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Benzathine Penicillin G for the Prevention of Rheumatic Fever and Rheumatic Heart Disease in the Developing World: A Global Survey of the Quality and Quantity of Supply

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A Global Survey of the Quality and Quantity of Supply

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Introduction

Rheumatic fever (RF) and rheumatic heart disease (RHD) are interrelated disease entities of historical significance that continue to afflict millions of people. Despite their widespread impact, these ailments have been relatively neglected by developed countries, most likely due to the current perception that these are diseases of distant, poor populations. Although now generally accepted as illnesses of developing and underserved countries, it was not always this way. The incidence of RF was widespread among American youth until the mid-20th century, when it was estimated at nearly 250,000 cases per year (Denny *et al*., 1950). The rapid economic development and hygienization of North America and Europe in the first half of the 20th century coincided with the near disappearance of RF from these societies. RF did, however, remain a serious problem in certain populations, most notably military recruits in the WWII era who became convenient and important subjects of numerous studies (Denny *et al*., 1950; Jones, 1944).

With each case of RF costing the US armed forces a staggering $16,000 in 1950 dollars (Denny *et al*., 1950) the middle of the 20th century saw the first of the three modern waves of research activity to combat RF/RHD. The second surge occurred in the late 20th century with a push to prevent and control RF/RHD in developing countries. Following a stagnation of research into RF/RHD prevention and control from the global agenda, we are now in the third wave in research activity (Carapetis and Zuhlke, 2011). Although the clinical components of RF were first described in the 1500s and RF was linked to carditis over 200 years ago (Seckeler and Hoke, 2011) the current era of globalization may finally lead us to the point of bringing effective preventive treatment or cure to all the world's people.

Background

Rheumatic Fever and Rheumatic Heart Disease

Acute RF is a non-communicable disease common to many developing countries that occurs in up to 3% of patients subsequent to untreated tonsillopharyngeal infection with group A β-hemolytic streptococcus (GAS) (Hewitson and Zilla, 2010). It is characterized by a constellation of potential signs and symptoms of varying penetrance, severity, and permanence (see "Diagnosis" below). It results from a still poorly delineated autoimmune reaction to GAS surface M-proteins with suspected production of anti-M-protein antibodies that react to self-proteins in susceptible victims. While potential targets including cardiac myosin, laminin, and vimentin have been identified, the carditis of RF is actually due to activated CD4+ T-cells. Genetic susceptibilities to RF have been proposed including identification of certain MHC and non-MHC genotypes that may be more susceptible than others (Guilherme and Kalil, 2010; Guilherme *et al*., 2007; Kumar and Tandon, 2013). However, research into these susceptibilities has yet to yield clinically relevant conclusions.

Acute RF is a predominately pediatric condition that is rarely fatal. However, 40-80% of acute RF patients have rheumatic carditis as part of the disease process and 90% of these patients develop the sequelae of chronic, progressive RHD. In developing countries, RHD is responsible for one-third to one-half of all cardiac admissions to hospitals, causes two-thirds of those suffering from it to drop out of school, and is difficult to treat without open-heart surgery (Hewitson and Zilla, 2010). It is important to note that the gold-standard preventive treatment of injection with benzathine penicillin G (BPG), either within 10-days of onset of infectious symptoms or prophylactically every

four weeks, has been recognized for over 60 years (Denny *et al*, 1950; Stollerman *et al*., 1955). Since 75% of previous RF patients progress to recurrent acute RF at reinfection with GAS, prevention or prompt treatment of infection is the key to preventing RF/RHD from developing (Hewitson and Zilla, 2010).

Diagnosis of Rheumatic Fever and Rheumatic Heart Disease

While rheumatic fever was recognized as a clinical entity in the 19th century, it took until the epidemiologic advances of the WWII era for a discussion within the literature to culminate in the first iteration of the Jones Criteria for the diagnosis of RF (Jones, 1944). These criteria have been revisited and revised from time to time by the American Heart Association (AHA) with the most recent revised Jones Criteria released 22 years ago (Dajani *et al.*, 1992). The criteria are intended for the diagnosis of an initial attack of RF and allow for retrospective diagnosis of RF based on exceptions to the Jones Criteria. As in 1992, there are no single pathognomic symptoms, signs, or laboratory tests to diagnose RF so a combination of these must be used, as outlined below.

Guidelines for the Diagnosis of Initial Attack of Rheumatic Fever*
(modified from Dajani *et al.*, 1992)

Major Manifestations
- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor Manifestations
- Arthralgia
- Fever
- Elevated acute phase reactants (ESR, CRP)
- Prolonged PR interval

Supporting Evidence of Antecedent Group A Streptococcal Infection
- Positive throat culture or rapid streptococcal antigen test

Elevated or rising streptococcal antibody titre

*If supported by evidence of preceding group A streptococcal infection, the presence of two major manifestations or of one major and two minor manifestations indicates a high probability of acute rheumatic fever.

The 1992 guideline continues to be the most commonly referenced throughout the world, though it is not the most up-to-date. The AHA revisited the guideline in a meeting in 2000 but did not produce an update, though they did foreshadow the utility of echocardiography in diagnosing and monitoring RHD (Ferrieri, 2002). An update to the Jones Criteria is expected to be published later in 2014 (Kathryn Taubert, personal communication, April 11, 2014). The World Health Organization (WHO) produced a technical report in 2004 that included RF and RHD diagnostic criteria based on the Jones Criteria (Bisno *et al*., 2004) and this was subsequently reaffirmed by the World Heart Federation (WHF) as the international standard for diagnosis (WHF, 2008).

It is important to note the distinction between acute RF and RHD, a chronic and often insidious non-communicable disease. As previously noted, RF is rarely acutely fatal. In fact, apart from the potential development of RHD, acute RF is otherwise clinically benign, albeit somewhat disturbing to patients and caregivers. Unfortunately, RHD is chronic, progressing in a step-wise fashion with subsequent bouts of RF. It was recognized decades ago and included in the initial Jones Criteria (Jones, 1944). Since that time, its impact has lessened in the developed world while persisting in many low and middle-income countries throughout the developing world.

Acute rheumatic carditis and chronic RHD were classically diagnosed clinically with identification of an enlarged heart, significant murmur, pericarditis, or congestive heart failure as diagnostic indicators (Jones, 1944). Because each of these entities occurs on a spectrum of clinical appearance and severity, one can see how their use as

diagnostics could vary widely between populations and providers. As diagnostics change, echocardiography has been recognized as the most sensitive and specific tool for RHD diagnosis (Ferrieri, 2002). RHD is known to occur in any of the four major heart valves, disrupting blood flow through the heart's chambers and resulting in cardiac dysfunction of varying degrees. Most apparent RHD occurs in the mitral valve followed by the aortic valve in a smaller but significant number of cases. Disease of the tricuspid and pulmonic valves is rare and much less likely to cause clinically significant disease (Kumar and Tandon, 2013). Recently, the WHF produced a guideline for the echocardiographic diagnosis of RHD that excludes the tricuspid and pulmonic valves from the diagnostic algorithm, simplifying identification of rheumatic lesions that would be of clinical importance (Remenyi *et al*., 2012). The utility of echocardiography in RHD diagnosis has been further verified in recent studies comparing echocardiographic screening to screening by classical auscultation. These echocardiographic screening programs have found rates of subclinical rheumatic carditis ten to twenty times higher than previous screening programs. The implications of this have yet to be fully determined as it is unclear whether preventive interventions to inhibit the transformation of subclinical rheumatic carditis to clinically apparent RHD are necessary or practical (Kumar and Tandon, 2013).

Epidemiology and RF/RHD Awareness

The epidemiology of RF and RHD are distinct and inherently difficult to assess. RF, as an acute disease, is better discussed in terms of incidence, while RHD is a disease best discussed in terms of prevalence. RF is a clinical diagnosis without a definitive

laboratory test (Jones, 1944; Dajani *et al.*, 1992). It presents differently in all patients, can mimic other diseases, and can be mimicked by still others (Jones, 1944). Diagnosis is generally based on the Jones Criteria as discussed above (Dajani *et al.*, 1992). RHD continues to be diagnosed primarily by community screening with auscultation for cardiac murmurs or via followup of patients diagnosed with RF. For largely practical reasons, echocardiography has become available only in the past decade for widespread use to diagnose RHD and evidence-based guidelines for its use weren't released until 2012 (Remenyi *et al*., 2012). Screening programs, largely school-based and dependent on the auscultation skills of healthcare providers, are unable to assess all those susceptible to developing RHD (McDonald *et al*., 2005). Even in areas with a relatively high prevalence, patients can present to healthcare providers and not have their condition recognized until far along in the disease process (Steer *et al*., 2006). Complicating this is a lack of national registers of RF/RHD patients in many countries. While some low and middle-income countries have adopted register-based programs for preventing and treating RHD, most harbor much larger populations of undiagnosed patients suffering from these afflictions (McDonald *et al*., 2005).

RF/RHD prevalence varies significantly between global regions, within regions, and even within countries and has changed significantly over time (Seckeler and Hoke, 2011). Denny *et al*. (1950) estimated the incidence of RF in the United States to approach 250,000 widespread cases/year. Modern outbreaks of RF in the United States tend to be small, numbering at most in the dozens, and rare (Seckeler and Hoke, 2011). In contrast, the global incidence of RF is estimated to approach 500,000 cases with an estimated RHD prevalence of 15-19 million cases resulting in 233,000 deaths each year (McDonald

et al., 2005; Seckeler and Hoke, 2011; Wyber *et al*., 2013). The great majority of these cases occur in developing countries throughout the world and in indigenous populations in developed countries of the South Pacific (Seckeler and Hoke, 2011; Steer and Carapetis, 2009). Since these data were gathered using various methods, the true burden may actually be much higher (Zuhlke and Steer, 2013). Accurate epidemiologic figures are important not just for understanding the scale of the problems posed by RF/RHD. Effective secondary prevention programs (discussed below) rely on appropriate use of registers and accurate epidemiologic data in order to function.

Primordial Prevention of RF/RHD

Primordial prevention of RF/RHD is thought to account for the vast majority of decline in the incidence and prevalence of RF/RHD throughout North America and Europe during the 20th century (Gordis, 2005). It requires the prevention of the development of risk factors for disease within the community. Examples include improved socioeconomic status, prevention of overcrowding, improved nutritional status, availability of prompt medical care, and public education about RF/RHD signs and symptoms (Kumar and Tandon, 2013).

