REVIEW OF THE EFFICACY AND SAFETY OF PROCAINE BENZYLÆPICILLIN IN NEONATES

REPORT

February 2009

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1. Background

At its first meeting in July 2007, the WHO Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines identified a number of questions about anti-infective medicines for children that needed further review. These included the need to obtain additional evidence of efficacy and safety about products that were already on the WHO model list of essential medicines. In October 2007, the WHO Expert Committee on the Selection and Use of Essential Medicines raised concerns about the use of procaine benzylpenicillin in neonates and requested a review of this drug in this specific age group. At its second meeting held in Geneva from 29 September to 3 October 2008, the WHO Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines considered a review of procaine benzylpenicillin by Dr. G. Kearns.

Dr. G. Kearns reports as follows:

Frequently used clinical compendia in the U. S. (American Academy of Pediatrics Redbook, 2006; Pediatric Dosage Handbook, Taketomo CK, Hodding JH and Kraus DM (eds), 14th edition, Lexi-Comp, American Pharmacists Association, 2008) recommend this drug (procaine benzylpenicillin) only for use in the management of congenital syphilis at a dose of 50,000 U/kg/day given intramuscularly (IM) for a period of 10 days. In contrast to recommendations given in the WHO Pocketbook of Hospital Care for Children (2005), there are no data to support the use of procaine benzylpenicillin for the treatment of neonatal infections where crystalline penicillin G is considered to be the drug of choice. This would include treatment of bacterial meningitis where the amount of drug available to the central nervous system following single daily IM injections of procaine benzylpenicillin would be predicted to be far lower than those achieved with currently recommended meningitic dose regimens for crystalline penicillin G and thus, potentially sub-therapeutic.

While the systemic adverse effect profile of penicillin might be expected to be comparable between procaine benzylpenicillin and crystalline penicillin (e.g. hypersensitivity reactions), the formulation containing procaine is associated with specific adverse effects. For example, transverse myelitis with permanent paralysis and gangrene of extremities proximal to the injection site have been associated with the inadvertent intravascular administration (including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries) of procaine penicillin. Sterile abscess formation with necrosis and sloughing of the injection site have been reported following IM injection of this formulation into both the thigh and buttocks. Quadriceps femoris fibrosis and atrophy have also been reported following repeated IM administration of procaine benzylpenicillin into the anterolateral thigh. For these reasons, the US Pediatric Dosage Handbook (2008) recommends avoiding the use of the (procaine benzylpenicillin) formulation in neonates who weigh ≤1,200 grams.

Finally, it should be noted that the incidence of all of the aforementioned adverse effects associated with procaine benzylpenicillin occur more frequently in neonates than in older patients (Pediatric Dosage Handbook, 2008); an association that likely has a developmental basis given the reduced muscle mass in both preterm and term neonates (contributing to less area for diffusion of the drug bolus injected into the muscle) and altered muscular blood flow (contributing to slower uptake of the formulation into the systemic circulation and increased residence time of the drug in the muscle bed).

Source: Comments for Meeting October 2008. Meeting of the Paediatric Subcommittee of the WHO Expert Committee on Essential Medicines.¹

The WHO Subcommittee’s considerations and response to this review are as follows:

The Subcommittee noted that (crystalline) benzylpenicillin is the preferred agent for serious infections such as neonatal sepsis and congenital syphilis. However, several guidelines,
including the American Academy of Pediatrics, and the CDC Sexually Transmitted Diseases Treatment Guidelines, recommend intramuscular procaine benzylpenicillin as an alternative for use in the management of proven congenital syphilis.

The Subcommittee noted that although the WHO Pocket Book of Hospital Care for Children recommends intramuscular procaine benzylpenicillin in combination with gentamicin as an alternative treatment to (crystalline) benzylpenicillin for the management of neonatal sepsis and meningitis in neonates, there is no evidence for the efficacy of procaine benzylpenicillin in the management of early onset Group B sepsis, or in the community management of sepsis and pneumonia in neonates. It was also noted that procaine benzylpenicillin has low CSF (cerebrospinal fluid) penetration and therefore, may be ineffective in treating infants who develop, or who are at risk of developing, bacterial meningitis. However, the Subcommittee also noted that procaine benzylpenicillin has been used as an alternative to (crystalline) benzylpenicillin as it can easily be administered in the community with once daily intramuscular dosing.

The Subcommittee took account of the safety concerns regarding the intramuscular administration of procaine benzylpenicillin in premature and low birth weight infants, with reports of injection site abscesses, muscle fibrosis and atrophy following intramuscular injection, particularly in premature and low birth weight neonates.

Notwithstanding justifiable reservations regarding the use of procaine benzylpenicillin in young infants, the Subcommittee agreed to endorse the listing of procaine benzylpenicillin as essential without age restriction. Its use in neonates should be avoided unless intravenous administration of (crystalline) benzylpenicillin is not possible. Therefore, the Subcommittee added a note to this effect on the EMLc (Essential Medicines List for Children). The Subcommittee noted that current studies of procaine benzylpenicillin given in combination with gentamicin as first-line treatment for infants with gram-positive infections are underway and the results will be considered when available.


The current document provides an updated review of the evidence to inform key stakeholders of the efficacy and safety of procaine benzylpenicillin in neonatal patients.

2. **International Non-propriety Name (INN, generic name) of the medicine**

   **INN:** Procaine benzylpenicillin
   **Generic name:** procaine penicillin G
   **Chemical name:** 2-diethylaminoethyl 4-aminobenzoate (6R)-(2-phenylacetamido) penicillinate monohydrate

3. **Formulation**

   **Cilicaine syringe:** 1.5g procaine penicillin in 3.4mls: pack of 5 pre-drawn disposable syringes with 5 sterile skin swabs (1 unit = 1 microgram procaine).
   **Penicillin G procaine:** 1,200 units penicillin G procaine in 2mls: pack 10 sterile cartridge-needle units.
   600 units penicillin G procaine in 1mls: pack 10 sterile cartridge-needle units.

4. **Global burden of disease**

   In the year 2000, there were approximately 4 million neonatal deaths from 130 million live births worldwide, this equates to a mortality rate of approximately 30 deaths per 1000 live
births (Table 4.1). Of these deaths 75% occurred within the first week of life. In developed regions of the world the neonatal mortality rate was 5 per 1000 live births, compared to 33 per 1000 live births in developing regions and 42 per 1000 live births in least developed countries. The largest number of neonatal deaths in 2000 occurred in Asia, with a neonatal mortality rate of 32 per 1000 live births. In comparison, the neonatal mortality rate was 43 per 1000 live births in India and 21 per 1000 live births in China. In the same year the average neonatal mortality rate in Africa was 41 per 1000 live births, with Liberia exceeding 65 neonatal deaths per 1000 live births. Low income per capita, less developed and least developed regions of the world account for 98% of all neonatal deaths.

