GLOBAL STATUS OF BPG REPORT

THE BENZATHINE PENICILLIN G REPORT
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This report was funded by Medtronic Foundation through support to RHD Action.

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<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>BPG</td>
<td>Benzathine benzylpenicillin</td>
</tr>
<tr>
<td>EML</td>
<td>Essential Medicines List</td>
</tr>
<tr>
<td>EMLc</td>
<td>Essential Medicines List for Children</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GAS</td>
<td>Group A streptococcus</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>INN</td>
<td>International Non-proprietary Names</td>
</tr>
<tr>
<td>IU</td>
<td>International units</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
</tr>
<tr>
<td>PEN</td>
<td>Package of Essential Noncommunicable Disease Interventions for Primary Health Care in Low Resource Settings</td>
</tr>
<tr>
<td>RhEACH</td>
<td>Rheumatic Heart Disease Evidence Advocacy Communication Hope</td>
</tr>
<tr>
<td>RF</td>
<td>Rheumatic fever</td>
</tr>
<tr>
<td>RHD</td>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td>TIPs</td>
<td>Tools for Implementing RHD Control Programs</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Emergency Fund</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WHF</td>
<td>World Heart Federation</td>
</tr>
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EXECUTIVE SUMMARY

Benzathine penicillin G (BPG) is an injectable antibiotic which provides a prolonged level of penicillin in the blood. There are two major global indications for BPG and a number of minor indications.

Syphilis and rheumatic heart disease are both major global public health challenges. Access to reliable, high quality formulations of BPG is a prerequisite for the treatment and control of both diseases. The importance of BPG is widely recognised, through inclusion on the World Health Organization’s Essential Medicines List and associated Special Indication Lists.

Despite considerable clinical need BPG has been the subject of widespread global shortages in recent years. Shortages have largely been attributed to difficulty securing quality assured active pharmaceutical ingredient for the manufacture of formulated product. Shortages of active pharmaceutical ingredient reflect the vulnerabilities of the global BPG market: procurement is fragmented by clinical indication, the number of manufacturers is small and total price of the drug is low. BPG shortages interrupt treatment regimens and increase the use of more expensive, less effective drugs which may accelerate development of resistance in other organisms. A reliable supply of high quality BPG is urgently needed to provide gold standard care and to support rational use of antibiotics. However, BPG and other older, off-patent antibiotics have been licensed on historic data which is insufficient for contemporary regulatory standards. Improving the quality and supply of BPG requires collective global action to redevelop the drug: answering outstanding scientific questions, integrating new data in regulatory bodies and communicating clearly about how, when and why the drug should be used.

BPG remains an essential medicine and tangible, multi-stakeholder, steps are needed for it to be made safe and available to the vulnerable populations who need it most.

BENZATHINE PENICILLIN G AND ITS USES

### Major indications for BPG

- Treatment of syphilis, particularly in pregnant women
- Prophylaxis against rheumatic fever to prevent rheumatic heart disease

### Minor indications for BPG

- Primary prevention of rheumatic fever
- Treatment of skin sores and pyoderma
- Treatment of yaws, bejel and pinta
- Prophylaxis in sickle cell disease
- Prophylaxis following splenectomy
- Prophylaxis of recurrent cellulitis
**Nomenclature**

The World Health Organization (WHO) maintains a global list of International Nonproprietary Names (INN). The INN is a list of unique, global names of individual pharmaceutical substances, also known as the generic name of a drug.1

Benzathine benzylpenicillin (BPG) has the following INN:  
- Latin - benzathini benzylpenicillinum  
- French - benzathine benzylpenicilline  
- Spanish - benzatina bencilpenicilina  
- Russian - бензатина бензилпенициллин  
- Arabic - بنزاثين بنيلبنيسيلين  
- Chinese - 苄星青霉素

BPG is known by other names in some countries or in informal use. These may cause confusion, particularly when similar to other drug names. A list of synonyms for BPG is in Table 1.

**Structure and mechanism of action**

Penicillin G (otherwise known as benzylpenicillin, the precursor of BPG) is a bactericidal beta-lactam antibiotic which inhibits synthesis of the microbial cell wall during multiplication.2 Penicillin G specifically inhibits the transpeptidase and D-alanine carboxypeptidase enzymes that would normally catalyse the final crosslinking step in the synthesis of the bacterial cell wall.3,4 The enzymatic inhibition interferes with peptidoglycan synthesis, creating defects in the cell wall.5 This affects the osmotic integrity of the cell wall, causing cell lysis and the eventual death of the microorganism.

The antimicrobial effect of penicillin was announced in the 1940 publication ‘Penicillin as a chemotherapeutic agent’ as a result of its effect on bacteraemia in rats.6 This new antibiotic produced impressive clinical outcomes in humans and was rapidly adopted to treat a wide range of infections.7 However, frequent injections were required to maintain therapeutic serum penicillin concentrations. Organic chemists focused on developing new formulations of penicillin G with predictable pharmacokinetic parameters. In 1951, Szabo, Edwards and Bruce synthesised a new penicillin salt N,N'-dibenzylethylenediamine dipenicillin, which became known as BPG.7

BPG is a crystalline powder produced by reacting two molecules of penicillin G with a single molecule of dibenzylethylenediamine base.8,9 The molecular structure of BPG is shown in Figure 1 and represented by the formula C_{16}H_{20}N_{2}(C_{16}H_{18}N_{2}O_{4}S)_{2}.

Characterised by low aqueous solubility (200 units of penicillin per milliliter of water at 40°C), BPG forms a depot in muscle tissue following intramuscular injection, slowing its release into the bloodstream and producing prolonged therapeutic serum concentrations.8,10 After intramuscular injection, BPG is converted to penicillin G via hydrolysis. It is the hydrolytic conversion to penicillin G, combined with the slow absorption of BPG from the intramuscular injection site, which leads to the lower, but prolonged, plasma levels found in humans.

The same spectrum of antimicrobial activity is displayed by BPG as by aqueous crystalline penicillin G; both are active against most members of the Streptococci and Neisseriae genus, as well as many anaerobes and spirochetes.11 The serum half-life of penicillin G after intramuscular administration is only 30 minutes, with levels undetectable after 3–6 hrs, while BPG has a much longer half-life of 4.1 days due to its low solubility.5,12 The excretion of penicillin G from the body occurs primarily via renal filtration and active tubular secretion, although excretion by the liver can also occur.8,5 In individuals with renal impairment, neonates and young infants, excretion of the drug is significantly delayed.8

### Table 1: Synonyms for benzathine benzylpenicillin

<table>
<thead>
<tr>
<th>Benzathine penicillin G</th>
<th>Commonly abbreviated to BPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzathine penicillin</td>
<td>Recognised by the United States Pharmacopeial Convention</td>
</tr>
</tbody>
</table>

**Similar sounding drugs which are not BPG**

<table>
<thead>
<tr>
<th>Benzylpenicillin</th>
<th>Penicillin G molecules without the benzathine molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine benzyl penicillin</td>
<td>Penicillin G combined with the local anaesthetic agent procaine</td>
</tr>
</tbody>
</table>

---

Figure 1: Chemical structure of benzathine penicillin G
Existing doses and formulations

BPG is typically available in three doses, standardised to international units (IU), and listed in Table 2. The IU of penicillin was developed as a standard measure of potency when the drugs were developed. By definition, the IU of penicillin is the penicillin activity contained in 0.6 mg of the crystalline sodium salt of penicillin G.13

Worldwide, BPG is available in two main formulations, outlined in Table 3. The vast majority of the world use the powdered form of BPG.

<table>
<thead>
<tr>
<th>Table 2: Standard doses of BPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>International units (IU)</td>
</tr>
<tr>
<td>600,000 IU</td>
</tr>
<tr>
<td>1,200,000 IU</td>
</tr>
<tr>
<td>2,400,000 IU</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Formulations of BPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>Lyophilised powder</td>
</tr>
<tr>
<td>Viscous liquid</td>
</tr>
</tbody>
</table>

BPG and Essential Medicines Lists

The WHO’s Essential Medicines List (EML) was established in 1977 and has been updated every two years since then. The list aims to draw together the medicines ‘that satisfy the priority health care needs of the population’, and which must be available within the health system at all times, in adequate amounts, as good-quality and affordable products.16

The WHO’s EML is often referred to as a ‘Model List’, as it is not designed as a global standard, but rather as a guide for the development of national or sub-national EMLs. Encouraged by the WHO, almost every country has drawn up their own national EML tailored to their population’s specific health needs, and many of these can be accessed online.17 For mapping of BPG within National Essential Medicines Lists see Annex A.

BPG has been included on the WHO EML since its first iteration in 1977 and in every subsequent EML update.18 In addition to the core EML, WHO also identifies Special Indications Lists which supplements the WHO EML for specific populations. BPG is included on a number of supplementary EML lists, as outlined in Table 4.