Antibiotics for GAS Infections/Primary Prevention of RF/RHD

Primary prevention of RF and RHD aims to prevent the diseases from occurring in the presence of risk factors for the conditions. For this discussion, this broadly means recognition of GAS tonsillopharyngitis and subsequent treatment with antibiotics. Sulfonamides were the first antibiotics found to be effective at treating GAS

tonsillopharyngitis and preventing RF as early as 1943. Resistance of GAS to these antibiotics was recognized soon thereafter along with the utility of injectable and oral penicillin for the treatment of GAS tonsillopharyngitis (Denny *et al*., 1950). The 2004 WHO guideline for RF/RHD prevention recommends any of five separate treatment choices be started within 9-10 days of symptom onset. These recommendations are, in order of preference: a single dose of intramuscular BPG, oral penicillin V 2-4 times/day for 10 days, oral amoxicillin 2-3 times/day for 10 days, oral first-generation cephalosporins 2-3 times/day for 10 days, or oral erythromycin 4 times/day for 10 days. At that time, trimethoprim, sulfonamides, and tetracyclines were not recommended due to ineffective eradication of GAS infection (Bisno *et al.*, 2004). Despite widespread use of oral penicillin and BPG, GAS continues to be fully susceptible to these medications while developing resistance to other classes such as macrolides, lincosamides, and streptogramins (Logan *et al*., 2012) in addition to the previously mentioned classes.

A more promising form of primary prevention involves development of a vaccine for GAS that has the potential to eliminate the need for primary and secondary prophylaxis altogether. GAS vaccine development was initiated as early as the 1940s with accelerated progress in the era of molecular biology (World Health Organization, 2004). Unfortunately, an effective GAS vaccine is far from clinical use due to the complexities between the many GAS strains, the potential for creating a vaccine that itself causes RF/RHD, as well as an industry kept apathetic by little promise of significant profits from the poor populations who would be the primary consumers of such a vaccine (Kumar and Tandon, 2013; Steer and Carapetis, 2009).

Antibiotics for Secondary Prevention of RF/RHD

Secondary prevention of RF/RHD involves continuous administration of antibiotics to patients with a history of RF or RHD in order to prevent GAS infection, thereby minimizing the possibility for recurrent RF attacks (World Health Organization, 2004). Its effective administration requires both identification of patients with RF/RHD and maintenance of a registry of these patients (Kumar and Tandon, 2004). Injectable penicillin was first shown to prevent RF/RHD in patients with GAS infection over 60 years ago (Denny *et al*, 1950). In the years following this study, BPG was shown to prevent GAS infection in patients who had previously suffered bouts of RF/RHD (Stollerman and Rusoff, 1952; Stollerman *et al*., 1955). In addition to showing the efficacy of BPG at preventing GAS infection and RF/RHD, the 1955 study by Stollerman *et al*. introduced the monthly regimen of benzathine penicillin G (BPG) injections that continues to be the gold standard of RF/RHD prevention. In this study, Stollerman *et al*. showed that a four-weekly regimen of injection with 1,200,000 units of BPG was more effective than daily oral administration of 200,000 units of penicillin or 1.0 grams of sulfadiazine. In fact, none of the patients on the injectable BPG regimen suffered a recurrence of RF/RHD during the 20-month follow-up period, showing that it was superior to both oral regimens in the long term. These findings were a tremendous breakthrough in the prevention of RF/RHD in the susceptible population.

Unfortunately, while it may be true that monthly injections of BPG proved to be effective in the past, more recent studies have questioned the validity of this regimen with the BPG that is available in today's global market (discussed below). Nevertheless, the WHO continues to endorse monthly BPG injections as the first line preventive treatment

for RF/RHD prophylaxis. Alternative protocols include oral penicillin V twice daily, oral sulfonamides once daily, or oral erythromycin twice daily. These treatments must continue for an extended duration in most patients – into adulthood for those with mild disease or lifelong for those with more severe disease. The oral regimens are cumbersome and require dedication because patients must fast for hours before and after medication administration. In addition, they often cause uncomfortable gastrointestinal side effects (Bisno *et al.*, 2004). Benzathine penicillin G, although not without side effects and other drawbacks of its own, has continued to be the most effective prevention for RF/RHD yet described (Wyber *et al*., 2013).

Chemical Characteristics of Benzathine Penicillin G

BPG was first developed in 1950 and its patent was accepted in the United States in 1953, though it had been in clinical use in the intervening years (Stollerman and Rusoff, 1952; Szabo *et al*., 1951; Szabo *et al*., 1953). Injectable penicillin initially needed to be administered every 48-72 hours to maintain serum levels adequate to inhibit GAS growth (Denny *et al*., 1950). With the development of BPG, a single 1,200,000 unit intramuscular penicillin injection would consistently produce serum levels adequate to inhibit GAS growth for four weeks (Stollerman and Rusoff, 1952; Stollerman *et al*., 1955). Initially developed as a sparingly water-soluble salt by Wyeth Pharmaceuticals (Stollerman and Rusoff, 1952), it is now off-patent and is made by multiple manufacturers. It is available in a powdered formation that is stable at ambient temperatures or in a suspension that must be refrigerated (Stollerman and Rusoff, 1952; Wyber *et al*., 2013).

Thirty years after the pioneering studies on BPG use to treat and prevent RF/RHD (Denny *et al*, 1950; Stollerman and Rusoff, 1952; Stollerman *et al.*, 1955), Ginsburt *et al.* (1982) reported that serum levels of BPG four weeks after injection were very low or undetectable. A few years later, Kaplan *et al*. (1989) performed a study to analyze serum levels of injected BPG over the course of four weeks. They showed that mean serum levels fell below the generally accepted mean inhibitory concentration (MIC) for most strains of GAS (0.02μg/ml) between three and four weeks after injection. This finding is important because it revealed a window period during the final week of suspected prophylaxis during which infection with GAS might occur. Of note, BPG injection within ten days of onset of GAS tonsillopharyngitis can prevent RF from occurring, so conceivably a one-week window period would not be too long for this regimen to remain effective. However, in two separate studies, Lue *et al*. (1986 and 1996) showed that administration of BPG every three weeks was more effective at preventing RF than injecting it every four weeks. Some troubling issues arise as a result of these studies. First, that prophylactic regimes consisting of 1,200,000 units of BPG injected every four weeks are not adequate. Worryingly, the three-week regimes used by Lue *et al*. were not completely effective at preventing RF either. Logically, then, it was important to test two-week regimens, different brands, and higher doses of BPG injection.

Kassem *et al*. (1996) showed that injection of BPG every two weeks was more effective at preventing RF than every four weeks. In addition, their study demonstrated that different brands of BPG have unique pharmacokinetics, despite equivalent doses of the medication in the vial. Currie *et al*. (1994) performed a study of the pharmacokinetics of increased doses of BPG. Assuming the minimum protective penicillin concentration to

be 0.25µg/ml, they found that significantly more subjects retained protective levels of penicillin after two, three, and four weeks when receiving 1,800,000 units of BPG. Serum penicillin levels after two, three, and four weeks were higher still in those injected with 2,400,000 units of BPG. Of note, only injection of 2,400,000 units provided protective levels in 100% of patients after two and three weeks. These findings led Currie and Kaplan (1996) to question the validity of the recommended dosing regimen of BPG. More recently, Broderick *et al*. (2011) showed that injection of 1,200,000 units of BPG consistently results in penicillin levels that fall below protective levels after just two weeks. Clearly, none of these recent studies on the subject indicate promising trends in the quality of available BPG.

These findings are troubling because they show disheartening inconsistencies in the quality of BPG available since the 1970's. Whereas, a four-weekly injection regimen of 1,200,000 units once produced adequate GAS prophylaxis throughout the treatment period (Stollerman and Rusoff, 1952; Stollerman *et al*., 1955), more recent research suggests much higher dosing or more frequent intervals may be necessary to provide protective penicillin levels (Currie *et al*., 1994; Currie and Kaplan, 1996; Broderick *et al*., 2011). Moreover, the inability to produce protective penicillin levels may not be the only concerning aspect of current formulations of BPG (Wyber *et al*., 2013).

Penicillin Reactions

While penicillin is a potential allergen, fear of serious allergic reactions to penicillin is far greater than the true risk of those reactions (Markowitz *et al*., 1991; Markowitz and Lue, 1996). In their 1955 study, Stollerman *et al.* monitored the 410

enrolled patients for reactions. While eight patients developed nonspecific, nonurticarial rashes during the study, only five patients were found to have penicillin hypersensitivities and none had fatal reactions. Despite these initial findings, fear of serious allergic reactions developed and has persisted despite having been addressed in the literature multiple times. In an 11-country study involving 1790 patients, and 32,430 injections through 2,736 patient-years of observation, only 57 patients (3.2%) had any type of allergic reaction. Of these, four had anaphylaxis (0.2% or 1.2/10,000 injections) and one died for a fatality incidence of 0.05% or 0.31/10,000 injections (Markowitz *et al*., 1991). Furthermore, the WHO (Bisno *et al.,* 2004) reports that most cases of anaphylaxis are reported in patients who have severe RHD with poor cardiac function. They add that these patients are more susceptible to life-threatening vasovagal reactions that may be retrospectively misdiagnosed as anaphylaxis. Despite these low numbers and availability of skin testing that can identify essentially 100% of true penicillin allergies, fear of anaphylaxis persists (Markowitz and Lue, 1996). Skin testing of all newly diagnosed RF/RHD patients for penicillin allergy has been suggested (Markowitz and Lue, 1996), and while the WHO does not recommend it for all patients, they acknowledge its utility as an acceptable and generally accurate method to determine risk of immediate penicillin reaction (Bisno *et al.*, 2004).

Rheumatic Fever/Rheumatic Heart Disease Prevention Guidelines

Rheumatic fever and RHD are complex diseases affecting diverse populations living in various political and economic climates throughout the world. As described above, they present and can be prevented and treated in a myriad of different ways.

Because of this, there are numerous guidelines covering RF/RHD diagnosis, prevention, and treatment available to clinicians. However, the WHO guideline (Bisno *et al*., 2004) is the standard reference document that is pertinent worldwide. This guideline continues to recommend injection of 1,200,000 units of BPG every four weeks as a starting point for RF/RHD prophylaxis (Bisno *et al*., 2004). However, this is simply a starting point suggested by the WHO that clinicians can use as guidance – in truth, each patient is unique. If a patient is still suffering from breakthrough GAS infections on a three or four week regimen of BPG injections, their healthcare provider may increase the frequency of injections or inject a greater amount of BPG. A single injection of 2,400,000 units of BPG is the recommended treatment for syphilis infection, so this formulation is available to many clinicians and it is conceivable that some may perform BPG prophylaxis with it. Of course, these conceptions are only speculation at this point because there is a lack of knowledge about how clinicians are actually treating their patients and what guidelines they subscribe to. Clinical guidelines are created for the purpose of improving outcomes in conditions that can be diagnosed and treated in more than one way. Current adherence to RF/RHD prophylaxis guidelines throughout the world is not known. Additionally, there is anecdotal evidence of widespread BPG shortages and clinical failures in patients receiving treatment under the various recommended RF/RHD prophylaxis guidelines (Bongani Mayosi, personal communication, July 29, 2011; Edward Kaplan, personal communication, September 20, 2011). It is not clearly known which countries have experienced BPG shortages or supply of poor-quality BPG, nor are the reasons for this clearly understood.