Table 4.1: Neonatal deaths in 2000 (infection and other causes)

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>Neonatal mortality rate (per 1000 live births)</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>41</td>
<td>1,240,000</td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>42</td>
<td>443,000</td>
</tr>
<tr>
<td>Middle Africa</td>
<td>46</td>
<td>204,000</td>
</tr>
<tr>
<td>Western Africa</td>
<td>49</td>
<td>463,000</td>
</tr>
<tr>
<td>Asia</td>
<td>32</td>
<td>2,517,000</td>
</tr>
<tr>
<td>South Central Asia</td>
<td>43</td>
<td>1,716,000</td>
</tr>
<tr>
<td>Europe</td>
<td>5</td>
<td>38,000</td>
</tr>
<tr>
<td>Latin America/Caribbean</td>
<td>15</td>
<td>175,000</td>
</tr>
<tr>
<td>North America</td>
<td>5</td>
<td>21,000</td>
</tr>
<tr>
<td>Oceania</td>
<td>26</td>
<td>7,000</td>
</tr>
<tr>
<td>Melanesia</td>
<td>28</td>
<td>6,000</td>
</tr>
<tr>
<td>World</td>
<td>30</td>
<td>4,002,000</td>
</tr>
</tbody>
</table>


Neonatal deaths account for 37% of all deaths in children under the age of 5 years worldwide and 25% of neonatal deaths are related to infections other than tetanus and diarrhoeal diseases. It is estimated that there are approximately 800,000 neonatal deaths annually in developing countries due to acute respiratory infections alone. Neonatal infections account for around 27% of neonatal deaths in Asia and Africa (Table 4.2). Neonatal infection is the predominant cause of neonatal death in developing countries, and acute respiratory infections account for the majority of neonatal infection deaths.

Table 4.2: Summary of causes of death for neonates worldwide 2000-2003

<table>
<thead>
<tr>
<th>Cause</th>
<th>% of neonatal deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asia</td>
</tr>
<tr>
<td>Premature and low birth weight</td>
<td>30%</td>
</tr>
<tr>
<td>Birth asphyxia and trauma</td>
<td>23%</td>
</tr>
<tr>
<td>Neonatal infections</td>
<td>27%</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>3%</td>
</tr>
<tr>
<td>Neonatal tetanus</td>
<td>4%</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
</tbody>
</table>

a Only member states with low neonatal mortality (USA and Canada)

Source: Mathers (2008)

4.1 Treatment of neonatal infections
Although, the WHO recommends parenteral antibiotic therapy (i.e. benzylpenicillin or ampicillin plus an aminoglycoside) in health care facilities as standard treatment for serious neonatal infections in developing countries, in many resource poor countries where the majority of births occur at home, families are often reluctant to seek care outside the home for neonatal illness.\textsuperscript{8} Bhutta \textit{et al.} (2009) suggest that in resource poor situations where prompt referral to a health care facility is not possible, health workers may have no alternative but to provide domiciliary care for the treatment of serious neonatal bacterial infections.\textsuperscript{9} Darmstadt \textit{et al.} (2009) claim that facility based care that includes a complete course of parenteral antibiotics may not be not feasible for many neonates in developing countries.\textsuperscript{8} However, Darmstadt \textit{et al.} (2009) found no data comparing oral and parenteral antibiotic treatment regimens in a community setting, and claimed that the incremental benefit of injectable over oral antibiotics is not known. In resource poor countries the choice of antimicrobial regimen requires a considered approach, taking into account the efficacy, safety, mode of administration, availability, storage, drug stability, dosing schedule and cost of each alternative therapy.

At the second meeting of the Subcommittee of the Expert Committee on the Section and Use of Essential Medicines (29 September to 3 October 2008) it was suggested that procaine benzylpenicillin was more practical than crystalline penicillin for the community management of neonatal sepsis because of the once daily dosing schedule, cost, availability and ease of administration.\textsuperscript{10} However, the Subcommittee noted that there is a paucity of data on the efficacy and safety of procaine benzylpenicillin in such settings. Further, the review by Dr. G. Kears (2008)\textsuperscript{1} states that, “In contrast to recommendations given in the WHO Pocket Book of Hospital Care for Children (2005), there is no data to support the use of procaine benzylpenicillin for the treatment of neonatal infections where crystalline penicillin G is considered the drug of choice.” Given this, there is an imperative to examine the efficacy and safety of procaine benzylpenicillin in neonates.

5. \textbf{Indications for use}

The indications for procaine benzylpenicillin are many and varied. In the case of adults, the United States Food and Drug Administration (FDA) approved indications for procaine benzylpenicillin include: anthrax, bacterial upper respiratory infection (streptococcal group A infection), bejel, congenital syphilis, diphtheria (treatment and prophylaxis), endocarditis (group A streptococcal, erysipelas (streptococcal), erysipeloid (Erysipelothrix rhusiopathiae), infection of the skin and/or subcutaneous tissue, neurosyphilis, pinta, pneumonia, rat bite fever, scarlet fever (streptococcal group A infection), streptococcal tonsillitis, syphilis (primary, secondary or late), Vincent’s infection, and yaws. However, in the case of paediatrics, the United States Food and Drug Administration (FDA) approved indications for procaine benzylpenicillin are much narrower and include: anthrax, congenital syphilis, pneumonia, and syphilis (primary, secondary or late).\textsuperscript{11}

The Australian Therapeutic Goods Administration (TGA) has approved procaine benzylpenicillin for the treatment of moderately severe infections due to penicillin sensitive organisms including: group A streptococcal infections, upper respiratory tract infections, skin and skin structure infections and scarlet fever; pneumococcal infections of the respiratory tract; susceptible staphylococcal infections; most gonococcal infections; syphilis; and fusospirochaetosis (Vincent's gingivitis and pharyngitis).\textsuperscript{12}
The 2006 British National Formulary for Children (BNFC) lists procaine benzylpenicillin as ‘available on named patient basis’ from specialist importing companies for the treatment of early and late latent syphilis. However, it is unclear whether the indication refers to neonates, children or adults.  

6. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

6.1  Dosage regimens

Table 6.1 summarises the indications and dose regimens of procaine benzylpenicillin used to treat neonatal infections.

<table>
<thead>
<tr>
<th>Indication/s</th>
<th>Dosage</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital syphilis*</td>
<td>50,000 IU/kg/day in a single IM dose</td>
<td>10 days</td>
</tr>
<tr>
<td>Group B streptococcal postpartum prophyaxis‡</td>
<td>50,000 IU/kg/day in a single IM dose</td>
<td>Once within 12 hours of birth</td>
</tr>
<tr>
<td>Early-onset neonatal sepsis &amp; pneumonia‡</td>
<td>50,000 IU/kg/day in a single IM dose</td>
<td>10 days</td>
</tr>
<tr>
<td>Late-onset neonatal sepsis &amp; pneumonia‡</td>
<td>50,000 IU/kg/day in a single IM dose</td>
<td>10 days</td>
</tr>
<tr>
<td>Diphtheria†</td>
<td>50,000 IU/kg/day in a single IM dose</td>
<td>7 days</td>
</tr>
</tbody>
</table>

Abbreviations: IU = international units; kg = kilogram; IM = intramuscular
† WHO (2005)

6.2  Reference to existing WHO and other clinical guidelines

The CDC (United States Centers for Disease Control) Sexually Transmitted Diseases Treatment Guidelines (2006) recommends aqueous crystalline penicillin, benzathine penicillin or procaine penicillin for the treatment of neonatal congenital syphilis.  

CDC recommendations for the treatment of proven congenital syphilis:
Aqueous crystalline penicillin G 100,000–150,000 units/kg/day by intravenous injection, for 10 days or procaine penicillin G 50,000 units/kg/dose by a single intramuscular dose for 10 days.

CDC recommendations for the treatment of suspected congenital syphilis:
Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, by intravenous injection for 10 days or procaine penicillin G 50,000 units/kg/dose by a single intramuscular injection for 10 days or benzathine penicillin G 50,000 units/kg/dose by a single intramuscular injection.

The WHO Guidelines for the Management of Sexually Transmitted Infections recommends that in neonates with congenital syphilis procaine penicillin be administered (50,000 IU/kg/dose by intramuscular injection, daily for 10 days) as an alternative regimen to benzathine benzylpenicillin (50,000 IU/kg/dose by intravenous injection every 8-12 hours, for 10 days).  