<table>
<thead>
<tr>
<th>Table 4: Essential Medicines Lists including BPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>List</td>
</tr>
<tr>
<td>Essential Medicines List16</td>
</tr>
<tr>
<td>First developed in 1977, the EML identifies medications which ‘satisfy the priority health care needs of the population’. The list is widely used by government and non-government organisations to prioritise and procure medicines.</td>
</tr>
<tr>
<td>Essential Medicines Lists for Children (EMLc)19</td>
</tr>
<tr>
<td>Developed in 2007, the EMLc has addressed the unique medication needs of children, including paediatric dosage forms (i.e. suspensions, chewable tablets, soluble tablets). Of note, the EMLc does not include a 0.6 million IU dose of BPG, although the smaller dose is indicated for children in a number of guidelines.</td>
</tr>
<tr>
<td>Essential Medicines for Reproductive Health20</td>
</tr>
<tr>
<td>Developed in 2006, the Essential Medicines for Reproductive Health guide supports the inclusion of reproductive medicines in national formularies.</td>
</tr>
<tr>
<td>Interagency Emergency Health Kit (IEHK)21</td>
</tr>
<tr>
<td>The IEHK is designed to provide sufficient medication for a population of 10,000 people for three months in an emergency situation. A large number of government and non-government agencies compile emergency supplies using the IEHK framework.</td>
</tr>
</tbody>
</table>

The IU of penicillin was developed as a standard measure of potency when the drugs were developed. By definition, the IU of penicillin is the penicillin activity contained in 0.6 mg of the crystalline sodium salt of penicillin G.13

Worldwide, BPG is available in two main formulations, outlined in Table 3. The vast majority of the world use the powdered form of BPG.

Formulation | Packaging | Manufacturer |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyophilised powder</td>
<td>Vials</td>
<td>Various trade and generic formulations [See annex B]</td>
</tr>
<tr>
<td>Viscous liquid</td>
<td>Pre-filled syringe</td>
<td>Pfizer, under the trade name Bicillin LA14</td>
</tr>
</tbody>
</table>

Cost of 1.2 million IU vial

Median global buyer price in 2014 = US$0.2215

Administration

Mixed with sterile diluent at point of care and injected intramuscularly

Cold chain dependent

Store in a refrigerator 2° to 8°C (36° to 46°F)14

Availability

All other countries

Licensed/registered in Australia, New Zealand, Canada and the United States of America

International units (IU) of penicillin

Generally suspended in 2 ml of sterile diluent (or 1 ml of Bicillin LA [Pfizer])14

Generally suspended in 3–5 ml of sterile diluent (or 2 ml of Bicillin LA [Pfizer])14

Generally suspended in 5 ml of sterile diluent (or 4 ml of Bicillin LA [Pfizer])14
Syphilis

Syphilis is caused by infection with the Treponema pallidum bacterium. An estimated 18 million people aged 15–49 years had syphilis in 2012. Each year, an estimated 5.6 million people in the same age group acquire a new infection. Syphilis is most common in low income economies, particularly in the African continent.

Syphilis is divided into early syphilis and late syphilis for the purpose of treatment guidelines. Treatment of syphilis requires the Treponema pallidum bacterium to be exposed to treponemicidal levels of antibiotics for 7–10 days in early syphilis and for longer in late syphilis. The development of penicillin in 1940 provided the first practical treponemicidal antibiotic. Widespread use of penicillin prompted a precipitous drop in cases in developed countries with access to the new drug. Penicillin levels of greater than 0.018 mg/L are sufficient for treponemicidal activity. Development of BPG made it possible to achieve these levels with a single 2.4 million IU injection.

All major clinical guidelines continue to recommend BPG as the first line treatment for syphilis. Adult treatment recommendations are summarised in Table 5. Clinical guidelines recommend that children are treated with smaller doses of BPG calculated by weight.

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>WHO Guidelines 2014</th>
<th>European Guidelines 2014</th>
<th>Centers for Disease Control and Prevention Guidelines 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early syphilis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary syphilis</td>
<td>Ulcer (chance) at the site of infection</td>
<td>Single dose of 2.4 million IU of BPG injected intramuscularly (or procaine benzylpenicillin 1.2 million IU daily for 10 consecutive days)</td>
<td>Single dose of 2.4 million IU of BPG injected intramuscularly (or procaine benzylpenicillin 0.6 million IU daily for 10–14 consecutive days i.e. if BPG is not available)</td>
</tr>
<tr>
<td>More infectious, better response to treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary syphilis</td>
<td>Skin rash, skin and membrane lesions, lymphadenopathy and condylomata</td>
<td>2.4 million IU of BPG once a week for 3 weeks injected intramuscularly (or procaine benzylpenicillin 1.2 million IU daily for 20 consecutive days)</td>
<td>2.4 million IU of BPG injected intramuscularly each week on day 1, 8 and 15 (or procaine benzylpenicillin 0.6 million IU daily for 17–21 consecutive days i.e. if BPG is not available)</td>
</tr>
<tr>
<td>Early latent syphilis</td>
<td>Asymptomatic infection &lt; 2 years duration*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late syphilis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latent syphilis</td>
<td>Asymptomatic infection &gt; 2 years duration*</td>
<td>2.4 million IU of BPG once a week for 3 weeks injected intramuscularly (or procaine benzylpenicillin 1.2 million IU daily for 20 consecutive days)</td>
<td>2.4 million IU of BPG injected intramuscularly each week on day 1, 8 and 15 (or procaine benzylpenicillin 0.6 million IU daily for 17–21 consecutive days i.e. if BPG is not available)</td>
</tr>
<tr>
<td>Less infectious, lower response to treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary syphilis</td>
<td>Gummatus syphilis</td>
<td>High dose intravenous penicillin regimens</td>
<td>High dose intravenous penicillin regimens</td>
</tr>
<tr>
<td>Cardiovascular syphilis</td>
<td>Late neurosyphilis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*<1 year duration in European syphilis guidelines

There have been some studies exploring the role of oral, non-penicillin antibiotics in treating syphilis. These have not yet been adopted as first line therapy because of technical difficulties, including resistance (erythromycin) and limited tissue penetration (erythromycin).

Syphilis in pregnant women

Syphilis infection during pregnancy is common. Worldwide, two million women each year test seropositive for syphilis while pregnant, a variable proportion have active infection. Without treatment, 25% of pregnancies during active infection will end in pregnancy loss or stillbirth. Most of the surviving babies will become infected in utero with syphilis, reflecting mother-to-child transmission. Babies with congenital syphilis infections may suffer from significant abnormalities of solid organs, skin, joints and cartilage. The irreversible and lifelong consequences of congenital syphilis are entirely preventable. Antibiotic treatment of pregnant women who are seropositive for syphilis prevents transmission to unborn babies. Testing pregnant women for syphilis and treating them is safe, cost-effective and prevents devastating disease outcomes for families. The only proven effective antibiotic for preventing congenital syphilis is BPG.

In 2007 the WHO identified syphilis as a feasible target for global elimination, describing it as ‘relatively simple to eliminate and it is inexpensive to detect and treat, making it a possible “easy win” in terms of cost, feasibility and speed of scale-up.’ In practice, supporting health systems in endemic countries to test pregnant women for syphilis and deliver appropriate BPG therapy has been challenging. Facilitating access to antenatal care, screening blood tests, reporting of blood test results and delivery of BPG therapy requires robust health systems to deliver a complex sequence of events. Shortages of BPG further complicate plans to eliminate congenital syphilis, even when the drug is appropriately prioritised for this indication. The WHO continues to prioritise elimination of congenital syphilis and has developed a late stage draft Health Sector Strategy on sexually transmitted infections (2016–2021). In particular, the WHO calls for action to ‘screen all pregnant women for syphilis, and ensure that those who are seropositive receive appropriate injectable penicillin therapy.’ Access to BPG underpins these efforts, making it a clear priority for global health.
Congo...
Prophylaxis against recurrent rheumatic fever

Young people who have had one episode of RF are at increased risk of recurrent RF following GAS infection. Without intervention, an estimated 50–75% of young people have recurrent episodes of RF, the majority within 5 years of their initial episode. Repeated GAS infections and recurrences of RF accelerate heart valve damage and the development of RHD. RHD causes heart failure and increases the risk of stroke, infective endocarditis, atrial fibrillation and maternal compromise during delivery. The Global Burden of Disease study estimates that 33 million people live with RHD worldwide and that 275,000 die from the disease each year. Secondary prophylaxis is the delivery of regular antibiotics to young people with a high risk of RF recurrence, i.e. those with a history of RF or with established RHD. Prophylaxis prevents RF recurrences and the immune reactions which would otherwise accelerate progression to RHD. Secondary prophylaxis is the only disease-altering therapy for RHD and is cost-effective.

BPG has been the first line antibiotic for secondary prophylaxis of RF since 1955. Regular intramuscular injections of BPG reduce the risk of RF recurrence by 87–96% and are therefore recommended in all major clinical guidelines (Table 6). The dose interval for these injections is contentious. It has been widely accepted that protection against GAS infection requires a plasma level of BPG to be maintained above the minimum inhibitory concentration (MIC) for GAS of 0.02 μg/ml for three to four weeks after a single intramuscular dose of BPG. The pharmacokinetic profile of BPG is such that soon after administration, a peak in serum penicillin G level is observed, which declines rapidly to below 0.01 μg/ml by day 21 post-injection. Plasma penicillin levels have also been shown to drop rapidly below the MIC of GAS within 2.5 weeks post-dosing, often much sooner. Clinical studies suggest that more frequent dosing (2 weekly) provides better protection than less frequent (4 weekly) dosing. However, in endemic settings with reliable access to high quality formulations of BPG, 4 weekly dosing appears to provide sufficient protection from recurrences. Twenty one or twenty eight day dosing is most commonly recommended in global guidelines (Table 6).

