicin were taken from the WHO Pocket Book for Hospital Care for Children (2005).

**Data for ceftriaxone in this table was compiled from Saez-Llorens and McCracken 2001; WHO Pocket Book for Hospital Care for Children (2005); and the Integrated Management of Pregnancy and Childbirth Managing Newborn Problems: A guide for doctors, nurses, and midwives (2003).

Appendix C: Formulation Details

Benzylpenicillin sodium for injection, USP, is sterile benzylpenicillin sodium powder for reconstitution. Benzylpenicillin sodium, a water-soluble benzylpenicillin, is a white to almost white crystalline powder, which is almost odorless, and/or after reconstitution a colorless solution. The pH of freshly constituted solutions usually ranges from 5.0 to 7.5.

Benzylpenicillin sodium for injection, USP, is supplied in vials equivalent to 5,000,000 units (5 million units) of benzylpenicillin as the sodium salt, with 1.68 mEq of sodium per million units of benzylpenicillin.

Gentamicin sulfate, USP, is a white to buff powder soluble in water. The drug formulation includes water for injection, methylparaben and propylparaben as preservatives, sodium metabisulfite, and edetate disodium.

Ceftriaxone for injection, USP, is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for IV or IM administration. It is a white to yellowish-orange crystalline powder, which is readily soluble in water, sparingly soluble in methanol, and very slightly soluble in ethanol. The color of ceftriaxone for injection ranges from light yellow to amber, depending on the length of storage, concentration, and diluent used. Ceftriaxone for injection, USP, contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

Appendix D: Economic Analysis of Gentamicin in the Uniject® Prefilled Injection System for Treatment of Neonatal Sepsis

In 2010, PATH conducted an economic analysis to determine the benefit of injectable antibiotics in terms of lives saved compared to oral antibiotics. The results of this analysis[††] in the table below indicate an increase in lives saved for both courses of treatment and an additional 25,000 lives saved with the use of injectable antibiotics over the oral option. Use of gentamicin in Uniject increases the cost per life saved by US$12.12 over the oral option and US$16.71 over the use of needle and syringe. However, because the cost of gentamicin in Uniject (US$1.00 to US$1.35) is significantly more than administration of gentamicin by autodisable needle and syringe (US$0.10), it will increase costs to national health systems considerably.

	2010	2011	2012	2013	2014	2015
Neonatal sepsis pneumonia deaths addressable with gentamicin in Uniject	**123,959**	**123,392**	**122,732**	**122,297**	**121,513**	**120,885**
Total system cost for needle and syringe (gentamicin + benzylpenicillin)	-	$32,153	$63,961	$95,602	$126,651	$157,497
Total system cost for Uniject (gentamicin + amoxicillin)	-	$255,416	$508,100	$759,448	$1,006,102	$1,251,133
Total system cost for orals	-	$57,731	$114,844	$171,655	$227,406	$282,789
Deaths prevented with injectable antibiotics (0% to 75% coverage)		**13,359**	**26,573**	**39,718**	**52,628**	**65,458**
Cost per life saved with needle and syringe (gentamicin + benzylpenicillin)		$2.41	$2.41	$ 2.41	$2.41	$ 2.41
Cost per life saved with Uniject (gentamicin + amoxicillin)		$19.12	$19.12	$19.12	$19.12	$19,11
Deaths prevented with oral antibiotics (0% to 75% coverage)		**8,252**	**16,415**	**24,534**	**32,505**	**40,425**
Cost per life saved		$7.00	$ 7.00	$ 7.00	$7.00	$ 7.00
Lives saved; difference between injectable vs. oral		**5,107**	**10,158**	**15,184**	**20,123**	**25,033**
Cost per life: Uniject vs. injection by needle and syringe		$16.71				
Cost per life: Uniject vs. oral delivery		$12.12				

[††] Economic analysis was conducted using the Spectrum Policy Modeling System and LiST module to conduct evidence-based estimates of intervention impact. (Spectrum Policy Modeling System and LiST are available at: http://www.jhsph.edu/dept/ih/IIP/list/index.html. Accessed March 29, 2010).Three scenarios were run using the Spectrum Policy Modeling System with country-level data for India: (1) no intervention, (2) introduction of injectable antibiotics with an effectiveness of 68%, (3) introduction of oral antibiotics with an effectiveness of 42% (Default Spectrum effectiveness data at <1 month against neonatal sepsis pneumonia was used for intervention scenarios). Adjustments were made to limit the results to only the addressable market, which includes only the 53 percent of births where no skilled attendant is available.

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