The WHO Pocket Book of Hospital Care for Children (2005) recommends that in symptomatic neonates with congenital syphilis procaine benzylpenicillin be administered (50,000 units/kg by intramuscular injection, as a single dose daily for 10 days) or aqueous
benzylpenicillin be administered (50,000 units/kg by intramuscular or intravenous injection, every 8-12 hours for 10 days).

6.3 Need for special diagnostic or treatment facilities and skills

Accessibility and cost are barriers to the use of neonatal care facilities in developing countries. Home-based neonatal care, provided by trained village health workers has been shown to significantly reduce neonatal mortality. In the study conducted in the Gadchiroli district of India by Bang et al. (1999) female village health workers (VHW) were trained to take histories of pregnant women, observe the process of labour, examine neonates, record findings, and case manage neonatal sepsis. When a diagnosis of neonatal sepsis was made (i.e. septicemia, meningitis, or severe pneumonia) female health workers administered intramuscular injections of gentamicin and oral syrup co-trimoxazole as per protocol. This strategy reduced the mortality rate associated with neonatal sepsis from 27.5% (1995-1996) to 6.6% (1997-1998) which represents an absolute reduction of 20.9% in neonatal mortality. Bang et al. (1999) suggest that home-based neonatal care, including sepsis management, is acceptable, feasible and could reduce neonatal mortality substantially in developing countries. It is also important to note that 97.5% of parents interviewed during this study, preferred care for their ill neonates from the female village health workers, because of availability within the village and the care was free of cost. Given that neonatal care is not available to most neonates in resource poor developing countries due to cost and inaccessibility, training community health workers to safely administer parenteral antibiotics may be an effective strategy to reduce the mortality associated with neonatal infections.

Of note, a recently published paper by Baqui et al. (2008) urged government and non-government agencies to develop home-based neonatal-care strategies in settings in which the health system is weak, care seeking is low, and the burden of neonatal mortality is high.

7. Summary of comparative effectiveness in a variety of clinical settings

7.1 Congenital neurosyphilis

7.1.1 Literature search

Medline (1950 – January 2009), the Cochrane Database of Systemic Reviews (Cochrane Library, Issue 4, 2008), the Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library, Issue 4, 2008) and the World Health Organization web site were searched to identify all published papers and trial reports that described the use procaine benzylpenicillin in children and neonates. Search terms used to identify studies included: intramuscular, procaine, penicillin, cilicaine, neonate, infant, child, syphilis, neurosyphilis, and congenital syphilis. Reference lists of retrieved articles were reviewed to identify any potentially relevant studies not identified during the database searches.

The literature search identified only one prospective randomised trial. This trial tested the comparative efficacy of procaine benzylpenicillin and aqueous penicillin G in treating congenital syphilis in neonates. A further three studies were identified that tested CSF levels of penicillin in neonates following intramuscular injection of procaine benzylpenicillin. The literature searches identified no systematic reviews of procaine benzylpenicillin.

7.1.2 Efficacy
Paryani et al. (1994) conducted a 2-year prospective study, randomly assigning 169 asymptomatic infants born to mothers with inadequately treated syphilis to treatment with either one dose of 50,000 units/kg benzathine penicillin G by intramuscular injection or 50,000 units/kg procaine benzylpenicillin by intramuscular injection daily for 10 days. Of the 152 infants included in the study, 84 were treated with aqueous penicillin G and 68 were treated with procaine benzylpenicillin. Eligible infants were scheduled for follow-up visits at 3, 6, and 12 months of age. Treatment failure was defined as any one of the following: clinical evidence of congenital syphilis in the newborn; less than a 4 fold decrease in Rapid Plasma Regain Test (RPR) titre at 3 months; and a reactive RPR finding at 12 months.

Paryani et al. (1994) found that there was no difference in the outcome of infants treated with aqueous penicillin G or procaine benzylpenicillin, and there were no treatment failures at 12 months in either group. A summary of these results is presented in Table 7.1.

<table>
<thead>
<tr>
<th>Evidence of efficacy at follow-up</th>
<th>Benzathine penicillin G n/N (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Procaine benzylpenicillin n/N (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No clinical evidence of syphilis</td>
<td>84/84 (100)</td>
<td>68/68 (100)</td>
</tr>
<tr>
<td>Four fold decrease in RPR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>68/68 (100)</td>
<td>61/61 (100)</td>
</tr>
<tr>
<td>Non-reactive RPR at 12 months</td>
<td>83/84 (99)</td>
<td>66/68 (99)</td>
</tr>
<tr>
<td>Either fourfold decrease in RPR or Non-reactive RPR at 12 months</td>
<td>84/84 (100)</td>
<td>68/68 (100)</td>
</tr>
<tr>
<td>Treatment failures</td>
<td>0/84 (0)</td>
<td>0/68 (0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are number with positive findings/number tested.  
<sup>b</sup> Rapid plasma regain test.

Source: Paryani et al. (1994)

7.1.3 Effective dose

Parental aqueous penicillin G remains the preferred treatment for congenital syphilis and neurosyphilis in adults and neonates, administered as 100,000-150,000 units/kg intravenously over two doses each day for 7 days, then 8 hourly for a total of 10 days. Procaine benzylpenicillin 50,000 units/kg by daily intramuscular injection daily over 10 days, achieves bacteriocidal serum levels, and is used where facilities for hospitalisation, intravenous administration or compliance with therapy are lacking. However, there are reports that treatment with procaine benzylpenicillin may result in sub-treponemicidal concentrations of penicillin in the cerebrospinal fluid (CSF).

Cerebrospinal fluid (CSF) levels

Bernard et al. (1994) examined CSF and serum levels of penicillin in 21 infants treated for congenital neurosyphilis following a single intramuscular injection of procaine benzylpenicillin or aqueous penicillin G. A single sample of CSF and serum was taken at between 1.5 to 6 hours post administration.

For aqueous penicillin G treponemicidal levels of penicillin in CSF (≥ 0.03µg/ml) were found in around 92% (11/12) of infants half-hour post administration, reaching a peak concentration of 0.17µg/ml at 2.5-3 hours, and remaining above 0.03µg/ml at 6 hours. For procaine benzylpenicillin, no penicillin could be detected in around 56% (5/9) of infants at 0.5-1.0 hour post administration, and only two infants achieved treponemicidal levels of penicillin in CSF (≥ 0.03µg/ml), those two reaching a peak concentration of 0.08µg/kg at 2.5 hours.
Bernard et al. (1994) concluded that both procaine benzylpenicillin and aqueous penicillin G achieved treponemicidal penicillin concentrations in the serum. However, as aqueous penicillin G reached a higher CSF concentration over a longer period it was a more appropriate choice for the treatment of congenital syphilis when central nervous system (CNS) involvement was known or was suspected.

Speer et al. (1981) studied 25 infants of mothers who had infectious syphilis, obtaining serial CSF and serum samples at 2, 4, 8, 12 and 24 hours following administration of 50,000 units/kg of procaine benzylpenicillin.

Table 7.2: Concentrations of penicillin in serum and CSF in infants of mothers with syphilis following administration of intramuscular procaine benzylpenicillin

<table>
<thead>
<tr>
<th></th>
<th>mean µg/ml</th>
<th>range µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 hours post administration</td>
<td>17.1</td>
<td>7.7-41.9</td>
</tr>
<tr>
<td>12 hours post administration</td>
<td></td>
<td>0.2-5.8</td>
</tr>
<tr>
<td>CSF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 hours post administration</td>
<td>0.70</td>
<td>0.09-1.98</td>
</tr>
<tr>
<td>24 hours post administration</td>
<td>0.12</td>
<td>0.03-0.27</td>
</tr>
</tbody>
</table>

Source: Speer et al. (1981)

Speer et al. (1981) suggested that treponemicidal concentrations of penicillin in the CSF of neonates could be achieved and maintained over 24 hours following 50,000 units/kg procaine benzylpenicillin by daily intramuscular injection. Speer et al. (1981) noted that the different results found by Bernard et al. may have resulted from them testing their samples before the peak levels recorded at 12 hours post administration could be reached.