Current Study

Central and South America, the Caribbean, Africa, and the Asia-Pacific region continue to have the highest rates of RF/RHD (Seckeler and Hoke, 2011) and the current adherence to RF/RHD prophylaxis guidelines in these regions is not known. The current study seeks to examine the scope of BPG supply issues and the extent of adherence to current RF/RHD prophylaxis guidelines in global regions with a high prevalence of RF/RHD. The specific objectives are: to determine which types of provider or institution and which countries have an inadequate supply of BPG; to determine which types of provider or institution and which countries have a supply of BPG that is of poor quality; to compare the quality and quantity of BPG supply to importation vs. domestic production status; to investigate the relationship between quantitative and qualitative deficiencies in the BPG supply according to practice setting; and to relate the quality and quantity of BPG supply to practice adherence to current WHO guidelines on prophylaxis against RF/RHD. The overall goals of the research will be to delineate BPG supply issues, determine what factors contribute to poor quantity or quality of BPG supply, and determine if healthcare practitioners are providing BPG appropriately.

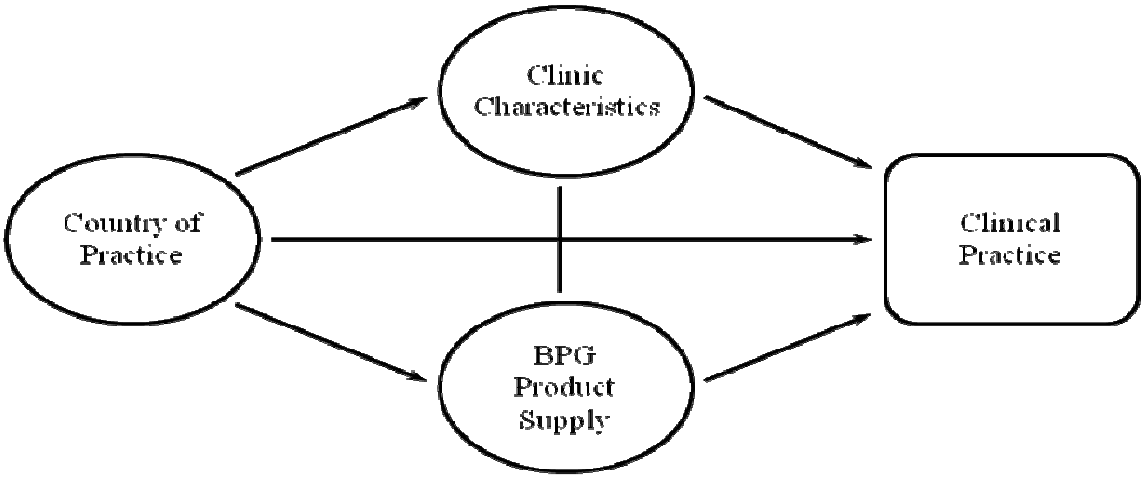
Methods

Research Design

A pilot study was conducted to determine current practice in the prevention of RF/RHD in developing countries. While the efficacy of successive BPG injections for secondary prophylaxis was established long ago (Stollerman *et al*., 1955), there are no known global studies on the effectiveness of this regimen. In order for a treatment to be

effective, it needs to be available, practical, and used appropriately. A descriptive project of this scale, dealing with as many developing countries as possible, was best undertaken by performing a global survey of healthcare providers about their clinical experiences. This survey attempted to address three main unanswered questions: which RF/RHD treatment guidelines are being followed, if following the guidelines is effective, and what are the barriers to effectively providing RF/RHD prophylaxis. This research attempts to fill one of the gaps in our knowledge of current practices in the prevention of RF/RHD.

Logic model



The following hypotheses were tested in this study:

1. Poor quality and quantity of BPG supply will be widespread, but especially in those countries without a domestic supply of BPG.
2. Specialist care (i.e., via cardiologists or infectious disease doctors) will be correlated with better quality and quantity of BPG supply.

3. Obtaining BPG from a secondary source (i.e., via UNICEF or a non-governmental organization (NGO)) will be correlated with better quality and quantity of BPG supply.
4. Practices in urban settings will be more likely to have better quality and quantity of BPG supply than rural settings.

Study Population/Sampling Approach

The survey (see Appendix 2) was designed to obtain essential information on quantitative and qualitative BPG supply issues in global regions that have a high burden of RF/RHD. It targeted healthcare providers – physicians and physician extenders – who perform primary and/or secondary RF/RHD prophylaxis using BPG in these global regions. Survey recipients were identified by scanning the WHF database of member health professionals for those with a clinical interest in RF/RHD in the following regions: Central and South America, Caribbean, Africa, and Asia-Pacific. Email addresses for recipients were identified and surveys with introductory emails in English, English and French, or English and Spanish (depending on the country of the recipient) were sent out in December 2011. Two additional follow-up emails were sent to non-responders in the first months of 2012. The survey introduction included a statement excluding providers who do not directly participate in RF/RHD prophylaxis. It also included a section for WHF-linked providers to include contact information of colleagues who also work in the RF/RHD field. Recipients identified in this manner were also contacted via email. The target sample size was 100.

Description of variables

1. Clinic characteristics. Apart from the commonality of treating RF/RHD patients, clinics have the potential to vary widely in their characteristics. Factors that can be used to describe clinics include the following:

Country refers to the country in which the clinic is located, i.e. where RF/RHD prophylaxis is performed.

Designation/Title refers to the professional title of the healthcare practitioner filling out the survey, whether they be a specialty or primary care doctor, nurse practitioner, pharmacist, or otherwise.

Organization is the entity, be it public or private, at which the BPG prophylaxis is performed by the clinician.

Practice setting refers to broad characteristics of individual clinics, whether they are in an urban or rural setting, primary care or specialty practices, hospital-based or free-standing clinic, and whether they are private or public. This information is important for examining the settings that may be predisposed to BPG supply issues.

2. BPG characteristics. BPG is sold in many forms that vary in their indications, utility, and storage. Not all forms may be available to each clinic so factors that can be used to differentiate types of BPG provided to individual clinics include the following:

Brand name refers to the company brand under which a particular batch of BPG is sold.

Manufacturer refers to the entity that manufactured a particular batch of BPG.

Supplier is the entity that provides the BPG to the organization that is using it.

Preparation is the state in which BPG is provided to the clinic, be it in solution or lyophilized into powder form.

Reconstitution is the process by which powdered BPG is brought back into solution when the product is delivered and stored in powdered form but needs to be injected in liquid form.

Diluent refers to the type of liquid that needs to be added to powdered BPG to bring it into solution. This can be sterile water, phosphate buffered saline, or solubilized lidocaine/lignocaine.

Dose formulations are the doses of BPG that are available to the clinic – typically 600,000 or 1,200,000 units (the recommended dosages for BPG prophylaxis depending on patient weight) or 2,400,000 units (the recommended dosage for treatment of syphilis).

Types of BPG formulations refers to solubilized BPG which can be provided solely in buffered saline solution, mixed with anesthetics such as lidocaine/lignocaine, or otherwise.

3. Quantity of available BPG. Clinics may vary in both the number of patients they have who require BPG and their ability to procure enough of the antibiotic. Factors that relate the number of patients each clinic can treat to the number of patients that require care include the following:

Primary prophylaxis refers to the practice of treating patients known to be suffering from GAS tonsillopharyngitis in order to cure the infection as well as prevent

the development of RF/RHD. It can be done by administering one of several different antibiotics, including BPG, given via injection or oral administration.

Secondary prophylaxis refers to the practice of providing regular BPG injections, typically every 3-4 weeks, in order to avert all GAS infections, thereby preventing the infection that leads to the development of RF/RHD.

External organization refers to a secondary supplier of BPG that procures the product on behalf of individual clinics and distributes it to them. Examples include UNICEF and a number of NGOs.

Antibiotic alternatives refer to a number of different antibiotics that can be used to treat GAS tonsillopharyngitis. It should be noted that they are all suitable alternatives for primary prophylaxis in certain circumstances while only some are suitable for secondary prophylaxis.

4. Quality of available BPG. BPG is produced by numerous manufacturers in countries throughout the world. Some companies make and sell BPG under their brand name while others buy from a primary manufacturer and redistribute the BPG under their own brand name. Because of the varying manufacturers, processes, and quality control standards, BPG from different companies (or even from different manufacturers but sold under the same brand name) can vary widely in quality. Factors that pertain to the quality of BPG supplied to each institution include the following:

Quality of BPG supply is a purely subjective measure based on the clinician's opinion of the current BPG stock in use.

Breakthrough rheumatic fever occurs when GAS infection and subsequent RF ensues despite a patient appropriately taking BPG secondary prophylaxis.

Rash is the dermatologic condition that is the most common side effect of BPG prophylaxis. It is anecdotally reported to occur more often with poor-quality batches of BPG.

Anaphylaxis is a serious allergic reaction that occurs rapidly and has the potential to cause death.

Skin testing can be performed on patients to determine if they're allergic to penicillin before injecting them with BPG.

5. National and international guidelines. A number of international organizations have developed RF/RHD prevention guidelines in order to promote and ensure access to appropriate preventive treatment. Factors related to guideline use include the following:

Structured national programs for RF/RHD control have been established in a number of countries to assist clinicians in tracking and treating patients.

National RF/RHD registries are lists of RF/RHD patients that are tracked in order to ensure continued treatment when they move from one area to another.

Recurrent RF is a condition where a patient who previously had RF gets it again. It should be noted that those that have previously developed RF are significantly more likely to develop it again if they are reinfected with GAS. When recurrent RF occurs while the patient is undergoing appropriate BPG prophylaxis, it is called breakthrough RF.

Scheduling refers to the timetable through which patients undergo secondary prophylaxis with BPG. The WHO recommends injecting BPG every four weeks for most patients but every three weeks for patients at high risk of recurrent RF or who suffer from breakthrough RF on every four-week injections.

Survey Development

Data were collected through a web-based survey that was modified from a previous version developed by the WHF and available for download on the RHDnet website (http://www.world-heart-federation.org/what-we-do/rheumatic-heart-disease-network/). The survey included six sections. The first section asked for identifying information to classify the respondent by country and clinical setting in addition to contact information to report the compiled results. The second asked for information about the most common brands of BPG currently in use including the brand names, manufacturer, manufacturer's address, supplier, expiration date, preparation method, reconstituted volume, type of diluent, available dose formulations, and types of formulations. Respondents were also prompted for general comments about the BPG currently being used. The third section asked for information about the quantity of BPG used at the practitioner's clinic including the approximate number of RF/RHD patients served and the approximate number of RF/RHD patients they're able to treat. They were also asked about any brand changes and the reasons why brands were chosen, secondary sourcing of BPG, antibiotic alternatives, as well as their general comments. The fourth queried respondents about the quality of the BPG supply including their general opinion about the quality of BPG used and any difficulties encountered including difficulty

reconstituting BPG, difficulty drawing BPG into syringes, evidence of breakthrough rheumatic fever, rash, anaphylaxis and death, skin testing for penicillin allergy, as well as space for general comments. The fifth section probed for adherence to national and international guidelines on the prevention of RF/RHD. Specifically, the survey included questions about the presence of a structured national program for RF/RHD control, a national RF/RHD registry, and whether the practitioner reports into it. This section also asked about guidelines used and BPG injection schedules followed. Finally, the sixth section provided space for the practitioner to recommend other healthcare professionals to contact. Once developed, the survey was professionally translated into French and Spanish (see Appendix 2).