The recommended duration of secondary prophylaxis depends on the clinical picture, age of the patient, ongoing GAS exposure and the risks associated with disease recurrence. Most guidelines recommend regular BPG injections for at least a decade following an episode of clinically significant RF.

### Table 6: Recommended protocols for secondary prophylaxis of RF

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Preferred antibiotic</th>
<th>IM BPG doses</th>
<th>Interval of BPG injections</th>
<th>Oral alternatives</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO (2001) BPG</td>
<td>&lt;30 kg 0.6 million IU</td>
<td>21 days if high risk</td>
<td>Phenoxymethyl-penicillin 250 mg twice daily</td>
<td>No evidence of carditis: 5 years since last attack or 18 years old*</td>
<td>Severe: 40 years or longer</td>
</tr>
<tr>
<td></td>
<td>&gt;30 kg T.2 million IU</td>
<td>28 days if low risk</td>
<td></td>
<td></td>
<td>Moderate-severe or surgery: lifelong</td>
</tr>
<tr>
<td></td>
<td>&lt;30 kg T.2 million IU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States BPG (2009)</td>
<td>&lt;27 kg 0.6 million IU</td>
<td>4 weeks (3 weeks for selected groups)</td>
<td>Phenoxymethyl-penicillin 250 mg twice daily</td>
<td>For patients with persistent valvular disease, prophylaxis is recommended for 10 years after the last episode of RF or until 40 years of age*</td>
<td>Severe: 40 years or longer</td>
</tr>
<tr>
<td></td>
<td>&gt;27 kg T.2 million IU</td>
<td></td>
<td></td>
<td></td>
<td>Moderate: Until 35 years old</td>
</tr>
<tr>
<td></td>
<td>&gt;27 kg T.2 million IU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia and New Zealand (2012) BPG</td>
<td>&lt;20 kg 0.6 million IU</td>
<td>4 weeks (3 weeks for selected groups)</td>
<td>Phenoxymethyl-penicillin 250 mg twice daily</td>
<td>No evidence of carditis: 10 years since last attack or 21 years old*</td>
<td>Severe: 40 years or longer</td>
</tr>
<tr>
<td></td>
<td>&gt;20 kg T.2 million IU</td>
<td></td>
<td></td>
<td>No RHD or mild: 10 years since last attack or 21 years old*</td>
<td>Moderate: Until 35 years old</td>
</tr>
<tr>
<td></td>
<td>&gt;20 kg T.2 million IU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India BPG (2008)</td>
<td>&lt;27 kg 0.6 million IU</td>
<td>&lt;27 kg: 15 days</td>
<td>Phenoxymethyl-penicillin Children: 250 mg twice daily</td>
<td>No evidence of carditis: 5 years since last attack or 18 years old*</td>
<td>Severe RHD or post intervention: lifelong or until 40 years of age</td>
</tr>
<tr>
<td></td>
<td>&gt;27 kg T.2 million IU</td>
<td>≥27 kg: 21 days</td>
<td></td>
<td></td>
<td>Moderate-moderate: 10 years since last attack or 25 years old</td>
</tr>
<tr>
<td></td>
<td>&gt;27 kg T.2 million IU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa BPG (1997)</td>
<td>&lt;30 kg 0.6-0.9 million IU</td>
<td>3 weekly</td>
<td>Phenoxymethyl-penicillin</td>
<td>No evidence of carditis: 5 years since last attack or 18 years*</td>
<td>Severe: post valve surgery: lifelong</td>
</tr>
<tr>
<td></td>
<td>&gt;30 kg T.2 million IU</td>
<td></td>
<td></td>
<td></td>
<td>Moderate: Until 35 years old</td>
</tr>
</tbody>
</table>

* whichever is longer
IM intramuscular

In low resource settings where RHD is endemic it is enormously challenging to deliver regular injections of BPG to children and adolescents for a decade. Substantial efforts to strengthen RHD control activities and to improve secondary prophylaxis have occurred in recent years, including the formation of the global RHD Action movement, development of the Tools for Implementing RHD Control Programs (TIPs) resource, publication of an e-refugee to document people living with RHD, development of Needs Assessment Tool (in press) and Roadmap for RHD control (in press). As these resources and activities have impact over the next few years, capacity to deliver prophylaxis, and therefore demand for BPG, is expected to grow. Similarly, the trend towards increasingly robust echocardiographic screening studies for RHD is expected to continue. These studies will provide new information about disease which is currently undiagnosed and unmanaged.

The growth in practical resources for RHD control is matched by increasingly strong political and scientific momentum. The African Union has demonstrated critical leadership through a 2015 communiqué identifying seven key actions to eradicate RHD in Africa. The communiqué calls on international stakeholders such as WHO, UNICEF and World Heart Federation (WHF) to ‘address the urgent but neglected issue of the supply of benzathine penicillin G, to ensure that all countries have access to a stable supply of high quality product at all times’. This echoes calls from the WHF to prioritise access to BPG as one of five key targets for RHD control.
Impetigo, also known as skin sores or pyoderma, are contagious bacterial skin infections almost always resulting from GAS infection and often coexisting with Staphylococcus aureus bacteria. The infection cause skin lesions which subsequently form crusts. These open sores can be painful, persistent and create a risk of developing non-suppurative autoimmune complications of GAS infection, particularly post streptococcal glomerulonephritis and possibly RF.

Treatment of skin sores requires antibiotics, and a wide range of topical and systemic antibiotics have been used for this purpose. A large number of studies have been conducted to identify the optimum management of skin sores. A 2012 Cochrane review suggests that topical antibiotics or non-penicillin oral antibiotics are the most appropriate first line therapy. However, this review included only a single study from highly endemic, low resource settings. New research shows that short course oral co-trimoxazole is a suitable alternative to BPG. However, BPG remains an important treatment option for skin sores in endemic areas where adherence to therapy may be challenging.

Prophylaxis against infection in hyposplenia and asplenia

The spleen is a solid, intra-abdominal organ that filters red blood cells and contributes to immune protection against polysaccharide encapsulated bacteria, particularly Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae. The spleen can be damaged by disease or injury. Without a functional spleen, immune mechanisms are impaired and the risk of sepsis from encapsulated microorganisms increases significantly. Mortality from overwhelming infection in these patients approaches 50%. Antibiotic prophylaxis is generally recommended to reduce this risk, although high quality clinical trial data supporting prophylaxis is limited.

The risk of serious infection from encapsulated organisms is greatest following surgical removal of the spleen (splenectomy). Typically, this occurs following trauma or spontaneous major bleeding from the spleen. Many guidelines recommend twice daily oral antibiotic prophylaxis for two years following splenectomy; longer if patients have other risk factors for infection. Many post-splenectomy patients prematurely discontinue their antibiotic prophylaxis, sometimes with devastating outcomes. An estimated 50,000 asplenic people live in the United Kingdom and would benefit from improved secondary prophylaxis against life-threatening infection.

Evidence-based management of sickle cell disease

The spleen is a solid, intra-abdominal organ that filters red blood cells and contributes to immune protection against polysaccharide encapsulated bacteria, particularly Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae. The spleen can be damaged by disease or injury. Without a functional spleen, immune mechanisms are impaired and the risk of sepsis from encapsulated microorganisms increases significantly. Mortality from overwhelming infection in these patients approaches 50%. Antibiotic prophylaxis is generally recommended to reduce this risk, although high quality clinical trial data supporting prophylaxis is limited.

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Table 7: Antibiotic prophylaxis recommendations for asplenia, hyposplenia and sickle cell disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Evidence-based management of sickle cell disease</th>
<th>Update of guideline for the prevention and treatment of infection in patients with an absent or dysfunctional spleen</th>
<th>Recommendations for the management of sickle cell disease in South Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer oral penicillin prophylaxis (125 mg for age &lt; 3 years and 250 mg for age ≥ 3 years) twice daily until age 5 years in all children with H&amp;SS.</td>
<td></td>
<td></td>
<td>There is debate on the prophylactic use of oral antibiotics in all patients with sickle cell disease. However, penicillin VK 125 mg twice daily orally for children under 3 years of age and 250 mg twice daily for children older than 3 years of age is recommended, and continued until adolescence. Erythromycin is recommended for patients who are allergic to penicillin.</td>
</tr>
</tbody>
</table>

*H&SS is the most severe form of sickle cell disease*
Absolute adherence with the secondary prophylaxis regimen appears critical to life saving outcomes. Missing even a single dose of antibiotic is associated with an increased risk of severe infection.90,91 Twice daily antibiotic administration is challenging in young children, even in developed settings.92 In low resource settings with a high burden of sickle cell disease, adherence may be even more difficult. Compliance may be further compromised by limited access to affordable paediatric suspensions of oral penicillin V. In addition, once the powered suspension is mixed with liquid, the product has a shelf life of only 14 days.93 Some have suggested that regular intramuscular injections of BPG are a reasonable alternative to twice daily oral medication. This approach was used with encouraging results in a long term program in Jamaica.94 Current formulations of BPG are unlikely to be acceptable or available for large scale prophylaxis of infection in asplenic patients. However, reformulation to reduce pain and increase dose interval could provide a novel opportunity to improve adherence. A more suitable formulation may reduce the costs associated with preventable morbidity and mortality from sepsis.