Azimi et al. (1994) studied three groups of infants (N=163) treated for congenital neurosyphilis. Group 1 received 50,000 units/kg of procaine benzylpenicillin by daily intramuscular injection (N=100), Group 2 received 100,000 units/kg of aqueous penicillin G by intravenous injection over 2-doses each day (N=23), and Group 3 received 200,000 units/kg of aqueous penicillin G by intravenous injection over 2-doses each day (N=40).

Table 7.3: Concentrations of penicillin in CSF in infants of mothers with syphilis following administration of intravenous aqueous penicillin G or intramuscular procaine benzylpenicillin

<table>
<thead>
<tr>
<th></th>
<th>Mean concentration over 24 hours µg/ml</th>
<th>Proportion achieving concentration ≥ 0.018µg/ml at 24 hours</th>
<th>Proportion achieving concentration ≥ 0.018µg/ml at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous penicillin G by twice daily intravenous injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100,000 units/kg</td>
<td>0.416</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>200,000 units/kg</td>
<td>0.493</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Procaine benzylpenicillin by daily intramuscular injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50,000 units/kg</td>
<td>0.077</td>
<td>33%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Source: Azimi et al. (1994)

Azimi et al. (1994) concluded that higher levels of penicillin in CSF are achieved using aqueous penicillin G by intravenous injection compared to procaine benzylpenicillin by daily intramuscular injection, with only 82% of infants treated with procaine benzylpenicillin achieving concentrations of ≥0.018µg/ml at any time, and 33% maintaining that
concentration at 24 hours following administration. However, the CSF penicillin concentration required to achieve effective treatment remains uncertain.

While the concentration of penicillin in the CSF required to achieve a therapeutic treponemicidal effect remains uncertain, aqueous penicillin G by intravenous injection consistently achieves higher levels of penicillin concentration in the CSF over a longer period compared to procaine benzylpenicillin by intramuscular injection. However, Payani et al. (1994) found no significant difference in the outcomes of infants with asymptomatic congenital syphilis treated with intravenous aqueous penicillin G or intramuscular procaine benzylpenicillin.

7.1.4 Adverse events

The incidence of adverse events was not reported in the clinical trial conducted by Paryani et al. (1994).

7.2 Early and late onset neonatal infectious diseases

Early-onset neonatal sepsis, pneumonia and group B streptococcal disease (GBSD) occur within the first week of life and neonates are most likely to be infected during or shortly before birth from the colonized maternal genital tract. Early onset neonatal infection including GBSD usually presents as bacteremia, sepsis or pneumonia. The most predominant organisms in full-term neonates are group B streptococci, E coli and Listeria monocytogenes. Preterm neonates are also susceptible to haemophilias influenzae and gram-negative bacilli.

Late-onset GBSD occurs from 1 week to 3 months of age with neonates most likely infected during delivery or from another local source. Meningitis, the most common presentation of late-onset infection, requires higher concentrations of penicillin in the CSF than can be achieved with intramuscular procaine benzylpenicillin.

The different pathogens implicated in early-onset and late-onset neonatal infections require specific empiric antibiotic regimens for each. Penicillin or third generation cephalosporins, often in combination with an aminoglycoside are generally effective in early-onset neonatal infections, while other antibiotic regimens have been proven effective in late-onset infections. Meningitis, the predominant presentation of late-onset neonatal infectious disease, is not effectively treated with procaine benzylpenicillin. As approximately 75% of neonatal deaths occur in the first week of life and procaine benzylpenicillin is rarely used in late-onset neonatal infections, the use of procaine benzylpenicillin in late-onset disease is not dealt with separately.

7.2.1 Literature search

Medline (1950 – January 2009), the Cochrane Database of Systemic Reviews (Cochrane Library, Issue 4, 2008), the Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library, Issue 4, 2008) and the World Health Organization web site were searched to identify all published papers and trial reports that described the use of procaine benzylpenicillin in children and neonates. Search terms used to identify studies included: intramuscular, penicillin, procaine, penicillin, clicoaine, neonate, infant, child, group B streptococci, pneumonia and sepsis. Reference lists of retrieved articles were reviewed to identify any potentially relevant studies not identified during the database searches.
In all, 716 publications were identified as being potentially relevant. One randomised, placebo controlled trial, two systematic reviews of randomised controlled trials and one literature review were identified as being relevant to the current review.

Eight non-randomised studies, testing the efficacy of penicillin in neonates following intramuscular injection of penicillin for the prevention of early-onset GBSD were identified by the literature searches. As no studies were identified that investigated the use of procaine benzylpenicillin for the treatment of GBSD and sepsis in neonates, studies involving the use of benzylpenicillin have been included to assess the efficacy and adverse events related to the use of penicillin.

McCracken et al. (1972) reviewed the pharmacokinetics of various penicillin preparations in newborn infants and reported that bactericidal levels of penicillin were achieved in the serum of young and older neonates following intramuscular injection of procaine benzylpenicillin, although these levels were substantially lower than those achieved by intravenous and intramuscular injection of penicillin G. However, McCracken et al. did not recommend the use of procaine benzylpenicillin for the treatment of serious infections in neonates in the absence of clinical trial evidence of efficacy.

### 7.2.2 Efficacy in Group B streptococci disease (GBSD)

#### Early onset GBSD

The systematic review conducted by Woodgate et al. (2004) identified five trials that studied the efficacy and safety of intramuscular penicillin in the prevention of early-onset GBSD. However, only one trial was included for review. None of the identified trials studied the use of procaine benzylpenicillin. Woodgate et al. concluded that there was no evidence supporting the use of prophylactic penicillin in the prevention of early-onset GBSD.

The systematic review conducted by Ungerer et al. (2004) investigated the effect of prophylactic versus selective antibiotic therapy for asymptomatic newborns of mothers with risk factors for neonatal infection. Of the six trials identified as being potentially relevant, only two were included for review. Three studies were excluded as prophylaxis was administered to all infants regardless of risk factors and one was excluded because it included intrapartum treatment of the mother as well as post partum prophylaxis.

The study by Gerard et al. (1979) enrolled 67 infants of mothers colonised with group B streptococci in a controlled trial of immediate prophylactic versus delayed selective penicillin G therapy. The study conducted by Wolf et al. (1976) randomly allocated 51 neonates born to mothers with risk factors for group B streptococci to a treatment group (penicillin 50,000 U/kg/d and kanamycin 10 mg/kg/d) or a non-treatment group. In review of these two studies, Ungerer et al. (2004) found no difference in the mortality or incidence of infection between neonates receiving immediate prophylactic antibiotics and those receiving delayed selective antibiotics. However, due to the small size of these two studies, the evidence was not considered strong.

In the unblinded, 52-month study conducted by Pyati et al. (1983), 1187 neonates at high-risk of infection were randomised into a treatment group administered intramuscular penicillin G within 60 minutes of birth (N=589) or to a control group (N=598).
Pyati et al. (1983)\textsuperscript{30} found that 2% (10 of 589) of infants in the treatment group and 2.3% (14 of 598) of infants in the control group presented with early-onset disease, with no significant difference in outcomes. Fatality rates were 60% (6 of 10) of infants with GBSD in the treatment group and 57% (8/14) in the control group, with no significant difference in outcomes. These results are summarised in Table 7.4 below.