Data Analysis

Data were compiled and analyzed using IBM SPSS Statistics 20 (IBM Corp., 2011). Descriptive statistics such as counts and percentages were produced for discrete variables. None of the data is of a continuous nature so descriptive statistics such as means were not produced. Relationships between variables were examined through a bivariate analysis comparing clinic characteristics and other independent variables to dependent variables of BPG product supply and clinical practice. Chi-Square and Fisher's exact tests (depending on sample size) were used to test for statistical significance.

Human subjects

All data were provided to the investigator directly by survey respondents and then broken down by country of practice to remove identifying information and preserve

confidentiality. The survey did not collect any specific patient health data or sensitive information about physician practices. Only the research staff had access to the data, which were stored on an encrypted, password-protected computer. Because of the limited data collected and safeguards in place, there was very little risk to subjects. Prior to data collection, the study was determined by the University of Connecticut Health Center Institutional Review Board not to be human subjects research.

Results

Response data

As is frequently the case with web-based surveys, the response rate was low. Eighty-nine recipients were identified in the WHF database for Africa and one additional referral was made by recipients. Eighty-one recipients were identified in the WHF database for the Asia-Pacific region and eight additional referrals were made. One-hundred-twenty-nine recipients were identified in the WHF database in Central and South America and two additional referrals were made. Twenty-three recipients were identified in the WHF database for the Caribbean region. A total of 333 recipients received introductory emails and surveys to return. Although 39 questionnaires were returned, not all were completely filled out so percentages were calculated based on the total number of responses to each question. This resulted in apparent discrepancies between the number of responses to a question and the percentage of responses that this represents.

The 39 completed surveys represent a gross 11.7% response rate. Twenty other email respondents self-identified as ineligible for the study. Five of these responses gave qualitative data about RF/RHD and BPG availability in their area but did not fill out the

survey. The net response rate was 12.4%. Please see Appendix 1 for all tables and figures describing the respondents and the results.

Eighteen respondents were from the Asia-Pacific region representing 46% of the total. Fifteen (39%) were from African countries while six (15%) were from Central and South America (Table 1). By country, India had by far the largest number of responses at ten, representing 25.6% of the total. Three responses were from Brazil. There were two each from Cameroon, Egypt, Ethiopia, and Malaysia. One response each was gathered from Bangladesh, China, Ghana, Guatemala, Honduras, Kenya, Lebanon, Mozambique, Nepal, Nigeria, Pakistan, Peru, Rwanda, South Africa, Tanzania, The Sudan, Uganda, and Yemen (Table 2). Demographic data could not be gathered from those who did not reply.

Supply Quantity Data

Sources of BPG varied widely. Over half of respondents (57%) reported obtaining BPG from a domestic source. For those respondents who had an international source, eight (53%) sourced from China, four (27%) from India, and three (20%) from Austria (Figure 1). Only one survey respondent reported no availability of BPG. The great majority (97%) reported access to at least some BPG. Six respondents (19%) reported that they require patients to supply some or all of their own BPG from a pharmacist/chemist for administration at the clinic/hospital, while the remainder reported providing BPG to their patients. Sixteen respondents (42%) reported issues maintaining their BPG supply. Sixteen respondents (42%) reported changing BPG brands in the previous two years (Table 3). Of those that reported changing brands in the previous two

years, 85% did so because of availability, 31% due to affordability, and 8% due to quality. Of note, no respondents reported changing due to packaging, storage requirements, or because an outside organization determined the need to change (Figure 2).

Six factors were assessed for their influence on choice of BPG brand. Seventy-six percent of respondents reported that their choice was influenced by availability of a particular brand, 53% by affordability, 34% by quality, 5% by packaging, and 11% by storage requirements. Only 13% had their choice of BPG determined by an external organization (Figure 3). Similarly, five respondents (14%) reported that their supply of BPG is dependent on an external organization. To further assess the adequacy of supply quantity, respondents were asked how many of their patients they would be able to treat according to the recommended prophylaxis guidelines. Sixty-five percent said that their supply is adequate to treat 100% of their patients appropriately. However, one respondent noted an ability to treat 87.5% of their patients appropriately, one reported 75%, another 67%, four replied an ability to treat 50% of their patients appropriately, and one noted a supply adequate to treat only 10% of their patients appropriately. Four indicated that they were unable to treat any of their patients with the recommended prophylaxis schedule (Figure 4). Thirty-two percent of respondents noted no access to oral penicillin, the second line RF/RHD preventive medication according to WHO guidelines (Table 3).

In spite of documented issues with the supply of BPG and other treatments, this analysis revealed that adherence to guidelines was unrelated to supply quantity factors including issues maintaining supply (2-sided Pearson $\chi 2=0.44$, $p=0.507$) or a brand change in the previous two years (2-sided Pearson $\chi 2=0.873$, $p=0.35$). In addition,

secondary sourcing was unrelated to supply quantity factors such as issues maintaining supply (2-sided Pearson $\chi 2=0.972$, $p=0.324$) or a brand change in the previous two years (2-sided Pearson $\chi 2=0.003$, $p=0.954$).

Supply Quality Data

Respondents were asked to rate the quality of their BPG supply. Nine percent reported that their supply was excellent, 34% rated it very good, 46% rated it good, 9% rated it fair, and 3% rated it of poor quality (Figure 5). Respondents were then asked about specific issues with BPG quality. Six percent reported difficulty reconstituting BPG prior to injection. Twenty-six percent reported difficulty drawing reconstituted BPG into syringes for injection. Eleven percent reported that they have had patients who experienced breakthrough RF despite being on an appropriate prophylaxis regimen. Three percent reported that rash is a common side effect of BPG administration. Twenty-six percent reported that they have had patients experience anaphylaxis while on the current BPG used in their clinic/hospital. Twenty-one percent of respondents reported that they have had one or more patients die due to anaphylaxis (Table 4). A follow-up question assessed changes in clinical practice following anaphylaxis to BPG. Five respondents reported no change to their clinical practice, one stopped using BPG, two changed brands of BPG, and three switched some patients to an oral antibiotic.

African countries were more likely to order their BPG from China with some respondents reporting domestic production. Whereas, most respondents in the Asia-Pacific region reported domestic production (mostly from India) and most from Central and South America reported domestic production as well (Table 5) (2-sided Pearson

$\chi 2=14.9$, $p=0.021$). The respondents' ratings of BPG quality were not related to country of production (2-sided Pearson $\chi 2=7.6$, $p=0.816$).

Sixty-percent of respondents reported performing penicillin allergy skin testing. However, the rate of skin testing was unrelated to whether a provider reported anaphylaxis at their site (Fisher's Exact Test $p=0.26$) or deaths from anaphylaxis (Fisher's Exact Test $p=0.68$).

Whether or not a provider had a domestic or international supplier was unrelated to their patients' tendency to suffer breakthrough RF (2-sided Pearson $\chi 2=1.2$, $p=0.273$), rash (2-sided Pearson $\chi 2=1.373$, $p=0.241$), or anaphylaxis (2-sided Pearson $\chi 2=0.001$, $p=0.982$). Furthermore, domestic vs. international supplier was completely unrelated to providers' perception of the quality of their BPG (Figure 7) (2-sided Pearson $\chi 2=4.51$, $p=0.342$).

Five respondents (14%) reported that they receive their BPG from a secondary source (Table 3). Statistical analysis revealed that whether or not a secondary source was used was unrelated to BPG quality factors including perceived quality (2-sided Pearson $\chi 2=7.225$, $p=0.124$), breakthrough RF (2-sided Pearson $\chi 2=0.455$, $p=0.5$), rash (2-sided Pearson $\chi 2=0.172$, $p=0.679$), or anaphylaxis (2-sided Pearson $\chi 2=1.395$, $p=0.238$).

Data on Guideline Usage

Data were gathered on which clinical practice guidelines for RF/RHD treatment and prophylaxis are used by clinicians. Seventeen respondents reported exclusive use of the WHO guideline, two used the AHA guideline (Gerber *et al.*, 2009), one used the WHF guideline, one used the guideline produced by The Cardiac Society of Australia and

New Zealand, one used that produced by the Pakistan Cardiac Society, two used that produced by the Brazilian Society of Cardiology, and eleven referenced multiple guidelines. Four respondents reported following no specific guideline. Only 32% of respondents reported using BPG dosages and schedules recommended by the WHO (Bisno *et al*., 2004). This analysis revealed that adherence to guidelines was unrelated to BPG quality factors including perceived quality (2-sided Pearson $\chi 2=1.645$, $p=0.801$), breakthrough RF (2-sided Pearson $\chi 2=0.185$, $p=0.667$), or anaphylaxis (2-sided Pearson $\chi 2=0.491$, $p=0.484$).

Discussion

The current study was a descriptive, pilot study that sought to examine the scope of BPG supply issues and the extent of adherence to current RF/RHD prophylaxis guidelines in global regions with a high prevalence of RF/RHD. The specific objectives were: to determine which types of provider or institution and which countries have an inadequate supply of BPG; to determine which types of provider or institution and which countries have a supply of BPG that is of poor quality; to compare the quality and quantity of BPG supply to importation vs. domestic production status; to investigate quantitative and qualitative deficiencies in the BPG supply to practice setting; and to relate the quality and quantity of BPG supply to practice adherence to current WHO guidelines on prophylaxis against RF/RHD. The overall goals of the research were to delineate BPG supply issues, determine what factors contribute to poor quantity or quality of BPG supply, and determine if healthcare practitioners are providing BPG appropriately.

Limitations

This study had several limitations inherent to survey-based studies, particularly those conducted by mail or email without personal contact. These limitations include low response rates and incomplete data collection because there is little control over who replies to survey requests or ability to follow-up on missing data. The number of responses was quite low. The snowball question at the end of the survey was meant to increase the study population. However, the effectiveness of this method is variable and unproven and was not of great benefit to this study. Potential study subjects were identified in the WHF database, a database which lacked demographic information on many of recipients of the survey. It is possible that many of those who received the survey deselected themselves without responding to the email requests. Furthermore, it is unlikely that the database contained contact information on many of the RF/RHD providers throughout the world, though it is the most complete database known to the author. These limitations may have led to selection bias in the research process.