Prophylaxis against recurrent cellulitis

Cellulitis is an infection of the skin and subcutaneous tissue. Infections are typically caused by GAS, S. aureus and some other streptococcal species. Extremities, particularly the lower limbs are most commonly affected. After a first episode of cellulitis, 15–30% of people will have recurrent infections.90,91 Risk factors for recurrent cellulitis appear to be local factors (skin disruption, fungal foot infections, leg surgery, oedema, and deep vein thrombosis) and a weaker effect of systemic factors (potentially including body mass index, smoking, and systemic causes of peripheral oedema). Diabetes has been considered a risk factor but evidence for this is weak. The global burden of cellulitis and recurrent cellulitis is high.90 Morbidity from acute cellulitis is substantial; each episode necessitates antibiotic treatment and may require hospital admission. Given the burden of recurrent disease, researchers have been exploring opportunities for antibiotic prophylaxis. A 2014 Cochrane meta-analysis of five studies identified that antibiotic prophylaxis is beneficial for reducing recurrent episodes of cellulitis (RR 0.46, 95% CI 0.26–0.79). Only one study included in the Cochrane review used BPG for prophylaxis and results from that individual study were not statistically significant.95 Economic analysis (based on oral prophylaxis) suggests that prevention of recurrent cellulitis is cost-effective.96 Overall, the majority of evidence suggests that penicillin prophylaxis against recurrent cellulitis is likely to be effective. Current recommendations are outlined in Table 8.

A formulation of BPG, which could provide protective serum penicillin levels without the need for daily antibiotics, may be more acceptable to patients, improve adherence and maximise clinical benefit. In high resource settings, where recurrent cellulitis is most amenable to prophylaxis, a sustainable BPG market may be possible.

Lyme disease

Lyme disease is caused by the Borrelia burgdorferi bacterium and is acquired by humans following the bite of an infected blacklegged tick. The disease manifests with fatigue, rash and joint and nervous system impairments. Diagnosis and treatment of Lyme disease is the subject of ongoing research and some controversy.101 Some guidelines recommend the use of BPG to treat the causative infection, but the overall role of the antibiotic remains unclear.

<table>
<thead>
<tr>
<th>Table 8: Guidelines on first line antibiotic prophylaxis to prevent recurrent cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious Diseases Society of America</strong>100</td>
</tr>
<tr>
<td><strong>United States 2014</strong></td>
</tr>
<tr>
<td>Administration of prophylactic antibiotics, such as oral penicillin or erythromycin twice daily for 4–52 weeks, or intramuscular benzathine penicillin every 2–4 weeks, should be considered in patients who have 3–4 episodes of cellulitis per year despite attempts to treat or control predisposing factors (weak, moderate).</td>
</tr>
</tbody>
</table>

**SHORTAGES OF BPG**

Overview

Australia

Brazil

China

India

South Africa

Timor-Leste

North America

Market vulnerabilities of BPG

Limited number of manufacturers for the active pharmaceutical ingredient

Poor visibility of demand

Overly aggressive price reduction practices in procurement

Fragmented and low volume markets

Business decisions by manufacturers
OVERVIEW

BPG has been subject to global stock outs over the last decade in both high and low resource settings.

The fragmented nature of manufacturers, suppliers and procurement agencies has complicated attempts to describe the sources of the drug or the scale of shortages. Irrespective of cause, it is clear that global shortages have had significant worldwide impact on countries and procurement agencies trying to purchase BPG.

Persistent anecdotal reports of BPG stock outs leading to disruption of secondary prophylaxis for RF were reported by the World Heart Federation in 2011. In a survey of 39 cardiologists in Asia-Pacific, Africa, Central and South America, almost all reported ‘minimal’ access to BPG and 35% reported inadequate supply to treat patients according to a recommended schedule of secondary prophylaxis injections.102,103 At a global meeting in Geneva in December 2015, three United Nations procurement agencies reported chronic shortages of BPG.104 This correlates with reports of shortages discussed by UNICEF representatives at the launch of RHD Action in New York, September 29th 2015.

Media and professional reports suggest that multiple drug shortages have occurred globally over at least the last 15 years, including Nepal (2003),105 New Zealand (2007),106 France (2013),107 Indonesia (2013),108 Poland (2014),109 and Egypt (2015).110

In a small number of countries, it has been possible to collect more detailed information; these case studies are presented in this report. However, the most vulnerable countries with the greatest need for BPG are likely to be misrepresented.

Australia

Australia does not have a formal list of essential medicines. Instead, clinical guidelines indicate that a single or short course of BPG injections is recommended for management of syphilis, skin sores and pharyngitis.111 An extended course of BPG is indicated for secondary prophylaxis against recurrent RF.112

BPG is subsidised by the Australian government through the Pharmaceutical Benefits Scheme (PBS) for most patients. As of April 2016, the maximum cost to the patient for Bicillin L-A (Pfizer) is AU$38.30.113 Indigenous Aboriginal and Torres Strait Islander Australians living in remote areas are able to access the drug at health clinics without cost.114

There have been five periods of BPG shortage in Australia in the 20 years from 1995–2015.115 Two of these shortages, in 2001 and 2014, resulted in only minimal disruption of services, while a prolonged shortage from 2006 to 2008 threatened to disrupt treatment protocols.116 The 2006–2008 shortage of BPG was reportedly caused by changes to the manufacturing practices by the single BPG manufacturer used in Australia and subsequent delays in regulatory submissions.117 A powdered formulation of BPG was introduced during this period to ensure supply, but resulted in widespread concerns about the acceptability, prescription and administration of the drug.118 Bicillin L-A, produced by Pfizer, was re-introduced to Australia in 2008.119 Subsequent shortages in 2012120 and 2014121 have been mitigated by careful management of the drug at pharmacy level but have raised ongoing concerns about reliance on a formulation produced by a single manufacturer in a single plant.122

Brazil

In Brazil, BPG (called benzilpenicilina benzatina) is included in the 2010 National Essential Medicines list (Relação Nacional de Medicamentos Essenciais) in 0.6 million and 1.2 million IU doses.123 Brand names used in Brazil have included two local products: Benzetacil (Eurofarma, Brazil) and Repeben (Teuto Laboratory, Brazil), and an earlier product Penicilina G Benzatina (Ariston, India). Formulation of the major Benzetacil product occurs in Brazil with active pharmaceutical ingredient (API) sourced from international third parties. In Brazil, nursing staff have been so concerned about the risks of adverse reactions when administering BPG in primary care settings the practice has previously been restricted by the nursing council.124 In 2015, given the increasing burden of congenital syphilis, a special resolution was passed allowing community administration of BPG.125

BPG in Brazil is usually free at point of care through the health care system. BPG can also be purchased directly from pharmacies for approximately 10 reals (US$2.5).

Shortages of BPG in Brazil reached critical levels in 2015 when widespread stock outs limited access to treatment of syphilis and RF.126 Shortages were primarily associated with reduced global access to API. A special hearing of the Social Security and Family Commission was convened on September 29th 2015, including public health officials and pharmaceutical industry representatives.127 Following this meeting, a committee was formed to establish strategies for improving BPG supply. Doctors in Brazil are awaiting updates on the activities and outcomes of this committee.

Prior to contemporary stock outs, access to BPG was reasonable by global standards. A 2001 review of access to essential medicines in Minas Gerais state was conducted by Management Sciences for Health.128 The study revealed that BPG was available in some public medical stores (50%) and public health facilities (43%). Stock of BPG was greater in charitable institutions (69%), private facilities (71%) and private pharmacies (95%).