Table 7.4: Efficacy of Penicillin G in preventing early-onset group-B streptococci infection in newborn infants

<table>
<thead>
<tr>
<th></th>
<th>Penicillin G n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset GBSD</td>
<td>10/589 (2.0%)</td>
<td>14/598 (2.3%)</td>
<td>0.73 (0.32, 1.62)</td>
</tr>
<tr>
<td>Deaths</td>
<td>6/10 (60%)</td>
<td>8/14 (57%)</td>
<td>0.78 (0.55, 1.11)</td>
</tr>
</tbody>
</table>

Source: Pyati et al. (1983)\textsuperscript{30}

Pyati et al. (1983)\textsuperscript{30} concluded that penicillin given at birth to neonates weighing 2000 grams or less does not prevent early-onset streptococcal disease or reduce excess mortality associated with disease. No systemic or local adverse reactions to penicillin were observed during the study.

The study conducted by Siegel et al. (1982)\textsuperscript{36} was a quasi-randomised study of 32,058 newborn infants over 41 months and examined the efficacy of a single dose of aqueous penicillin G administered within one hour of delivery in preventing neonatal group-B streptococcal infections. Infants were assigned on alternate weeks to be treated (for gonococcal ophthalmia) with either topical tetracycline ointment (N=15,976) or aqueous penicillin G 50,000 units/kg in infants with a birth weight >2000 grams and 25,000 units/kg in infants with a birth weight <2000 grams (N=16,082).

The results of this study showed a significant decrease in early-onset GBSD in those infants treated with intramuscular penicillin G compared to placebo (p<0.001). Siegel et al. (1982)\textsuperscript{36} reported no observed cases of hypersensitivity reactions in treated infants. There was an increase in diseases caused by penicillin resistant organisms, however, this difference was not statistically significant. These results are summarised in Table 7.5.

Table 7.5: Efficacy of aqueous Penicillin G in preventing early-onset group-B streptococci infection in newborn infants

<table>
<thead>
<tr>
<th></th>
<th>Penicillin G N = 16,082</th>
<th>Placebo N = 15,976</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early-onset n (%)</td>
<td>Total n (%)</td>
<td>Early-onset n (%)</td>
</tr>
<tr>
<td>Penicillin sensitive</td>
<td>3 (0.02)</td>
<td>10 (0.06)</td>
<td>24 (0.15)</td>
</tr>
<tr>
<td>Penicillin resistant</td>
<td>12 (0.08)</td>
<td>35 (0.22)</td>
<td>4 (0.03)</td>
</tr>
<tr>
<td>Total</td>
<td>15 (0.09)</td>
<td>44 (0.27)</td>
<td>28 (0.18)</td>
</tr>
<tr>
<td>GBS</td>
<td>3 (0.02)</td>
<td>9 (0.06)</td>
<td>19 (0.12)</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>5 (0.03)</td>
<td>18 (0.11)</td>
<td>5 (0.03)</td>
</tr>
</tbody>
</table>

Abbreviations: NS = not statistically significant
Source: Siegel et al. (1982)\textsuperscript{36}

A single institution retrospective chart review examining the incidence of GBS sepsis in neonates routinely given a single dose of intramuscular aqueous penicillin G within one hour of birth noted a decrease in the incidence of GBSD in infants of less than 2,500 grams in
weight. Subsequently, Patel et al. (1999)\textsuperscript{39} conducted a large prospective study of 10,998 neonates examining the efficacy of a single dose of intramuscular aqueous penicillin G within one hour of birth for the prevention of GBSD, sepsis and mortality in neonates.

In the study conducted by Patel et al. (1999)\textsuperscript{39} all neonates admitted to the study institute from October 1992 to September 1995 were assigned in blocks of 2-3 months to either 50,000 units/kg of aqueous penicillin G by intramuscular injection within 1 hour of birth (N=5,389), or to a no-treatment control group (N=5,609). The first assignment block (3 months) was randomised, then each 2-3 month block assignment alternated between treatment and no-treatment groups. Blood cultures were taken after administration of aqueous penicillin G, and the primary outcome was clinical sepsis. All neonates suspected of having clinical sepsis were reviewed prior to 1 month of age.

Patel et al. (1999)\textsuperscript{39} found that there were statistically significantly fewer neonates requiring sepsis work-up or with clinical sepsis in the groups treated with aqueous penicillin G compared to no treatment. However, in neonates of 36 weeks gestation or less there was no significant difference between treatment and no treatment.

Overall, mortality from sepsis was significantly lower in the treatment groups. However, in neonates of 36 weeks gestation or less there was no significant difference between treatment and no treatment. Overall, the study found that neonates given 50,000 units/kg of aqueous penicillin by intramuscular injection within 1 hour of birth had a significantly reduced incidence of clinical sepsis, GBSD and mortality. These results are summarised in Table 7.6.

<table>
<thead>
<tr>
<th>Table 7.6: Efficacy of a single dose of intramuscular aqueous penicillin in preventing group-B streptococci infection, sepsis and mortality in neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All gestations N = 10,998</strong></td>
</tr>
<tr>
<td>Penicillin N=5,389</td>
</tr>
<tr>
<td>No treatment N=5,609</td>
</tr>
<tr>
<td>p value</td>
</tr>
<tr>
<td><strong>≤ 36 weeks gestation N=2,864</strong></td>
</tr>
<tr>
<td>Penicillin N=1,400</td>
</tr>
<tr>
<td>No treatment N=1,464</td>
</tr>
<tr>
<td>p value</td>
</tr>
<tr>
<td><strong>≥ 37 weeks gestation N=8,134</strong></td>
</tr>
<tr>
<td>Penicillin N=3,989</td>
</tr>
<tr>
<td>No treatment N=4,145</td>
</tr>
<tr>
<td>p value</td>
</tr>
</tbody>
</table>

Source: Patel et al. (1999)\textsuperscript{39}

Benitz et al. (1999)\textsuperscript{33} conducted a literature review of antimicrobial prevention of early-onset group B streptococcal sepsis in neonates. This review examined antepartum and intrapartum treatment of mothers suspected or known to be infected with group B streptococci during pregnancy, and the post partum treatment of neonates of these mothers.

Benitz et al. (1999)\textsuperscript{33} concluded that post partum penicillin prophylaxis reduced the incidence of early onset GBSD in newborns of colonised mothers. However, Benitz et al. also noted an
increase in neonatal mortality due to penicillin resistant organisms, and concluded that while post-partum prophylaxis for newborns of mothers colonised with group B streptococci is effective in reducing early-onset GBSD, universal prophylaxis for all newborns is not recommended. The results of the meta-analysis conducted by Benitz et al. (1999) are presented in Table 7.7.