Survey responders may have been more likely to have a stronger emotional connection with RF/RHD and BPG supply issues, perhaps because of a lack of supply or poor supply. On the other hand, those clinicians with the poorest supply may be in areas with no internet connection and thus an inability to receive or fill out the survey. The sampling method itself is of questionable completeness as the original study subjects must have voluntarily contacted the WHF, indicated an interest in RF/RHD, and agreed to have their name and contact information added to the database of healthcare professionals. These limitations may have led to both selection and detection bias in the research process.

The survey was a cross-sectional study of BPG supply and use at one point in time. The survey was performed as a pilot study that was meant to provide descriptive statistics and a launching pad for further research. Because a global survey of BPG availability and RF/RHD guideline use has not been performed before, there were no similar studies to compare the results to.

Finally, due to the limited number of responses, several statistical tests could not be performed while others produced data that would not have been helpful in addressing the objectives. These include analyzing BPG supply quantity and quality between types of provider, practice setting, countries, and regions. Despite these limitations, the results of the study are suggestive and worthy of further investigation.

Objective 1: Determine which types of provider or institution and which countries have an inadequate supply of BPG

Hypothesis 1 stated that poor quantity of supply would be widespread. Unfortunately, due to the erratic response rate, statistical analyses for patterns of poor supply were inconclusive. However, this survey confirmed that BPG supply shortages occur and many providers are unable to provide the recommended prophylaxis to their patients (see Table 3, Figure 2, and Figure 4). In addition to the tallied survey results, the principle investigator received two emails from respondents with 'regrets' that they couldn't fill out the questionnaire due to lack of access to any BPG. Thus, there were actually three out of 41 email responders (7%) who reported no access to BPG (two from India and one from Lebanon), even though only one of the three filled out the survey. A review of the available literature about availability of essential medicines revealed an

article which showed availability of BPG at both public and private facilities in India was extremely poor (Kotwani, 2013). In light of the current analysis, these results are not particularly surprising.

Objective 2: Determine which types of provider or institution and which countries have a supply of BPG that is of poor quality

Hypothesis 1 stated that poor quality of supply would be widespread. This survey assessed BPG quality from two directions. First, providers were asked to assess the quality of their supply. A strong majority of providers rated their BPG of good, very good, or excellent quality (Figure 5). However, these results do not appear to agree with the providers' responses to questions directed toward specific BPG quality issues (Table 4). For example, many providers reported difficulties with BPG preparation and there were a fair number who reported breakthrough cases of RF among their patients while on BPG prophylaxis. Most importantly, an alarming number of providers reported cases of anaphylaxis due to BPG with nearly as many reporting deaths in these patients. These last two points warrant further discussion because a single case of anaphylaxis has the potential to destroy a secondary prophylaxis program (Markowitz *et al*., 1991). Anaphylaxis is a serious allergic reaction that can be fatal if untreated. However, accurate recognition of the symptoms followed by prompt treatment dramatically improves the chances of survival. WHO guidelines don't explicitly recommend that all patients be tested for penicillin allergy (Bisno *et al*., 2004) and only 60% of respondents reported testing their patients despite the essentially 100% accuracy that the test can pick up patients who may suffer anaphylaxis from BPG injection (Markowitz and Lue, 1996).

The reasons for this are unclear. It may be due to availability or affordability of testing supplies. It may also be due to clinician preference not to test, a lack of testing of all patients, or imprecise testing methods since this study showed that penicillin testing was unrelated to whether or not patients were suffering anaphylaxis.

Objective 3: Compare the quality and quantity of BPG supply to importation vs. domestic production status

Hypothesis 1 stated that poor quality and quantity of supply would be worst in those countries without a domestic supply of BPG. This investigation showed that domestic vs. international supplier was unrelated to various indicators of BPG quality. Specifically, it was unrelated to providers' perception of quality and the tendency of the providers' patients to suffer breakthrough RF, rashes, or anaphylaxis.

Objective 4: Investigate the relationship between quantitative and qualitative deficiencies in the BPG supply according to practice setting

Hypothesis 2 stated that specialist care would be correlated with better quality and quantity of BPG supply and hypothesis 4 stated that practices in urban settings will be more likely to have better quality and quantity of BPG supply than rural settings. However, virtually all respondents self-identified as specialists in an urban hospital, making it impossible to draw conclusions about BPG supply patterns in relation to specialty or practice setting. The lack of participation from clinicians practicing in non-hospital settings and in rural areas leave it an open question about BPG practices in these settings.

Hypothesis 3 stated that obtaining BPG from a secondary source would be correlated with better quality and quantity of BPG supply. Five respondents reported that they receive their BPG from a secondary source. Statistical analysis revealed that whether or not a secondary source was used was unrelated to BPG quality factors including perceived quality, breakthrough RF, rash, or anaphylaxis. Furthermore, secondary sourcing was unrelated to supply quantity factors including issues maintaining supply or a brand change in the previous two years.

Objective 5: Relate the quality and quantity of BPG supply to practice adherence to current WHO guidelines on prophylaxis against RF/RHD

Only 32% of respondents reported using BPG dosages and schedules described in the WHO guideline (Bisno *et al*., 2004). While many of the respondents reported using other guidelines, these tend to mirror the WHO guideline with few minor differences. It is surprising that so many respondents reported different dosages or dosing schedules than would be expected and it was hoped that this survey would reveal reasons for the discrepancies. However, the analysis revealed that adherence to WHO guidelines was unrelated to BPG quality factors including perceived quality, breakthrough RF, or anaphylaxis. Unexpectedly, adherence was unrelated to supply quantity factors including issues maintaining supply or a brand change in the previous two years. Thus, it is difficult to draw conclusions as to why practice patterns are different than expected.

Implications

The overall goals of the study were to delineate BPG supply issues, determine what factors contribute to poor quantity or quality of BPG supply, and determine if healthcare practitioners are providing BPG appropriately. Very little is known about the topics covered in the survey so this is a unique study that has the potential to provide the global community interested in RF/RHD with insight into the issues surrounding appropriate RF/RHD prophylaxis. RF/RHD prevention guidelines are under constant review as there have been several changes in the field in the past few years – better detection techniques have led to improved and earlier diagnosis that has increased the observed disease burden significantly in some countries (Kumar and Tandon, 2013), while resistance to some antibiotics other than BPG has led to changes in prophylaxis protocols over the years (Bisno *et al*., 2004). In addition, there has been a push in recent years to determine what should be the research priorities in the field of RF/RHD prevention and treatment (Carapetis and Zuhlke, 2011; Wyber *et al*., 2013).

This project did not narrow the prospects for further research. By putting numbers on the anecdotes of poor BPG supply it shined light on the problem while also leaving us with more questions than answers. It is hoped that this pilot study will act as a nidus for further research to more fully describe where supplies are poor and the reasons for the quality of supply. Because of the internet-based survey methodology, the results were limited in their ability to describe the problems of BPG supply and RF/RHD treatment and prevention. More focused country-by-country in-person or telephone interviews could be used to garner a more accurate and detailed description of the problems each provider and each country faces. Many contacts were identified in the WHF database for

practical reasons. However, the database was incomplete and out of date, making it a less than ideal source for finding practitioners who treat RF/RHD throughout the world. That said, there is no other known similar database in which to find contacts and a more rigorous identification of potential survey participants was beyond the scope of this project given the time and resource constraints. Therein lies the opportunity for a follow-up study with time and resources to locate and contact a larger sample of practitioners and perform a more qualitative, interview-based study, as is commonly done after pilot projects such as this.

As a pilot study that provided limited information on reasons for poor BPG supply, there is little in this work to support policy implications at this point. Research leading to more rigorous identification of factors that result in poor BPG supplies is the logical next step in the process and will be much more valuable for determining relevant public policy changes to improve supplies throughout the world.

RF and RHD were major problems worldwide until the 20th century, the century in which RF and RHD were nearly eradicated from developed countries (Jones, 1944; Seckeler and Hoke, 2011). However, as we settle into the 21st century, RF and RHD continue to plague developing countries and indigenous populations in some developed countries as well (Seckeler and Hoke, 2011; Zuhlke and Steer, 2013). Given the socioeconomic characteristics of the populations at high risk for development of RF/RHD, treatment regimens must be inexpensive, effective, and easily adhered to. Until this study, there was much speculation and little data about the global supply of BPG. It is hoped that the results of this work will shine light onto the erratic nature of the global

BPG supply so that we can provide this essential medicine in high quality to all those who need it.

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Appendix 1: Tables and Figures

Table 1. Number and Percent of Responses by Region

	Number	Percent
Africa	15	39%
Asia-Pacific	18	46%
Central & South America	6	15%

Table 2. Number and Percent of Responses per Country

Country	Number	Percent
India	10	25.6%
Brazil	3	7.7%
Cameroon, Egypt, Ethiopia, Malaysia	2 each	5.1% each
Bangladesh, China, Ghana, Guatemala, Honduras, Kenya, Lebanon, Mozambique, Nepal, Nigeria, Pakistan, Peru, Rwanda, South Africa, Tanzania, The Sudan, Uganda, Yemen	1 each	2.6% each
Total	39	100.0%

Table 3. Percent of Respondents in Agreement to Statements Relating to Supply Criteria

Statement	Percent in agreement
Any availability of BPG	97%
Patients required to supply their own BPG from a pharmacy/chemist in part or for all doses	19%
Any issues maintaining BPG supply	42%
BPG brand change within the past two years	43%
BPG supply is dependent on an external organization	14%
Access to oral penicillin	68%

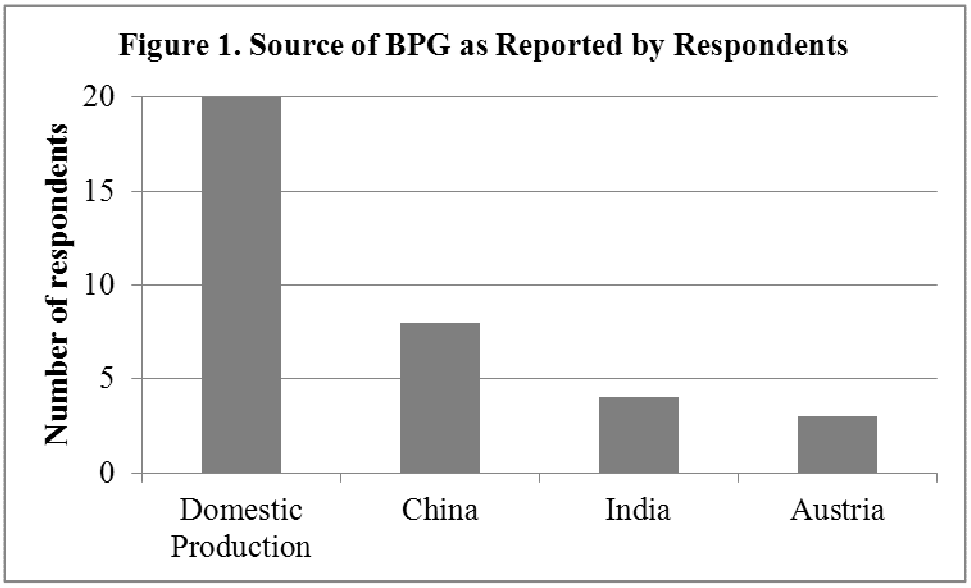
Table 4. Percent of Respondents Reporting Specific Issues with BPG Quality