Despite these challenges, the Brazilian national health system Sistema Único de Saúde (SUS) uses a human rights approach to health which supports universal access to primary health care.129

China

In China, BPG (called 干青霉素) is included on the national Essential Drugs List and on provincial lists. The China Food and Drug Administration (CFDA) lists three doses of BPG in 0.3 million, 0.6 million and 1.2 million IU increments. A number of local manufacturers are identified by the CFDA.130

The price of BPG in China is determined by the government and covered by the health care reimbursement scheme, intended to cover all medications on the Essential Drugs List.131,132 In July 2011, the maximum retail price of BPG was set at 9 Chinese yuan (CHY) for 1.2 million IU dose (US$1.39). Additionally, informal sources of information for clinicians in China suggest the retail price of BPG from one manufacturer ranges from CHY 2.28 to 9.5 (for 1.2 million IU dose, equivalent to US$0.54–1.39) for providers in 7 locations across the country.133

There is limited formal information on supply, availability and quality of BPG in China. However media reports, including accounts reported in Chinese Government administered publications online suggest that stock outs occur, consistent with international experience.134,135

Image credit: National Yaws Control Programme, Ghana

Health care worker preparing benzathine penicillin in a yaws treatment campaign, West Akin district, Ghana.
India

In India, BPG (referred to as benzyl benzathine penicillin) is included in the most recent 2011 edition of the National List of Essential Medicines of India in 0.6 million IU and 1.2 million IU doses.133 The earlier 2003 edition had also included 2.4 million IU doses.134 BPG also appears on the National Formulary of India, indicated for ‘mild to moderate infections of upper respiratory tract due to susceptible streptococci, syphilis, prophylaxis of rheumatic fever’.135

Anecdotal reports of poorly characterised adverse reactions are common in India prompting concern about the quality and safety of BPG products. In India, skin testing for allergy is recommended before doses of BPG.136 Concerns about adverse reactions have reportedly prompted restrictions on the use of BPG in some states, including Kerala and Tamil Nadu, sometimes extending to outright bans on BPG administration.137

The price of BPG in India is determined by the government of India and the National Pharmaceutical Pricing Authority. In 2007, the price of a 1.2 million IU vial of BPG was set at 13.08 rupees (US$0.20).138

In 2007, the price of a 1.2 million IU vial of BPG was set at 13.08 rupees (US$0.20).137 The government of South Africa supports medication transparency through its South African Medicines Price Registry website.139 As of April 2016, the site indicates that two doses of BPG (1.2 million IU and 2.4 million IU) are registered for use by the South African Medicines Control Council from three manufacturers: Biotech Laboratories, Caps Pharmaceuticals and Fresenius Kabi South Africa. Cost of medication is usually borne by patients/families and costs range from R4.31 to R26.09 (US$0.34–2.09) per single dose of 2.4 million IU and R6.36 to R26.62 for 1.2 million IU (US$0.35–2.13); however financial assistance, dependent on the patient’s resources and age, is generally available at public health facilities.

In 2015 South Africa was struck by significant shortages of BPG, affecting both 1.2 million IU and 2.4 million IU doses. The shortages were attributed to stock outs of API necessary for drug manufacture. The National Department of Health was forced to investigate use of a Section 21 application to allow for drug manufacture. The National Department of Health is expected to resolve by July 2016.138 This shortage prompted advice from the Public Health Agency of Canada to restrict the use of Bicillin L-A to specific indications, noting that these ‘may differ from the preferred and alternative treatment recommendations in the Syphilis chapter of the Canadian Guidelines on Sexually Transmitted Infections’.139

South Africa

BPG is an essential medicine in South Africa and is listed in the national formulary for the treatment of RHD, prevention of recurrent RF, and syphilis.135 The government of South Africa supports medication transparency through its South African Medicines Price Registry website.139 As of April 2016, the site indicates that two doses of BPG (1.2 million IU and 2.4 million IU) are registered for use by the South African Medicines Control Council from three manufacturers: Biotech Laboratories, Caps Pharmaceuticals and Fresenius Kabi South Africa. Cost of medication is usually borne by patients/families and costs range from R4.31 to R26.09 (US$0.34–2.09) per single dose of 2.4 million IU and R6.36 to R26.62 for 1.2 million IU (US$0.35–2.13); however financial assistance, dependent on the patient’s resources and age, is generally available at public health facilities.

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The 2010 ‘Essential Medicines List for Timor-Leste’ includes two dose sizes of BPG under a ‘vital’ designation.140 BPG is intended to be available at all levels of the health system (Level 1 District Health Posts, Sub-District Level Health Centres, District Level Health Centres and at referral hospitals). BPG is needed in Timor-Leste for the treatment of syphilis and prophylaxis of RF.

In Dili, the country’s capital, physicians and paediatricians at the Hospital Nacional Guido Valadares frequently diagnose cases of severe RHD. BPG is usually available within the hospital, but stock outs have occurred. On discharge, children with RHD are advised to attend their local community health centre to receive monthly BPG injections.

One prominent non-government organisation (NGO) healthcare institution in Timor-Leste is the Bairo Pita Clinic, based in Dili. The clinic has a small registry of people living with RHD, who attend the clinic regularly for BPG injections for secondary prophylaxis, although national stock outs of BPG have compromised the program at times.

BPG available in Timor-Leste appears to be an Indonesian product Benzatil Benzil Penisilin (Phapros Pharmaceuticals). This product is manufactured in Indonesia, and there is understood to be a reasonable supply of this drug at National Hospital Pharmacy via the national procurement agency Serviço Autônomo de Medicamentos e Equipamentos de Saúde (SAMES).

Timor-Leste

North America

Shortages of BPG also periodically occur in the United States and Canada, most recently in 2002144 and in 2006.115 In April 2016, Pfizer notified the Food and Drug Administration (FDA) that all three dose sizes of Bicillin L-A were ‘currently in shortage’ because of manufacturing delays. Backorder is expected to resolve by July 2016.145 This shortage prompted advice from the Public Health Agency of Canada to restrict the use of Bicillin L-A to specific indications, noting that these ‘may differ from the preferred and alternative treatment recommendations in the Syphilis chapter of the Canadian Guidelines on Sexually Transmitted Infections’.146

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Drug shortages are an increasingly well-documented global challenge, affecting both high and low resource settings. Some kinds of drugs are more vulnerable to shortage than others. A recent WHO report identified a number of risk factors for drug shortage: older products, off-patent drugs, difficult to formulate, tight or defined shelf life and few/single manufacturers. The report also identified that sterile injectables are particularly at risk of drug shortages. Reasons for this vulnerability are identified below, with particular reference to BPG.

**Limited number of manufacturers for the active pharmaceutical ingredient**

Production of pharmaceutical end-products involves a number of steps, each of which may be undertaken by different companies, outlined in Figure 2. This is certainly the case for BPG where a small number of companies produce API for others who later formulate and package the product. Information about API manufacturers is generally proprietary, however there are indications that access to Good Manufacturing Practice (GMP)-certified API is challenging.

For example, a number of contemporary stock outs have been attributed to problems with GMP certification of API from a major Chinese supplier. In November 2014, API for BPG produced by the North China Pharmaceutical Group Semiyntech Co. Ltd. was found to be non-compliant with GMP regulations by the French National Agency for Medicines and Health Products Safety. The API had been used to develop finished drug product by Phanpharma and subsequently sold to purchasers. These BPG products had been supplied to Ethiopia and Liberia and were subsequently recalled. This was followed by a European Union statement of non-compliance and a WHO statement on the inspection results. In the Philippines, accreditation of BPG quality was contested in court in 2007 during a contracting dispute. Shortages of buffers and reagents required for formulation of BPG may amplify difficulties accessing API.

The small number of manufacturers in the BPG market is likely to be a persistent challenge. In 2013 the United States FDA issued guidance on reducing product contamination for manufacturing plants producing penicillin and other beta-lactam API and antibiotic formulations. This guidance recommends dedicated production areas including facilities, air handling equipment and processing equipment be reserved for the production of high sensitising materials. The infrastructure required to meet these guidelines is substantial, creating a barrier to new manufacturers entering the market. Decommissioning of penicillin production facilities is also complicated, making it difficult for companies to recoup their infrastructure investment if companies decide to manufacture other product lines.

**Overly aggressive price reduction practices in procurement**

The price for BPG is low (Table 9). In some countries the price is fixed by the government, further limiting financial sustainability of the product. This focus on price at the expense of quality may be undermining the BPG market in a way which ultimately undermines access to the product.

**Table 9: Median prices of BPG in 2014**

<table>
<thead>
<tr>
<th>Product</th>
<th>Setting</th>
<th>Median price per vial</th>
<th>Price paid by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzathine penicillin G 1.2 million IU</td>
<td>Global supplier price average</td>
<td>US$0.13</td>
<td>Wholesale sales price</td>
</tr>
<tr>
<td></td>
<td>Global national purchaser average</td>
<td>US$0.22</td>
<td>National purchase price</td>
</tr>
<tr>
<td>Benzathine penicillin G 2.4 million IU – buyer prices</td>
<td>Global supplier price average</td>
<td>US$0.26</td>
<td>Wholesale sales price</td>
</tr>
<tr>
<td></td>
<td>Global supplier price average</td>
<td>US$0.28</td>
<td>National purchase price</td>
</tr>
</tbody>
</table>

# table adapted from Management Sciences for Health, International Drug Price Indicator Guide[20]
**Fragmented and low volume markets**

BPG procurement is plagued by fragmentation across different indications. UN procurement agencies are involved in the BPG market include the United Nations Population Fund and the UNICEF. Even large UN agencies have reported recent difficulties in sourcing BPG. At a national level, procurement is much smaller in scale and more difficult. For example, the UN Agency for Palestine Refugees sought expressions of interest to supply 100 vials of 1.2 million IU of BPG, 2015.