Table 7.7: Efficacy of post-partum prophylaxis on early-onset Group B streptococcal sepsis

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment Regimen</th>
<th>Treatment</th>
<th>Control</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lloyd 1979</td>
<td>50,000 units/kg/day</td>
<td>0</td>
<td>537</td>
<td>0.10 (0,0.55)</td>
<td></td>
</tr>
<tr>
<td>Pyati 1983</td>
<td>100,000 units/kg once only</td>
<td>10</td>
<td>589</td>
<td>0.72 (0.32, 1.6)</td>
<td></td>
</tr>
<tr>
<td>Patel 1994</td>
<td>25,000-50,000 units/kg once only</td>
<td>8</td>
<td>5892</td>
<td>0.25 (0.12, 0.53)</td>
<td></td>
</tr>
<tr>
<td>Siegal 1982 &amp; 1996</td>
<td>25,000-50,000 units/kg once only</td>
<td>4</td>
<td>16082</td>
<td>0.21 (0.07, 0.59)</td>
<td></td>
</tr>
<tr>
<td>Siegal 1996</td>
<td>25,000-50,000 units/kg once only</td>
<td>40</td>
<td>63727</td>
<td>0.32 (0.23, 0.45)</td>
<td></td>
</tr>
<tr>
<td>Pooled OR</td>
<td></td>
<td></td>
<td></td>
<td>0.317 (0.25, 0.42)</td>
<td></td>
</tr>
</tbody>
</table>

*a* Early Onset Group B Streptococcal Sepsis

Source: Benitz et al. (1999)

Velaphi et al. (2003) conducted a case review of all delivered mother/neonate pairs from 1995 to 1999 following the introduction of routine prophylaxis for early-onset GBSD with maternal intrapartum ampicillin and newborn post-partum single dose intramuscular penicillin G at Parkland Memorial Hospital, Dallas, USA. Velaphi et al. (2003) identified 32 positive cases of GBSD from over the 5 year period, a rate of 0.47 confirmed neonatal GBSD per 1000 live births compared to 1.95 per 1000 live births for the period from 1986 to 1994 when prophylaxis was not routinely given. Velaphi et al. concluded that post-partum newborn prophylaxis with a single dose of penicillin was effective in reducing the incidence of early-onset GBSD in newborns.

Stillova et al. (2007) examined 250 neonates (mean birth weight 3441 grams ± 459 grams) in a prospective study applying risk criteria based on culture results, neonate leucocyte count and obstetric risk factors, to assess the need for postnatal antibiotic prophylaxis (penicillin G) in each case. Of the 250 neonates included in the study, 146 presented with some risk of group B streptococcal sepsis. However, only 15.6% of the neonates (39/250) qualified for post-partum antibiotic prophylaxis. In the 60% of mothers not given intrapartum antibiotic prophylaxis, 20% of neonates born received post-partum antibiotic prophylaxis. In the 40% of mothers who were given intrapartum antibiotic prophylaxis, 13% of neonates born received post-partum antibiotic prophylaxis. No cases of clinical group B streptococcal infection or sepsis were reported.

Stillova et al. (2007) concluded that the strategy of applying a selection criteria to post-partum antibiotic prophylaxis dosing of neonates of group B streptococci positive mothers was effective in decreasing the incidence of early-onset GBSD.

In summary

This review identified limited evidence on the use of intramuscular procaine benzylpenicillin for the treatment of early-onset or late-onset neonatal sepsis. Overall, there is no evidence supporting the routine prophylactic administration of penicillin to all neonates. There is
evidence that the treatment of “at risk” neonates with either aqueous penicillin G or procaine benzylpenicillin post-partum is effective in reducing the incidence of early on-set GBSD. While both intramuscular and intravenous penicillin are proven to be effective in the treatment of neonatal infections, there is a preference for use of intravenous ampicillin with gentamycin compared to intramuscular procaine benzylpenicillin. Procaine benzylpenicillin is recommended when issues of compliance, limited resources or poverty make intravenous therapy difficult.

### 7.2.3 Beta lactam monotherapy versus beta lactam aminoglycoside combination therapy

Gordon et al. (2005) reviewed 13 clinical studies of comparative antibiotic regimens for the treatment of late-onset sepsis in newborn infants. Of the 13 studies identified as being potentially relevant, 12 were excluded on that basis that the late onset data could not be separated from early onset data or there was a lack of adequate randomisation. None of the excluded or included studies presented separate data for penicillin. However, Gordon et al. concluded that there was no clinical evidence in favour of any particular antibiotic regimen for the treatment of suspected late-onset neonatal sepsis.

### 7.3 Efficacy in the community setting

In developing countries, approximately 70% of sick newborns referred for treatment to hospitals and other health facilities are instead treated in the home without trained health care worker review or appropriate antibiotic therapy. Borghi et al. (2005) report a refusal of newborn hospital referrals of 90% in Nepal. The majority of guidelines and protocols developed for the treatment of neonatal sepsis, pneumonia and congenital syphilis, have been developed on principles assuming the delivery of health services through centralised health infrastructure. Establishing best practice in developing countries requires consideration of factors particular to individual target communities (i.e. per capita income, cultural and gender issues, historical behavioural patterns and health service access). This in turn requires critical assessment of strategies that not only provide effective, safe and cost effective treatment, but can overcome the behavioural and logistic impediments to service delivery and optimal health outcomes.

Sazawal and Black (2003) conducted a meta-analysis of community-based trials to examine the effectiveness of case management in reducing neonatal mortality due to pneumonia in developing countries (India, Pakistan, Bangladesh, Tanzania and Nepal). Of the five trials included in the meta-analysis, only two trials used procaine benzylpenicillin by intramuscular injection in the home treatment of neonates with severe infections and pneumonia, in conjunction with antenatal education and community health worker review. Sazawal and Black (2003) concluded that the summary effect on neonatal mortality due to pneumonia from the home and community based case management approach was an overall reduction in neonatal mortality of 27% (95% confidence interval [CI] 18% to 35%), with a reduction in pneumonia related neonatal mortality of 42% (95% CI 22% to 57%). While it was not possible to separate efficacy data for procaine benzylpenicillin in these trials, the use of procaine benzylpenicillin by intramuscular injection appears to be an important option in the delivery of effective and safe antimicrobial therapy to neonates in the home and community based setting.
The study conducted by Baqui et al. (2008)\textsuperscript{21} examined the effectiveness of a community based newborn care intervention strategy for severe neonatal infections in the Sylhet district of Bangladesh. This study was a cluster-randomised controlled study comparing home care and community care strategies with current practice. The study population included all women from 15 to 49 years of age in 24 clusters, with 8 clusters in each study arm; 14,769, 16,325 and 15,350 live births in the home care, community care and current practice (control arm) arms respectively.

In the home care arm of the study, one health care worker with 6 week practical training was allocated to four villages (approximately 4,000 people). Community health workers were able to provide two antenatal and three early postnatal home visits, including birth and newborn care education, iron and folate supplements at birth and reviews of neonatal health. Neonates diagnosed by a community healthcare worker as having very severe infective disease or possibly very severe infective disease with more than one sign, were given 50,000 units/kg intramuscular procaine benzylpenicillin and referred to sub-district hospitals. If the families were unable or refused to attend a hospital, the neonate was treated in the home with intramuscular procaine benzylpenicillin and gentamycin, and ongoing community health worker visits. In the 2004-2005 period, of the 609 neonates with or suspected of having very severe disease, 194 (32%) were successfully referred to sub-district hospitals and 253 (42%) were treated at home. Intramuscular procaine benzylpenicillin with gentamycin was effectively used in the home care study arm in combination with antenatal follow-up by a trained caregiver. Neonatal mortality in the home care arm of the trial was 34% lower in the last 3 months of the study and 30% lower in the last year of the study compared to current practice.\textsuperscript{21}

The results of the study by Baqui et al. (2008)\textsuperscript{21} showed that, with the exception of 2005, there was no statistically significant difference between home care or community care and current practice. However, there was a consistent reduction in the neonatal death rate in the home care group over the period from 2002 to 2005 which reaches statistical significance in the last half of 2005 compared to current practice. A summary of these results is presented in Table 7.8.