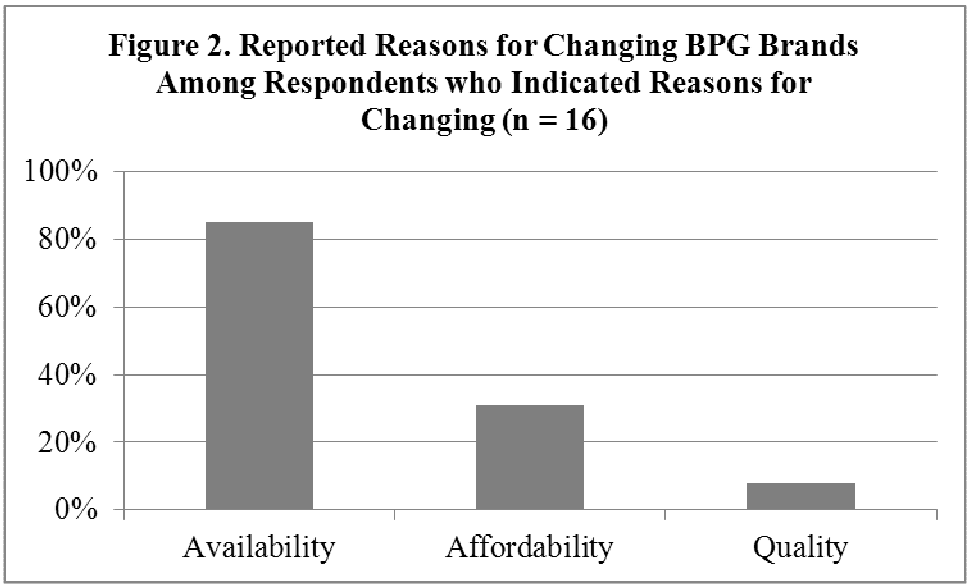
BPG quality issue	Percent
Difficulty reconstituting BPG	6%
Difficulty drawing BPG into syringe	26%
One or more patients have had breakthrough RF while on BPG prophylaxis	11%
Rash is a common side effect of BPG	3%
One or more of their patients have had anaphylaxis on current brand of BPG	26%
One or more of their patients have died due to anaphylaxis from BPG	21%

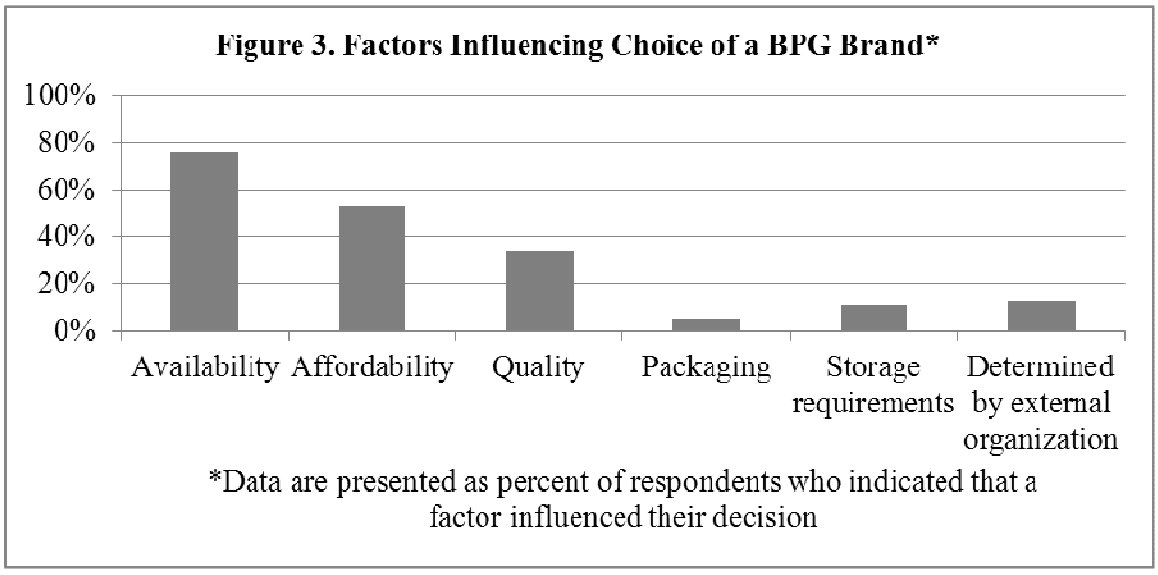
Table 5. Location of BPG Production for Each Region (n=35)*

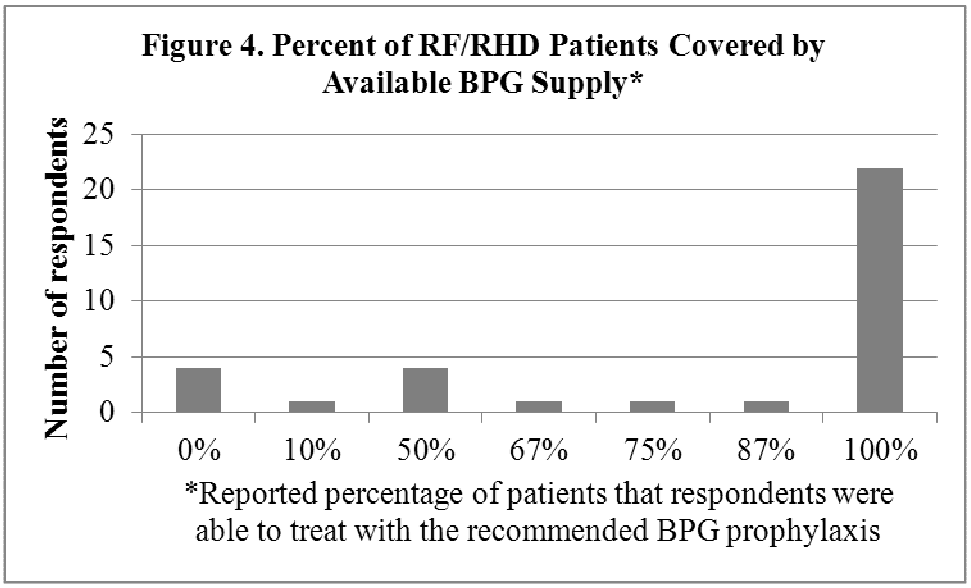
	State that produces BPG for organization			
Region	**Domestic production**	**China**	**India**	**Austria**
Africa	5	8	1	1
Asia-Pacific	12	0	2	2
Central & South America	3	0	1	0

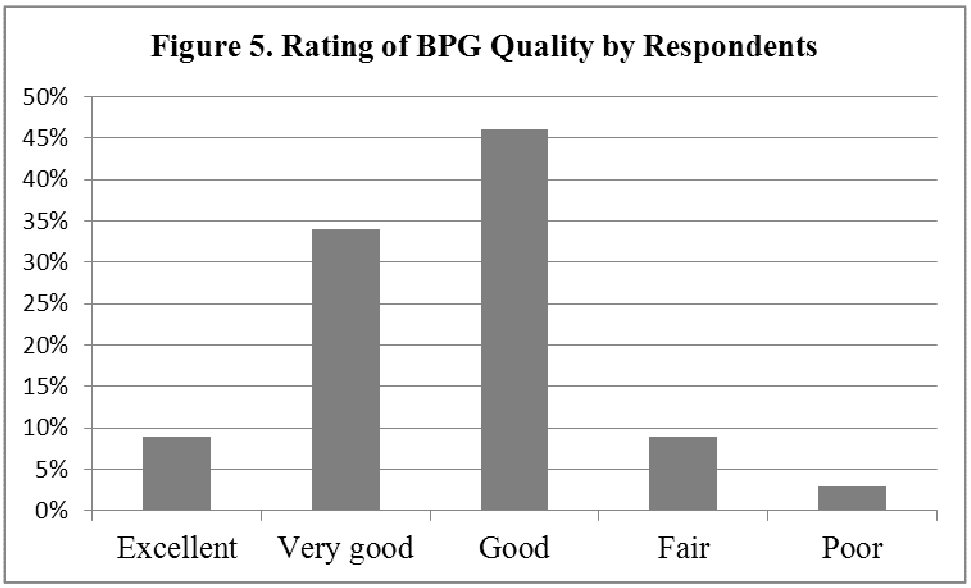
*2-sided Pearson $\chi 2=14.9$ ($p=0.021$)