**Business decisions by manufacturers**

The highest volume indications for BPG (syphilis and secondary prophylaxis against RF) occur in low resource settings where procurement systems, supply chain management and diagnosis are weakest. This means that although there is a clear clinical need for the drug, there is not always a well-developed system for delivery. Erratic supply and demand complicate supply chain management, particularly for multi-dose regimens for prophylaxis. Patients who are unable to access or purchase BPG are less likely to return for subsequent doses, paradoxically reducing demand even when clinical need has been identified and BPG prescribed.

BPG is identified in a report to the World Health Assembly as a sentinel example of a sterile injectable subject to frequent drug shortages. Opportunities identified by WHO to mitigate drug shortages include reporting mechanisms, notification of expected stock outs and identification of a minimum price for products such as BPG which have a limited market. Market shaping opportunities, including minimum price points, are addressed in the Actions and Recommendations section of this report.

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**Adverse drug reactions to BPG**

**Systemic adverse reactions**

**Local adverse reactions**

**Quality and behaviour of BPG**

**Duration of action**

**Suitability for suspension**

**High rates of idiosyncratic adverse reactions**

**Antibiotic resistance**
ADVERSE DRUG REACTIONS TO BPG

The WHO defines an adverse drug reaction (ADR) as a response to a drug that is noxious, unintended or undesired occurring at doses normally used for the prevention, diagnosis or treatment of illness.100

An ADR may be systemic, affecting the whole body, or localised to the site of administration. Systemic and local adverse reactions to BPG are a global concern for clinicians and consumers of the product.

Systemic adverse reactions

Systemic ADRs can be further classified into Type A reactions (pharmacologic, dose related, effects of the drug including side effects, toxicity and drug interactions) and Type B reactions (unpredictable, dose independent, hypersensitivity).163 Type B reactions are the predominant reactions occurring at doses normally used for the prevention, diagnosis or treatment of disease'.162

Globally, penicillin is considered one of the commonest causes of Type B ADR.164 Up to 10% of people report a history of penicillin allergy.165 However, the absolute risk of true anaphylaxis to penicillin in an individual is low.166

There have been a number of studies quantifying the specific risk of BPG injections, either intentionally or through incidental reports. A 2013 systematic review analysed 12 of these studies (1954–2012), plus one large study of all forms of penicillin prescription.173 The systematic review authors noted that results were highly heterogeneous across time and geography. However, pooled analysis confirm that the risk of serious adverse reaction from BPG injections is low (Table 10).

The 2013 systematic review confirmed that the risk of an adverse reaction was higher when patients were exposed to BPG on multiple occasions.178 There have been long-standing concerns about the safety of ongoing doses of BPG for prophylaxis. In 1991, the International Rheumatic Fever Study Group (IRFSG) conducted a large scale, prospective international study to document adverse reactions to BPG, particularly for patients receiving repeated doses of the drug over time.179 The IRFSG study included 1,790 patients from 11 different countries who received 32,430 injections of BPG. The drug was sourced from 12 different manufacturers and given to patients aged 5–23 years. This study reported allergic reactions in 57 patients (3.2%), immediate anaphylactic reactions in four patients (0.2%) and one fatality (0.05%, 0.31/10,000 injections). The frequency of anaphylactic reactions was calculated at 1.23 per 10,000 injections.179

Since the IRFSG study, only two studies have reported on the rates of allergic reaction to BPG for RHD. A 2011 retrospective study in Nepal of 77,000 injections given to 4,700 patients reported 65 patients with allergic reactions (1.4%), five of those being anaphylactic reactions (0.1%). Eight episodes of vasovagal syncope were also reported (0.16%).180 A 2014 retrospective study in Turkey found suspected allergy in 11 patients (2%), with no anaphylactic reactions.181 A United States FDA analysis of long term penicillin therapy concluded ‘Although there are no specific studies that directly assess the safety of these antibiotics when given over an extended period of time, there is a significant amount of information that supports the safety of such therapy.’182

Although rare, fatalities in RHD patients receiving BPG prophylaxis have been reported: in 1958,183 1962,184 1991,188 and 2000.189 The majority of these fatalities have occurred in patients with severe RHD disease manifested as cardiac complications. The presence and nature of any association between severe cardiovascular disease and death associated with BPG injections remains unclear. It is feasible that severe episodes or fatalities, particularly if they occur in patients with severe RHD, may be due to vasovagal episodes rather than a reaction to the injected substance.

Serious systemic reactions from BPG are rare. The risk of adverse reactions is certainly less than the morbidity and mortality associated with syphilis infection, RHD and other indications for BPG. Fear of anaphylaxis should not prevent people with a clear indication for BPG therapy from receiving appropriate treatment. However, anecdotal reports suggest that fear of adverse events prevents health care staff from delivering injections when indicated.193

In Nepal, there are reports that health workers have been assaulted or jailed following adverse reactions to BPG.194 In Brazil, nursing staff have been so concerned about the risks of administering BPG in primary care the nursing council limited the practice.195 There are unconfirmed reports that BPG has been banned in some states in India (Kerala and Tamil Nadu) because of fear of ADR.196,197 In Zambia, fear of anaphylaxis prevented health care workers adhering to standard treatment guidelines.198

A public-private partnership is underway in Zambia to eliminate RHD.199 Partners include the University Teaching Hospital Lusaka, Ministry of Health, Ministry of Education, University of Zambia, University of Cape Town and the pharmaceutical company Novartis.184 As part of this partnership, a two-day workshop on penicillin allergy was held in 2013. The curriculum was delivered by a visiting professor and based on guidelines from the World Allergy Organization. Twenty nine attendees had demonstrably improved knowledge following the workshop and reported that training would change their clinical practice.185 Allergy kits have also been developed to be stocked at health clinics which are part of the RHD control program.196

Table 10:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of patients receiving 1 or more BPG injections</th>
<th>Number of events during observation</th>
<th>Absolute risk % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2,108,117</td>
<td>4</td>
<td>0.169 (0.073%–0.257%)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>2,108,117</td>
<td>54</td>
<td>0.002 (0.0–0.003%)</td>
</tr>
<tr>
<td>Adverse reaction</td>
<td>3,465,322</td>
<td>6,377</td>
<td>0.169 (0.073%–0.257%)</td>
</tr>
</tbody>
</table>

# table adapted from Galvao et al (2013)172

Local adverse reactions

Local ADRs include effects at the site injection, such as pain and redness.

Intensity of pain

Pain on injection of BPG has been a problem since the product was initially developed. Although anecdotal reports of pain are common, only a small number of studies have used validated scales to quantify the experience of BPG. In a New Zealand study, 405 patients (5 years of age to adults) reported a mean pain score of 5.4/10 during administration of Bicillin L-A (Pfizer).171 In the Middle East, 117 paediatric patients [10–10 years] were given injections of powdered BPG diluted in 3.2 ml of sterile water for prophylaxis of RF. The mean score for pain on administration was 6.7/10 (range 4–10).190

Duration of pain

A number of studies suggest that pain from BPG injection lasts a number of days. In Australia, 30% of 165 children receiving BPG injections for treatment of sore skin reported pain two days after BPG injection and five children required pain relief.180 A recent Australian case study provided radiologic evidence of myositis following routine BPG injection in a 7 year old boy. Despite uncomplicated administration of the Bicillin L-A (Pfizer), the child limped for a number of days after injection.191

Determinants of pain

The determinants of injection site pain for BPG are unclear. Potential contributors include:

VOLUME OF INJECTION

BPG is routinely administered in volumes between 2–5 ml, but intramuscular (IM) injection of up to 8 ml has been reported. Most users define large volume IM injections as greater than 3 ml.180 A recent study in France provides some information about the tolerability of different volumes of BPG injection. In France, 50 adult patients receiving three doses of BPG for treatment of syphilis received either 2.4 million IU of BPG mixed with 7 ml of saline and 1 ml 1% lignocaine, or two injections of 1.2 million IU of BPG mixed with 3.5 ml of saline and 0.5 ml of 1% lignocaine. Mean pain was 3.1/10 (range 0–8) with the 2.4 million IU dose and 2.7/10 (range 0–7) with two 1.2 million IU doses. The difference between the reported pain scores was not statistically significant (p = 0.36).180 When participants were allowed to choose the dose delivery for their third and final BPG dose they were evenly split between options.
**FORCE OF INJECTION**

IM injections should be given slowly, allowing muscle fibres to accommodate the volume of injection. However, the difficulty suspending powdered formulations of BPG means that needles are frequently blocked. This requires staff giving the injection to increase the force applied to the needle stopper, sometimes causing a period of high velocity when the obstruction clears. On some occasions needles are irreversibly blocked and a new injection must be given, which is traumatic for patients and staff and may be associated with inaccurate dosing of product.

**INJECTION SITE AND TECHNIQUE**

There is an extensive body of nursing literature on IM injections, including optimal positioning, approach and technique. There are few definitive conclusions on best practice, nor a clear indication of how these apply to BPG. It is possible that some local injection practices may increase pain associated with injection. In Australia, Pfizer has supported the development of a video resource outlining recommended injection technique for the Bicillin L-A product.