<table>
<thead>
<tr>
<th></th>
<th>Home Care</th>
<th></th>
<th></th>
<th></th>
<th>Community Care</th>
<th></th>
<th></th>
<th>Current Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NMR \textsuperscript{a} n/1000</td>
<td>Relative Risk \textsuperscript{b} (95% CI)</td>
<td>NMR \textsuperscript{a} n/1000</td>
<td>Relative Risk \textsuperscript{b} (95% CI)</td>
<td>NMR \textsuperscript{a} n/1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All live births</td>
<td>46.9</td>
<td>1.03 (0.69, 1.53)</td>
<td>46.7</td>
<td>1.01 (0.69, 1.48)</td>
<td>48.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002 \textsuperscript{c}</td>
<td>44.8</td>
<td>0.94 (0.74, 1.19)</td>
<td>51.1</td>
<td>0.98 (0.78, 1.23)</td>
<td>47.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>32.8</td>
<td>0.79 (0.54, 1.16)</td>
<td>45.5</td>
<td>1.09 (0.86, 1.38)</td>
<td>43.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>31.2</td>
<td>0.70 (0.56, 0.87)</td>
<td>43.5</td>
<td>0.91 (0.71, 1.18)</td>
<td>43.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan – Jun 05</td>
<td>33.8</td>
<td>0.74 (0.48, 1.15)</td>
<td>40.6</td>
<td>0.84 (0.59, 1.20)</td>
<td>41.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jul – Dec 05</td>
<td>29.2</td>
<td>0.66 (0.47, 0.93)</td>
<td>45.2</td>
<td>0.95 (0.69, 1.31)</td>
<td>43.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Neonatal Mortality Rate (NMR) as n/1000 live births
\textsuperscript{b} Adjusted for mother's age and education, household wealth, newborn gender and birth order.
\textsuperscript{c} Baseline value
Source: Baqui et al. (2008)\textsuperscript{21}

A recent review conducted by Bhutta et al. (2009)\textsuperscript{9} identified nine district studies of community based management of newborn infections. Pooled analysis of data from five controlled trials showed a reduction in all cause neonatal mortality of 27% (95% CI 18% to
and a reduction in pneumonia related neonatal mortality of 42% (95% CI 22% to 57%) in community based case management strategies compared to existing hospital based management strategies. Bhutta et al. (2009)\(^9\) concluded that there was substantial benefit in the application of community based case management strategies for neonatal sepsis. However, it was not possible to ascertain the precise contribution of any particular antibiotic therapy to the success of this approach due to methodological limitations.

In a review of parenteral antibiotics used for the treatment of neonates in developing countries, Darmstadt et al. (2009)\(^16\) suggest that intramuscular procaine benzylpenicillin in combination with gentamicin is the preferred antibiotic regimen in community based and first-level health care facilities. Darmstadt et al. (2009), referring to the work of McCracken et al. (1973),\(^26\) notes that 50,000 units of intramuscular procaine benzylpenicillin achieves peak serum levels at approximately 4-6 hours, maintaining a mean level of 7-9µg/ml for up to 12 hours in young neonates, and maintains therapeutic levels in young and older neonates for up to 24 hours.

Zaidi et al. (2009)\(^54\) point out that there is marked variation in the predominant causative pathogens in early-onset and late-onset neonatal infection between developed, high income countries and developing, lower income countries due to the continuing practice of home birthing in developing countries. Home birthing exposes mothers and neonates to a different spectrum of pathogens than those encountered in hospital based antenatal services, where the majority of present best practice based guidelines have been researched and developed. Causative pathogens also vary between developing countries,\(^55\) with different emerging patterns of antibiotic sensitivity and resistance.\(^56\) Therefore, if there is a continued shift in perinatal care strategy towards home and community based management, further ongoing research is required to determine the most effective antimicrobial therapy in individual regions.

### 8 Safety

#### 8.1 Penicillin hypersensitivity

Hypersensitivity to penicillin (not specifically related to procaine benzylpenicillin) may result in diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site, superinfection (including candidiasis) and less commonly, fever, vomiting, erythema, exfoliative dermatitis, and angioedema.\(^11\) No reports of hypersensitivity to penicillin in neonates were identified in the literature.

Schauf et al. (1985)\(^57\) conducted a placebo controlled trial investigating the incidence of penicillin hypersensitivity in 2 year old children who had been given penicillin in the neonatal period. Schauf et al. found no difference in the rates of hypersensitivity to penicillin between children who received penicillin as neonates and those who did not.

#### 8.2 Anaphylaxis

No reports of anaphylactic reactions in neonates given penicillin or procaine benzylpenicillin were identified in the literature.

#### 8.3 Localised injection site reaction
Intramuscular injection of penicillin preparations may be associated with redness, pain and swelling at the site of injection.\textsuperscript{43,58} Meyler’s Side Effects of Drugs states that the incidence of such reactions to the administration of procaine benzylpenicillin is about 0.2\%.\textsuperscript{58}

Bass (1996)\textsuperscript{43} examined the localised reactions in children to benzathine penicillin G (pain and tenderness) and found that the combination of 300,000 units procaine benzylpenicillin with 900,000 units benzathine penicillin G (CR Bicillin 900/300) decreased the incidence of these reactions by approximately 5-10\% while providing equivalent efficacy in the treatment of streptococcal pharyngitis.

### 8.4 Necrosis, ischemia and nerve injury

On rare occasions Nicolau Syndrome (embolia cutis medicamentosa), involving necrosis of the skin and subcutaneous tissue at and about the site of injection, has been reported.\textsuperscript{58,59} Severe events may include muscle necrosis, necrosis of an appendage or limb and intestinal or renal haemorrhage.\textsuperscript{58,60-62}

Case reports of ischemic and necrotic events following intramuscular injection of penicillin formulations are found in the literature.\textsuperscript{60,63,64} These reports vary both in the severity of the events, and in the mechanism of injury proposed by the authors.

Darby \textit{et al.} (1973)\textsuperscript{60} report irregular ecchymotic and cyanotic areas over the lower abdomen, right flank, right buttock, scrotum and right leg following intragluteal injection of benzathine penicillin G in a one year old child. Inadvertent intravenous or intra-arterial injection was considered as the most plausible explanation.\textsuperscript{60}

Kayikcioglu \textit{et al.} (1996)\textsuperscript{63} report semi-circular lipo-atrophy following the intragluteal injection of 1,200,000 units of benzathine penicillin in a 3-year old child. There was no reported redness, swelling or discomfort and physical examination revealed a 4-5cm diameter oval depression with no discolouration. Inadvertent intra-arterial injection was considered as a plausible explanation.\textsuperscript{63}

Ghosh \textit{et al.} (2002)\textsuperscript{64} report two case studies of necrosis progressing to gangrene following intramuscular injection of benzathine penicillin G into the anterolateral thigh of children under 10 years of age resulting in lower limb amputation.

Prior to 1984 flawed syringe design and the viscous nature of the penicillin solution supplied in the pre-filled syringes meant that it was not possible to visualise blood drawn back into the syringe during administration. Thus, it was very difficult to ascertain whether the needle had inadvertently entered a vein or artery. While syringe design was altered to facilitate visualisation of blood, there is no evidence that this has reduced the number of inadvertent intravascular injections of procaine benzylpenicillin.\textsuperscript{61}

No literature was identified that reported incidence rates for necrosis and ischemia following intramuscular injection of procaine benzylpenicillin or other penicillin preparations. However, considering the number of case studies in the literature and the number of doses given to neonates over time, the incidence appears to be low. As noted above, the incidence of injection site reactions is approximately 0.2\%.\textsuperscript{58}
In 1966, Shaw\textsuperscript{65} reported a case of a 15 month old child suffering transverse spinal cord lesion at the level of T-10 following intramuscular injection of benzathine penicillin and procaine benzylpenicillin in the right gluteal muscle. Within minutes of the injection, blanching at the injection site had spread to the lower limb on the same side, followed by flaccid paralysis of both lower limbs, bladder and bowel. Shaw\textsuperscript{65} also reports a similar episode in a 2.5 year old child given an intramuscular injection of benzathine penicillin and procaine benzylpenicillin in the left gluteal muscle. Similar cases reported in the literature, mostly involving small children, are unclear on the mechanism of injury. However, most report that symptoms occurred shortly after injection into the gluteal muscle of newborns or young children.\textsuperscript{60,61,66}

Animal studies conducted by Schanzer \textit{et al.} (1985)\textsuperscript{61} found that intra-arterial injection of benzathine penicillin and procaine benzylpenicillin in the limbs of rabbits produced ischemia, necrosis and nerve damage in the limb injected. None of the rabbits injected with normal saline, or receiving peri-arterial penicillin injections developed abnormalities, and there was no evidence of transverse myelitis.