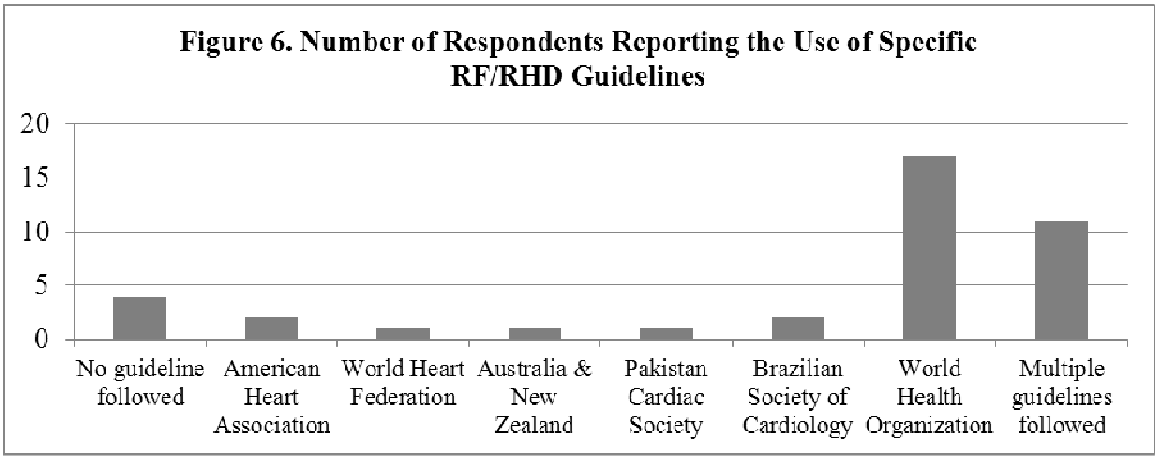


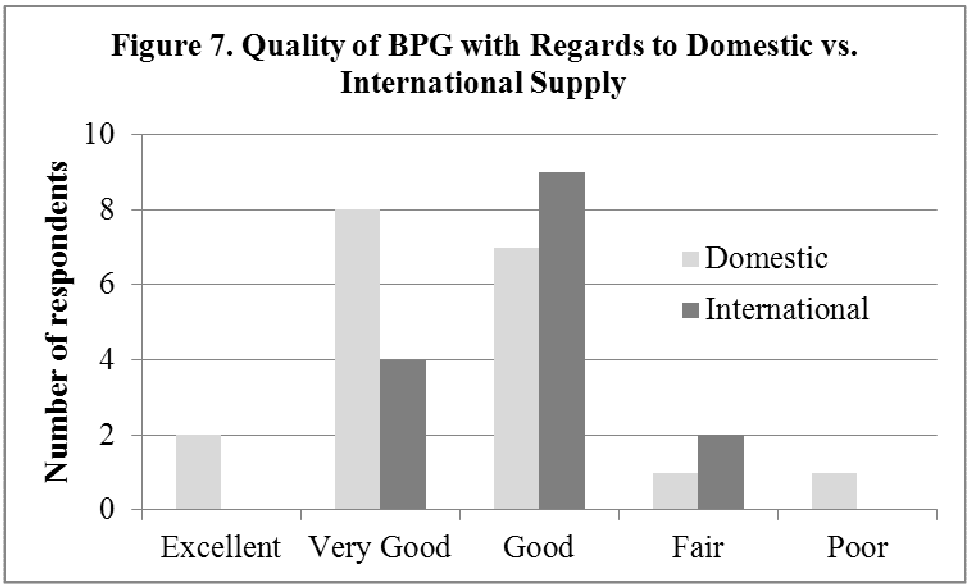












Appendix 2: Introductory Emails and Surveys

English-Only Introductory Email

Dear Dr. _____,

You are being contacted because we, at the World Heart Federation, have identified you as having a clinical interest in rheumatic fever or rheumatic heart disease. You have been chosen to participate in an important survey-based study that seeks to recognize treatment protocols currently in use by clinicians who perform primary or secondary prophylaxis on rheumatic fever or rheumatic heart disease patients. We are attempting to define and assess quantitative and qualitative benzathine penicillin G supply issues in global regions with a high burden of rheumatic fever and rheumatic heart disease. You know how important it is for your RHD patients to receive appropriate care and we have had reports of penicillin shortages and poor quality penicillin. The attached survey should take approximately 15-30 minutes to complete. You may be the only survey respondent in your country so don't let your country's voice go unheard! Individual results will be held confidential and compiled results will be distributed to all survey respondents. Your individual participation in this survey is extremely important and the validity of the study depends on adequate numbers of respondents - every response counts. If you have any questions about the study or the validity of this email, please don't hesitate to contact me by hitting 'reply' or writing to Stephen.Marko@worldheart.org. You may also call me at +1 802-324-5803 (please note that my time zone is GMT minus five hours). I look forward to your reply.

Thank you,
Stephen Marko
World Heart Federation
University of Connecticut MD/MPH candidate

English and French Introductory Email

Docteur _____,

Nous faisons une étudie pour déterminer les traitements utilisés par les médecins pour prévenir la fièvre rhumatismale et des cardiopathies rhumatismales. Nous avons été informés des pénuries dans la fourniture de Pénicilline G Benzathine (BPG), le traitement préventif recommandé par l'Organisation Mondiale de la Santé et d'autres organisations. Si vous êtes un médecin qui traite des patients atteints de fièvre rhumatismale et des cardiopathies rhumatismales, s'il-vous plaît remplissez l'enquête, qui est attachée en français et en anglais. Pour une explication plus complète s'il vous plaît voir l'enquête.

Cordialement,
Stephen Marko
Fédération Mondiale de Cardiologie

Dr. _____,

You are being contacted because we, at the World Heart Federation, have identified you as having a clinical interest in rheumatic fever or rheumatic heart disease. You have been chosen to participate in an important survey-based study that seeks to recognize treatment protocols currently in use by clinicians who perform primary or secondary prophylaxis on rheumatic fever or rheumatic heart disease patients. We are attempting to define and assess quantitative and qualitative benzathine penicillin G supply issues in global regions with a high burden of rheumatic fever and rheumatic heart disease. You know how important it is for your RHD patients to receive appropriate care and we have had reports of penicillin shortages and poor quality penicillin. The attached survey should take approximately 15-30 minutes to complete. You may be the only survey respondent in your country so don't let your country's voice go unheard! Individual results will be held confidential and compiled results will be distributed to all survey respondents. Your individual participation in this survey is extremely important and the validity of the study depends on adequate numbers of respondents - every response counts. If you have any questions about the study or the validity of this email, please don't hesitate to contact me by hitting 'reply' or writing to Stephen.Marko@worldheart.org. I apologize for my rudimentary French, the survey (attached in French and English) has been translated by a professional service. I look forward to your reply.

Thank you,
Stephen Marko
World Heart Federation

English and Spanish Introductory Email

Estimado Dr. _____,

Estamos contactándole porque nosotros, en the World Heart Federation, le hemos identificado ser una persona con un interés clínico en fiebre reumática o enfermedad reumática del corazón (RF/RHD). Usted ha sido seleccionado para participar en un importante encuesta que intenta de reconocer protocolos de tratamiento utilizado por trabajadores de la salud que cuidan a pacientes de RF/RHD. Estamos tratando de definir y evaluar los temas cuantitativos y cualitativos del suministro de penicilina benzatina G (BPG) en regiones del mundo con alta incidencia de RF/RHD. Usted sabe que es importante para sus pacientes tener cuida adecuada y hemos tenido reportes de escasez de la penicilina y tambien penicilina de mala calidad. La encuesta adjunta deberá durar aproximadamente 15-30 minutos. Es posible que usted será el demandado sólo en su país, ¡no deje que la voz de su gente falta! Su participación individual en esta encuesta es de suma importancia y la validez del estudio depende de un número suficiente de participantes - cada respuesta es importante. Si usted tiene alguna pregunta sobre el estudio o la validez de este correo electrónico, por favor no dude en ponerse en contacto conmigo por escribiendo a Stephen.Marko@worldheart.org. Lo

siento por mi Español rudimentario, la encusta (adjuntado en Español y Inglés) ha sido traducido por un servicio profesional. Espero su respuesta.
Muchas gracias,
Stephen Marko
World Heart Federation
Universidad de Connecticut MD/MPH Candidato

Dear Dr. _____,

You are being contacted because we, at the World Heart Federation, have identified you as having a clinical interest in rheumatic fever or rheumatic heart disease. You have been chosen to participate in an important survey-based study that seeks to recognize treatment protocols currently in use by clinicians who perform primary or secondary prophylaxis on rheumatic fever or rheumatic heart disease patients. We are attempting to define and assess quantitative and qualitative benzathine penicillin G supply issues in global regions with a high burden of rheumatic fever and rheumatic heart disease. You know how important it is for your RHD patients to receive appropriate care and we have had reports of penicillin shortages and poor quality penicillin. The attached survey should take approximately 15-30 minutes to complete. You may be the only survey respondent in your country so don't let your country's voice go unheard! Individual results will be held confidential and compiled results will be distributed to all survey respondents. Your individual participation in this survey is extremely important and the validity of the study depends on adequate numbers of respondents - every response counts. If you have any questions about the study or the validity of this email, please don't hesitate to contact me by hitting 'reply' or writing to Stephen.Marko@worldheart.org. I apologize for my rudimentary Spanish, the survey (attached in Spanish and English) has been translated by a professional service. I look forward to your reply.

Thank you,
Stephen Marko
World Heart Federation
University of Connecticut MD/MPH candidate

<u>English Follow-Up Email</u>

Dear Dr. _____,

A short time ago, I emailed you the attached survey regarding benzathine penicillin G supply. I have not received your completed survey and we are lacking information on benzathine penicillin G supply in your country. If you are qualified to complete the survey, it is extremely important that we learn what supply issues you are having, if any at all. If you are not having supply issues, it is important that we know that as well! As before, we have chosen you to participate in a survey-based study that seeks to define and assess quantitative and qualitative benzathine penicillin G supply issues in global regions with a high burden of rheumatic fever and rheumatic heart disease. The attached survey

should take approximately 15-30 minutes to complete. You may be the only survey respondent in your country so don't let your country's voice go unheard! Individual results will be held confidential and compiled results will be distributed to all survey respondents. Your individual participation in this survey is extremely important and the validity of the study depends on adequate numbers of respondents - every response counts. If you have any questions about the study or the validity of this email, please don't hesitate to contact me by hitting 'reply' or writing to Stephen.Marko@worldheart.org. You may also call me at +1 802-324-5803 (please note that my time zone is GMT minus five hours). I look forward to your reply.

Thank you again,
Stephen Marko
World Heart Federation
University of Connecticut MD/MPH candidate

Surveys

Please see the next page for surveys provided in English, Spanish, and French.

WORLD HEART FEDERATION®

Rheumatic Fever and Rheumatic Heart Disease Prevention

ABOUT THIS STUDY:

- The principal investigator of this study is Stephen Marko, a Doctor of Medicine and Master in Public Health candidate at the University of Connecticut working in collaboration with the World Heart Federation
- The purpose of this study is to define and assess quantitative and qualitative benzathine penicillin G (BPG) supply issues in global regions with a high burden of rheumatic fever (RF) and rheumatic heart disease (RHD)
- This survey is being sent to healthcare practitioners in selected countries throughout the world
- Survey participants should be healthcare practitioners who perform primary or secondary prophylaxis treatment on RF/RHD patients
- Survey participants should have ready access to the current stock of BPG used at their clinical site, if applicable
- This survey should take approximately 15-30 minutes to complete
- Your participation in this survey is voluntary and you may skip any question
- You may be the only survey respondent in your country – don't let your country's voice go unheard!
- Answers should be provided to the best of your ability
- Completion and return of the survey implies consent to use the information it contains
- Individual results will be held confidential
- Compiled results will be distributed to all survey respondents
- The results of the study will be used in the production of Mr. Marko's Master's thesis
- Questions can be addressed to Mr. Marko at Stephen.Marko@worldheart.org

INSTRUCTIONS:

- Click X with the computer mouse to select a box ☒
- Type into each **field** and the spaces will expand automatically
- Press SAVE each time the form is closed
- Please answer as completely as possible, more information is better than less
- **Please FORWARD COMPLETED QUESTIONNAIRE to**: Stephen.Marko@worldheart.org

Your Country:
Your Name:
Your Designation/Title:
Your Organization:
Practice setting (e.g. urban/rural,

clinic/hospital, etc.):
Date questionnaire completed:

Please provide the name and contact information of the person we should communicate with in the future about BPG at your institution (e.g. yourself, another clinician, pharmacy representative):

Name:
Organization/Address:
Phone number (+country code):
Facsimile number (+country code):
Email address:

1. **Concerning the most commonly used <u>current brand of BPG</u> that is used at your institution for primary and/or secondary prophylaxis of RF/RHD [information available on vials/packaging]:**

Brand name:
Manufacturer:
Country where manufactured:
Supplier:
Expiration date:
Preparation (e.g. pre-filled syringe, powder, etc.):
If powder form, volume used for reconstitution (mLs):
Type of diluent (e.g. sterile water, lignocaine, etc.):
Available dose formulations (e.g.1.2 million units, 2.4 million units):
Types of BPG formulations (e.g. mixed with aqueous penicillin, procaine penicillin, or other preparations):
Comments regarding formulations:
Check this box if your institution does not have access to BPG: ☐

2. **Concerning the quantity of BPG available to your institution:**

a) Please estimate how many patients your institution <u>currently</u> has that <u>require</u> secondary prophylaxis for RF/RHD using BPG:

b) Given your BPG supply, please estimate how many patients your institution <u>currently</u> is <u>capable</u> of treating with secondary prophylaxis for RF/RHD:

c) Has your institution experienced any problems maintaining a BPG supply adequate for RF/RHD primary and/or secondary prophylaxis?
☐ No
☐ Yes: How recently?

d) Is there more than one brand of BPG currently used by your institution?