**CHEMICAL PROPERTIES OF BPG**

It is possible that properties of BPG or excipients cause more injection site pain than other similarly sized injections. Certainly, BPG injections appear to be more painful than 4 ml injections of oil based depot preparations of testosterone. If research indicates that physical properties of BPG contribute to pain then pharmacologic interventions/additives may need to be prioritised as a pain reduction strategy.

**Interventions to reduce injection site pain**

Pain and fear of pain may be a barrier to adherence, particularly when multiple doses of BPG are required, as in late syphilis and prophylaxis against RF. The evidence for the impact of pain on adherence is variable, pain is not reported as a major determinant in secondary prophylaxis studies from Australia or India, although it is a significant barrier in Uganda.

A number of interventions have been suggested to reduce the pain on IM injection. However, the best practice, nor a clear indication of how these apply to BPG is currently unknown.

**ADDITION OF LOCAL ANAESTHETIC**

Many authors have suggested adding local anaesthetic to reduce the pain of BPG injections. There is some evidence that this is effective in reducing pain and does not appear to affect serum penicillin concentration. The practice occurs widely: it is recommended in the Syphilis Treatment Guidelines from the United Kingdom [noting that this is an unlicensed indication] and in the New Zealand guidelines for the ‘Preventing Rheumatic Fever’ Program.

**VIBRATION, COLD AND RELAXATION**

An increasing number of adjunctive techniques for managing injection site pain have been explored. In New Zealand, use of a vibrating cold pack has been acceptable to patients (particularly those under 13 years) and is associated with reduced pain and fear.

Clinicians routinely express concern about the quality of BPG products available. These concerns are generally based on observation of drug administration or action: that it is difficult to give BPG, that there are an unexpectedly high number of adverse reactions or that the drug appears to ‘fail’ in settings where resistance is not expected.

**QUALITY AND BEHAVIOUR OF BPG**

Data from the 1950s suggests the serum concentration of penicillin could be detected above the MIC (generally considered between 0.01–0.03 μg/ml) for GAS three or more weeks after BPG injection. However, contemporary studies suggest that serum concentration levels fall faster than expected than for earlier studies.

In a population of 164 male military recruits receiving a quality-assured form of BPG (Bicillin L-A, Monarch Pharmaceuticals), the mean serum penicillin level fell below 0.02 μg/ml by day 11 post-injection. This finding compares with an earlier study of 86 male military recruits who received a 1.2 million IU dose of BPG (Bicillin L-A, Wyeth-Ayerst laboratories). Only 34 participants had detectable serum penicillin on day 7 post-injection (mean = 0.01 μg/ml) and in only three participants by day 14 (mean = 0.016 μg/ml). No penicillin was measurable on day 21 or day 28. In contrast, in a study from Thailand, 20 male and female patients with RHD were given 1.2 million IU of an undisclosed BPG formulation. Eighty percent of patients had serum penicillin concentrations greater than 0.02 μg/ml on day 28 following injection. In Australia, 25 male and female patients received 1.2 million IU of BPG (Bicillin L-A, Wyeth) for RF prophylaxis. At day 14 only 11/16 (69%) had serum penicillin levels considered protective (0.025 μg/ml), by day 21 this fell to 8/16 (50%) and further to 4/17 (24%) by day 28.

Pharmacokinetic modelling applied to BPG dosing suggests that the majority of children and adults given 1.2 million IU will have a serum penicillin level less than 0.02 μg/ml two weeks after injection.

A 2013 meta-analysis of 27 articles, including these and similar studies on BPG concentration, found that studies conducted after 1990 were associated with lower serum penicillin concentrations. This raises the possibility that changes in formulation or manufacturing before and after 1990 may be associated with variation in observed pharmacokinetics. Variation in pharmacokinetic and bioavailability parameters between BPG formulations is supported by a 1996 study of 360 patients with RHD in Egypt. The change from older boissayes to contemporary quantitative assays may also have altered the sensitivity of measuring serum penicillin concentrations, although more sensitive modern methods would be expected to show longer rather than shorter duration of action.

**Suitability for suspension**

Clinicians report that difficulty suspending BPG powdered formulations for injection is considered a marker of a ‘poor quality’ product. There does seem to be some empirical evidence that BPG from different manufacturers is associated with different solubility and needle blocking. There are few records of regulatory agencies responding to these issues. However, in 2015 the Food and Drug Administration of the Philippines advised of a voluntary recall of two lots of the BPG product Zalpen (YSS Laboratories Co. Inc.) over concerns about inability to dilute the powder fluid.

**High rates of idiosyncratic adverse reactions**

Highly anecdotal reports suggest that the rate of adverse reactions to BPG is higher than would be expected, given what is known about penicillin allergy. Reactions appear to be idiosyncratic, including possible syndrome and systemic malaise after injection. These are often informally attributed to ‘impurities’ in BPG or other drug quality issues. It is impossible to interpret or investigate these cases without systematically collecting pharmacovigilance data to evaluate patterns of events. In the absence of clear evidence of idiosyncratic adverse reactions to BPG, clinicians should be educated about the expected prevalence of anaphylaxis and trained in its management.
Antibiotic resistance is one of the greatest threats to the delivery of modern health care. Clinicians and policy makers are understandably concerned that increasing access to BPG – particularly the protracted courses of prophylaxis – may contribute to antibiotic resistance. Target organisms treated with BPG remain exquisitely susceptible to penicillin. Although reassuring, the cause of persistent susceptibility is poorly understood.

Treponema pallidum

There have been no documented cases of penicillin resistance in T. pallidum. Serologic treatment failure does occur, often in the setting of HIV, or more commonly in association with reinfection. Relapse may also occur when T. pallidum enters the central nervous system and is therefore protected from treponemical levels of penicillin by the blood–brain barrier. Theoretic pathways for development of T. pallidum resistance to penicillin do exist. However, over sixty years of susceptibility to penicillin suggests that the bacterial genetic mutations required for T. pallidum resistance are complex and evidently rare events.

Group A streptococci

There have been no documented cases of penicillin resistance in GAS. Persistent nasopharyngeal colonisation after BPG is relatively common but is attributable to a protected intracellular niche rather than true treatment failure. Continued susceptibility of GAS is particularly remarkable given high rates of nasopharyngeal carriage and widespread exposure to penicillin over many decades. The mechanisms for this ongoing susceptibility remain unclear but may include prohibitively complex requirements for bacterial genetic transfer, toxicity associated with genes for resistance or evolutionary cost in the development of low-affinity penicillin binding proteins.

There are also risks that widespread use of BPG could drive resistance in other, non-target, bacteria. Studies exploring this possibility have reported mixed results. In Israel, viridans streptococci cultured from children receiving monthly injections of BPG for prophylaxis of RF remained sensitive to penicillin G and a number of other antibiotics.

There was no significant change in resistance patterns relative to a control group of children not receiving BPG injections. Similarly, in Brazil, long term BPG therapy for RF prophylaxis did not alter penicillin susceptibility of oral flora Str. sanguinis and Str. oralis. However, widespread use of oral penicillins – particularly for viral infections – has been correlated with increased antibiotic resistance, particularly in Str. pneumoniae.

The role of population dynamics in driving antibiotic resistance remains poorly understood. In overcrowded settings where children have multiple early infections and a high bacterial load, transfer resistance determining genetic material between organisms may be accelerated, irrespective of antibiotic use. However, in these settings the use of BPG in preference to newer, more expensive antibiotics may actually reduce the risk of population level antibiotic resistance. The use of antibiotics in developing countries requires special consideration but proven treatments should not be withheld from vulnerable populations. The Lancet Infectious Diseases Commission notes that RHD control programs equipped with a central register and a supply of BPG is an appropriate intervention and highlights that ‘the challenge in all these efforts will be to scale-up antibiotic used but to minimise drug resistance from unnecessary or inappropriate use.’ Limiting use of BPG for appropriate indications, to be administered by trained health workers using agreed protocols (and diagnostic tests where available) provides the best opportunity to treat disease and minimise the development of resistance.
Paediatric doses

BPG is recommended for children, particularly for the treatment of syphilis (neonates) and for secondary prophylaxis against RF (commonly over 5 years of age). In some countries, BPG is widely used for treatment of impetigo in young children or primary prophylaxis of GAS pharyngitis. Some clinical guidelines recommend paediatric dosing by weight for these indications. However, neither powdered or liquid formulations of BPG are suitable for precise calculation of incremental doses. In practice, smaller doses are often calculated by volume of drug decanted into a smaller syringe. Practically, this entails suspending powdered products in diluent and then drawing up a fractional dose by volume, a process which assume the drug is evenly distributed in the diluent. This is associated with a high risk of under-dosing (potentially causing treatment failure) or over-dosing (increasing the risk of volume-related adverse events). Although the absolute number of children receiving BPG globally is modest, product innovation to facilitate paediatric dosing would be a valuable safety addition. For example, it may be possible to validate graduations or other markings on vials/syringes of existing formulations to indicate fractions of the medication dose. As a minimum intervention, increasing access to 0.6 million IU dose formulations should be supported.

Reduction of injection site pain

Reducing the pain of BPG injections is a critical determinant of product acceptability. As discussed, pain following injection is moderate to severe and may last up to 48 hours after injection. This particularly reduces adherence to BPG prophylaxis when multiple doses are required. Further study is needed to better understand the determinants of BPG injection site pain.