While there are a few reports of similar cases in humans,\textsuperscript{61} the incidence of these events appears to be very rare. However, considering the severity of the risk and the small mass of the neonatal gluteal muscle, gluteal injection of procaine benzylpenicillin in neonates is discouraged. It is recommended that best practice for the safe intramuscular injection of neonates should be followed at all times.\textsuperscript{67}

### 8.5 Acute non-allergic reaction

Acute non-allergic reactions to procaine benzylpenicillin were first described by Batchelor \textit{et al.} in 1951.\textsuperscript{68} The symptoms have also been described as Hoigne’s Syndrome, embolic toxic reaction, panic attack syndrome, acute psychotic reaction and pseudo-anaphylaxis. The acute non-allergic reaction is a severe reaction occurring within minutes of injection of procaine benzylpenicillin or benzathine penicillin, characterised by symptoms of immediate severe apprehension or fear; auditory, vestibular, visual, gustatory, olfactory or kinaesthetic disturbances or hallucinations; vasomotor disturbances including tachycardia, systolic hypertension or cyanosis; depersonalisation; and seizures.\textsuperscript{68-72}

Symptoms are usually of short duration, ranging from a few minutes to an hour, with a small number of patients continuing to complain of some effects for 24 hours to several months. The mechanism of injury has been attributed to inadvertent intravenous injection or venous infiltration of procaine benzylpenicillin, causing a procaine induced limbic kindling and associated behavioural and perception symptoms.\textsuperscript{69} However, similar reactions have been associated with histamine penicillin preparations without procaine.\textsuperscript{59,69}

In doses of between 0.6 – 1.2 million units of procaine benzylpenicillin, the frequency of acute non-allergic reactions to procaine benzylpenicillin is estimated to be approximately 1 to 3 cases per 1000 in adults and children. With repeated doses of procaine benzylpenicillin there is an increase in the likelihood of acute non-allergic reactions.\textsuperscript{58} No reported cases of acute non-allergic reactions in neonates were identified in the literature.
8.6 Muscle contracture

In newborns the gluteal region has poor muscle mass. The preferred site for intramuscular injection in neonates and infants up to 6 months of age is the anterolateral thigh in the quadriceps femoris, the largest muscle mass at birth.\textsuperscript{61,62,67,73} One of the most commonly reported serious complications following intramuscular injection into the anterolateral thigh of children is muscle contracture.\textsuperscript{62}

Repeated intramuscular injection into the same muscle appears more likely to result in severe muscle fibrosis and contracture.\textsuperscript{58,59,74} In 1964, Lloyd-Robert and Thomas\textsuperscript{74} described six cases of children suffering loss of functional flexion of the knee joint requiring surgical intervention following injections or infusions into the thigh at birth or soon after.

8.7 Penicillin resistant infections

The study conducted by Seigel\textit{ et al.} (1982)\textsuperscript{36} found that there was a non-significant increase in the rate of penicillin resistant infections in neonates given intramuscular penicillin G at birth compared to neonates not given penicillin. However, Benitz\textit{ et al.} (1999)\textsuperscript{33} reviewed the results reported by Siegel\textit{ et al.} (1982),\textsuperscript{36} and suggested that there was a significant increase in mortality related to penicillin resistant organisms following intramuscular penicillin G at birth.

8.8 Benign intracranial hypertension

In 1969, Scmitt and Krivit\textsuperscript{75} reported a case of benign intracranial hypertension in a nine year old girl with a history of sore throat treated with penicillin V without effect and then 600,000 units procaine benzylpenicillin by intramuscular into the right buttck. The injection site became swollen and ecchymotic, spreading over the much of the right leg over the next 3 to 4 days. The patient developed headache, severe bilateral papilledema, clonus and a CSF pressure of 410mm at rest on lumbar puncture. No other similar reports were identified in the literature. No reports were identified in the literature that referred to this condition in neonates.

9 Conclusion

There is very little reliable evidence on the efficacy and safety of procaine benzylpenicillin and penicillin preparations generally in neonates. Much of the available evidence is several decades old and not derived from randomised, placebo controlled trials. It is difficult to assess the direction and magnitude of any biases that might be present in these studies.

However, from the evidence identified it appears that generally, the use of procaine benzylpenicillin in the treatment of congenital syphilis in neonates is effective and safe when attended by appropriately trained personnel following best practice guidelines currently recommended by the World Health Organization in the WHO Pocket Book of Hospital Care (2005).\textsuperscript{14} The available data show that penicillin levels achieved in the CSF are lower with procaine benzylpenicillin than with aqueous penicillin G. The limited clinical data from one relatively small trial showed no difference in efficacy of the two penicillin preparations.

There is evidence that intramuscular aqueous penicillin G is effective in the treatment of severe neonatal infection and sepsis. However, the serum penicillin levels achieved from the administration of intramuscular procaine benzylpenicillin are substantially lower than those
achieved with aqueous penicillin G. There are no clinical trials examining the efficacy of procaine benzylpenicillin in the treatment of severe neonatal infection and sepsis.

The studies by Sazawal and Black (2003), Baqui et al. (2008), Bhutta et al. (2009), and Darmstalt et al. (2009), provide some insights into the effectiveness of home and community management strategies for reducing neonatal mortality and morbidity. The evidence from these studies suggests improved mortality and morbidity outcomes for neonates. However, while the use of intramuscular procaine benzylpenicillin appears to be an integral component of these successful strategies, it is not possible to separate the effect of procaine benzylpenicillin from that of other components.

Consequently, further research is necessary to ascertain the effectiveness of intramuscular procaine benzylpenicillin in the home and community based management of serious neonatal infection and sepsis.

In terms of safety, the studies reviewed have involved the administration of thousands of doses of aqueous penicillin G, and a lesser but substantial number of procaine benzylpenicillin doses to neonates over several decades. While none of the identified studies have reported an analysis of the incidence of adverse events, over this time it has generally been reported that procaine benzylpenicillin has been well tolerated. Despite published case reports of serious adverse events these appear to be rare when viewed in context of the number of newborns treated.

The use of procaine benzylpenicillin in neonates appears to provide a long acting, once daily administered antibiotic therapy that can be effectively and safely managed in the community setting by appropriately trained community health workers when access to preferred antibiotic therapy is not available. Safety data available do not provide a compelling case for recommending that procaine benzylpenicillin should not be used in neonates.
References


17 World Health Organization. Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries. 2000; 1-175.


preliminary study. Biomedical papers of the Medical Faculty of the University Palacký, Olomouc, Czechoslovakia. 2007; 151(1): 79-83.


46 Zaidi AKM. Efficacy Study of Community-Based Treatment of Serious Bacterial Infections in Young Infants. 2008.