In the interim, manufacturers and regulators should consider allowing or endorsing the use of lignocaine as a diluent for BPG injections. There is reasonable evidence that the practice is safe, it already recommended in a number of guidelines, and informal use of lignocaine is widespread. Providing definitive advice on how much lignocaine should be used and any restrictions on use would be a practical first step to mitigating injection site pain.

Other strategies to reduce pain may include developing formulations of BPG which are less likely to block the needle, producing high force/high velocity injections. The have been some preliminary attempts to develop BPG formulations more amenable to suspension. Adjunct innovations, including improvements to syringes, diluent or suspension technique may be possible and should be explored.

Longer acting formulations

One of the major benefits of BPG is protracted serum penicillin concentrations. This feature makes BPG uniquely suitable for prophylaxis against sensitive organisms and underpins its existing role in prophylaxis. BPG may also be acceptable and convenient prophylaxis for other indications (hyposplenism prophylaxis, prevention of recurrent cellulitis) if the dose interval could be prolonged. Certainly, adherence to secondary prophylaxis in people living with RHD would be considerably enhanced by a longer acting, more acceptable formulation. Calls for reformulation of BPG have come from the RHD community but improved formulations may well be applicable to other indications. A small number of studies have explored opportunities for dose interval reformulation, including microemulsions and implantable drug monoliths. Efforts to develop a safe, quality assured, long-acting formulation of BPG are critical to global RHD control and are likely to enhance disease control efforts for other indications. Well designed trials to prove that sustained serum level above the MIC prevent GAS infection in prophylaxis are needed. Public-private research initiatives will then be required to identify candidate formulations and regulatory requirements.
Regulatory issues

Regulation of BPG is challenging, even for existing formulations. In the United Kingdom BPG remains entirely unlicensed, attributed by some authors as ‘probably due to low demand’.232 Regulatory arrangements in other countries remain somewhat opaque, necessarily responsive to the formulations of BPG available for purchase.

The challenge of historic licensing data

Existing regulatory data on BPG are limited; in many cases licensing data predates the contemporary era of study design and evidence of efficacy. The US Centers for Disease Control and Prevention guidelines on the treatment of syphilis acknowledges ‘the effectiveness of penicillin for the treatment of syphilis was well established through clinical experience even before the value of randomised controlled clinical trials was recognised. Therefore, nearly all recommendations for the treatment of syphilis are based not only on clinical trials and observational studies, but many decades of clinical experience.’23

The absence of historic data makes it difficult for manufacturers to demonstrate that their product can meet existing standards or demonstrate bioequivalence. Companies seeking to license any new BPG formulations may be mandated to complete studies which demonstrate the efficacy of penicillin against target organisms per se. This uncertainty about regulatory requirements is likely to have a chilling effect on new market entrants.

A number of older antimicrobials are candidates for ‘re-development’, a process which includes updating trial data to contemporary standards, conduct of high quality studies and clearly communicating to users appropriate indications for each product.233 BPG is an ideal candidate for the redevelopment process, particularly to define standard assays, pharmacokinetic profile, acceptable MIC and, for some indications, mechanism of action. Given the largely generic market for BPG, low volumes and limited profits of the product, manufacturers will be unable to support all of the work necessary to update regulatory dossiers for BPG. The requirements for redevelopment necessitates intellectual, financial and goodwill input from academia, regulators, industry, governments, international agencies, clinicians and communities.

Extending licensing to novel indications

There are a number of reformulation options for BPG, spanning from incremental improvement to substantial redevelopment of BPG into a less painful, longer acting formulation. Substantial reformulation may make the product acceptable for new indications, particularly prevention of cellulitis and in prophylaxis following hyposplenism. The United States FDA has issued guidance on the non-clinical safety evaluation of reformulated drug products and products intended for administration by an alternate route.234 In particular, they identify that it may be possible to ‘rely on the finding of safety and effectiveness of a listed drug and establish a clinical bridge to that listed drug’.234 Given the existing quality of regulatory data for BPG, the opportunity to bridge to existing listings is likely to be limited. Approval for a reformulated product or for novel indications is likely to be prohibitively complex unless regulatory dossiers for existing BPG can be updated.

Actions and recommendations

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High quality BPG is a safe, effective and affordable antibiotic for which there is decades of clinical experience. BPG remains the drug of choice for major indications because the target organisms – Treponema pallidum and group A streptococci - remain exquisitely sensitive. However, global shortages of BPG are common. These shortages increase the use of more expensive, less effective drugs which are may accelerate development of resistance in other organisms. BPG remains an essential medicine and tangible steps are needed for it to be made safely available to the vulnerable populations who need it most.

The challenges of BPG – concerns about supply, safety, quality and end point use – are common to many older antibiotics, particularly sterile injectables. As the world confronts growing antibiotic resistance with few new antimicrobials there are increasingly urgent calls to optimize the use of older drugs. Specifically, ‘strategies are urgently needed to ‘re-develop’ these drugs to modern standards, integrating new knowledge into regulatory frameworks and communicating the knowledge from research bench to bedside’.

1. Convene stakeholders in the global BPG market to develop a joint strategy to revive and re-develop the drug. This Global Status of BPG Report, a formal market analysis and local consultation should provide background resources for decision making. Critical questions for this group should include:
   A. What is the existing market and global demand for BPG?
   B. How can existing manufactures and emerging manufactures be engaged to increase and sustain production in diverse geographies?
   C. What existing data are available to guide re-development of BPG? How can raw, unpublished and historic data best be shared?
   D. What are the priority preferred product characteristics for reformulated products?
   E. What are the unanswered scientific questions about BPG and which studies are required to answer these questions?
   F. What procurement mechanisms are most effective for BPG and can an appropriate lead agency be identified?
   G. What are the best options for sustainable financing for BPG?
   H. What is the best way to ensure effective communication between all stakeholders in the BPG supply chain?

1. Develop regional partnerships with neighbouring countries that also require a supply of BPG, through seeking technical assistance and support from WHO regional offices.
2. Establish or integrate with existing regional procurement mechanisms, which:
   A. Include emergency funds to guarantee payment for procurements of BPG in cases of stock outs;
   B. Allow and encourage neighbouring countries to loan any excess stock of BPG medicines to each other in emergency situations;
   C. Secure price reductions for BPG where appropriate.
NATIONAL ACTIONS

1. Review BPG recommendations in national Essential Medicines Lists and Formularies to ensure recommendations from the WHO Essential Medicines List have been incorporated.

2. Engage with ongoing efforts, led by the World Health Organization Secretariat, to develop a systematic approach to prevent and manage shortages of essential medicines, which include methods to support BPG manufacture and supply.147

3. Include the procurement of BPG in national health budgets, as a cost-effective measure included in the WHO Package of Essential Noncommunicable Disease Interventions for Primary Health Care in Low Resource Settings (PEN) Package236 of interventions for non-communicable diseases.

4. Advocate for the WHO to replace the standard adult dose for BPG included in the current WHO Essential Medicines List for Children (EMLc)19 with a specific paediatric dose in the next edition of the EMLc in 2017.

5. Consider a national stakeholder mapping in order to identify all relevant in-country actors involved in the BPG supply chain. This may include manufacturers, suppliers, regulators, procurement agencies, international partners, civil society organizations, government, patients, health care professionals, pharmacists, researchers and academics. Stakeholders representing different clinical indications for BPG (including syphilis and rheumatic heart disease) should be explicitly identified.

6. Establish a body or forum for discussion and decision-making about the BPG supply chain, ensuring that all relevant stakeholders are included.

7. Create an emergency national plan for cases of unpredictable shortages and stock outs where adequate or sufficient quality BPG is unavailable.

8. Define standardized protocols to fast-track alternative supplies of BPG in cases of shortages and stock outs,160 including:
   A. Qualifying criteria;
   B. Mechanisms for flexibilities – creation of conditions of approval;
   C. Agreed-upon standards to conform with stringent regulatory requirements;

9. Develop or support national pharmacovigilance programs to capture reports of adverse reactions to BPG and other drugs.237

10. Establish or strengthen country-led, integrated inventory and distribution management for BPG, including the monitoring of stock data.

11. Develop or support mechanisms for clinicians and communities to notify drug shortages or to be alerted of expected shortages.

12. Establish an effective communication mechanism among all stakeholders along the in-country supply chain.

13. Enhance country-led BPG data collection tools by collaborating with civil society.

LOCAL ACTIONS

1. Ensure clinical guidelines outline the appropriate indications for BPG.

2. Ensure all clinical staff giving BPG injections have received appropriate training in injection technique and management of complications including anaphylaxis.

3. Ensure that adrenaline is available when BPG injections are given.

4. Engage communities and people living with disease in redevelopment of BPG.

ANNEXES AND REFERENCES
ANNEXES

ANNEX A: Mappings of BPG National Essential Medicines Lists

http://rhdaction.org/resources/mapping-bpg-national-essential-medicines-lists

ANNEX B: Known trade names of BPG

http://rhdaction.org/resources/known-trade-names-benzathine-penicillin

REFERENCES


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