☐ No
☐ Yes: Please list all currently used brands:

e) Has there been a brand change of BPG in the past 2 years?
☐ No
☐ Yes:

i. If yes, please list all other known brands have been used in the past 2 years:

ii. If yes, have there been changes in any of the following characteristics of BPG (check all that apply):
☐ Preparation
☐ Reconstitution volume
☐ Type of diluent
☐ Dose formulation
☐ Type of formulation
☐ Other:

iii. If yes, what were the reasons for changing? (check all that apply):
☐ It was determined by an external organization
☐ Availability on the market
☐ Affordability
☐ Quality
☐ Packaging
☐ Storage requirements
☐ Other:

f) Is the supply of BPG dependent upon an external organization? (e.g. an NGO, UNICEF, etc.)
☐ No
☐ Yes. Please state the name of the organization that sources BPG for your institution:

g) What factors influence the decision regarding the choice of the brand of BPG used in your institution? (check all that apply):
☐ It is determined by an external organization
☐ Availability on the market
☐ Affordability
☐ Quality
☐ Packaging
☐ Storage requirements
☐ Other:

h) Does your institution have antibiotic alternatives in the event that the BPG supply is not adequate?
☐ No
☐ Yes:
☐ Oral penicillin
☐ Aminopenicillins (e.g. Amoxicillin, amoxicillin-clavulanate, etc.)
☐ Cephalosporins (e.g. cefdinir, cefpodoxime, cephalothin, etc.)

☐ Macrolides (e.g. azithromycin, erythromycin, etc.)
☐ Lincosamides (e.g. clindamycin, etc.)
☐ Sulfonamides
☐ Other:

i) Please state any general comments on the quantity of BPG your institution is able to acquire:

3. Concerning the quality of the BPG supply at your institution:

a) How would you rate the quality of the current BPG supply?
☐ Excellent
☐ Very good
☐ Good
☐ Fair
☐ Poor

b) Have you experienced difficulty reconstituting particular batches of BPG?
☐ No
☐ Yes. Please state the brand in use at the time:

c) Have you experienced difficulty drawing reconstituted BPG into syringes?
☐ No
☐ Yes. Please state the brand in use at the time:

d) Has there been evidence of breakthrough rheumatic fever with particular BPG batches?
☐ No
☐ Yes. Please state the brand in use at the time:

e) Is rash a common side effect of the current BPG formulation in use at your clinical site?
☐ No
☐ Yes. Please state the estimated incidence of rash due to BPG:

f) Have any of your patients experienced anaphylaxis after receiving a BPG injection?
☐ No
☐ Yes
i. If yes, please state the brand in use at the time:
ii. If yes, how has this affected the way secondary prophylaxis is performed?

g) Have any of your patients died from anaphylaxis following a BPG injection?
☐ No
☐ Yes
i. If yes, please state the brand in use at the time:
ii. If yes, how has this affected the way secondary prophylaxis is performed?

h) Do you inject BPG beyond the expiration date?
☐ No
☐ Yes

i) Is skin testing for penicillin allergy performed at your site?
☐ No
☐ Yes
i. If yes, what percentage of patients are you able to test before initiating treatment?

j) Please state any general comments on the quality of BPG your institution is able to acquire:

4. Concerning national and international guidelines on RF/RHD prophylaxis:

a) Is there any structured national program for RF/RHD prevention and control in your country?

- ☐ No
- ☐ Don't know
- ☐ Yes

b) Does your country have a national RF/RHD registry?

- ☐ No
- ☐ Don't know
- ☐ Yes
  - **i.** If yes, does your organization report into it?
    - ☐ No
    - ☐ Yes

c) What RF/RHD prevention guidelines are currently used by your organization?

- ☐ None
- ☐ World Health Organization
- ☐ American Heart Association
- ☐ World Heart Federation
- ☐ India
- ☐ Australia and New Zealand
- ☐ Other; please provide the name of the guidelines here:

d) For patients at low risk of recurrent RF, how frequently do you provide prophylaxis?

e) For patients at high risk of recurrent RF or patients who have had breakthrough RF on 4 week prophylaxis, how frequently do you provide prophylaxis?

f) If no schedule is followed, or another schedule is followed, please explain:

g) For adults and children weighing 30kg or more, how many units of BPG are injected, if applicable?

h) For children weighing less than 30kg, how many units of BPG are injected, if applicable?

5. Concerning additional healthcare providers who treat RF/RHD:

a) Please provide names and contact details for any other individuals or organizations which you feel might have additional information pertinent to this questionnaire:

Thank you for your interest and participation

Please forward the completed questionnaire to: Stephen.Marko@worldheart.org

WORLD HEART FEDERATION®

La Prevención de Fiebre Reumática y Enfermedad Reumática del Corazón

SOBRE ESTE ESTUDIO:

- El investigador principal de este estudio es Stephen Marko, estudiante para Doctor en Medicina y Master en Salud Pública en la Universidad de Connecticut que trabaja en colaboración con la Federación Mundial de Cardiología
- El propósito de este estudio es definir y evaluar los temas cuantitativos y cualitativos del suministro de penicilina G benzatina (BPG) en regiones del mundo con alta incidencia de fiebre reumática (RF) y enfermedad reumática del corazón (RHD)
- Esta encuesta está siendo enviada a médicos en países de todo el mundo
- Los participantes de la encuesta deben ser médicos que tienen pacientes de RF/RHD
- Los participantes de la encuesta deben tener fácil acceso a las existencias de BPG en uso en su clínica, si la clínica tiene acceso a BPG
- Completar este instrumento de la encuesta no debe llevar más de 15-30 minutos
- Su participación en esta encuesta es voluntaria y se puede dejar de contestar cualquiera de las preguntas
- Podría ser el único en su país que esté respondiendo a esta encuesta – ¡no deje que la voz de su país no sea escuchada!
- Las respuestas deben contestarse lo mejor que se pueda
- Completar y devolver este cuestionario implica consentimiento para que la información que contiene sea usada
- Resultados individuales estará dejado confidencial
- Un compilado de los resultados les será enviado a todos los que hayan respondido a la encuesta
- Los resultados del estudio serán utilizados en la producción de la tesis de Master del Sr. Marko
- En caso de preguntas, pueden ser enviadas al Sr. Marko a Stephen.Marko@worldheart.org

INSTRUCCIONES:

- Marque X con el mouse del ordenador para seleccionar un casillero ☒
- Escriba en cada **campo** y los espacios se expandirán automáticamente
- Marque GUARDAR cada vez que cierre el formulario
- Por favor responda lo más completamente posible, es mejor que haya información de más y no de menos
- **Por favor REENVÍE EL CUESTIONARIO COMPLETADO a**: Stephen.Marko@worldheart.org

Su País:

Su Nombre:
Su Designación/Título:
Su Organización:
Ubicación del consultorio (por ej. urbano/rural, clínica/hospital, etc.):
Fecha en la que completó el cuestionario:

Por favor indique el nombre y la información de contacto de la persona con la que debemos comunicarnos a futuro sobre BPG en su institución (por ej. usted, o un clínico / representante farmacéutico):

Nombre:
Organización/Dirección:
Teléfono (+código país):
Facsímil (+código país):
Dirección email:

6. **Referente a la marca actualmente más comúnmente en uso de BPG en su institución para profilaxis primaria y/o secundaria de RF/RHD [información disponible en las ampollas/embalajes actualmente en uso]:**

Marca:
Fabricante:
País del fabricante:
Proveedor:
Fecha de vencimiento/caducidad:
Preparación (por ej. jeringa pre-cargada, polvo, etc.):
Si es en polvo, volumen que se usa para reconstituir (mLs):
Tipo de diluyente (por ej. agua esterilizada, lignocaína, etc.):
Formulaciones de dosis disponibles (por ej. 1,2 millones de unidades, 2,4 millones de unidades):
Tipos de formulaciones BPG (por ej. combinada con penicilina acuosa, penicilina procaína, u otras preparaciones):
Comentarios referentes a las formulaciones:
Marque X con el mouse del ordenador si su institución no tiene acceso a BPG: ☐

7. **Referente a la cantidad de BPG disponible en su institución:**

k) Por favor estime cuantos pacientes su organización tiene actualmente que requieran profilaxis secundaria para RF/RHD que estén usando BPG:

l) Dada sus existencias de BPG, por favor estime cuantos pacientes su organización es actualmente capaz de tratar con profilaxis secundaria para RF/RHD:

m) ¿Su institución ha experimentado algún problema en mantener existencias suficientes de BPG para profilaxis primaria y/o secundaria de RF/RHD?

- ☐ No
- ☐ Sí: ¿Hace cuánto tiempo?

n) ¿Hay más de una marca de BPG actualmente en uso en su organización?

- ☐ No
- ☐ Sí: Por favor liste todas las marcas en uso actualmente:

o) ¿Han cambiado de marca de BPG en los últimos 2 años?

- ☐ No
- ☐ Sí:
  - **i.** Si respondió sí, por favor liste todas las demás marcas conocidas utilizadas en los últimos 2 años:
  - **ii.** Si respondió sí, ¿han habido cambios en cualquiera de las siguientes características de BPG? (marque todas las que correspondan):
    - ☐ Preparación
    - ☐ Volumen de reconstitución
    - ☐ Tipo de diluyente
    - ☐ Formulación de dosis
    - ☐ Tipo de formulación
    - ☐ Otros:
  - **iii.** Si respondió sí, ¿cuáles fueron los motivos del cambio? (marque todos los que correspondan):
    - ☐ Fue decidido por una organización externa
    - ☐ Disponibilidad en el mercado
    - ☐ Asequibilidad en costo
    - ☐ Calidad
    - ☐ Embalaje
    - ☐ Requisitos de almacenamiento
    - ☐ Otros:

p) ¿Las existencias de BPG dependen de una organización externa? (por ej. una ONG, UNICEF, etc.)

- ☐ No
- ☐ Sí. Por favor indique el nombre de la organización que le proporciona BPG a su institución:

q) ¿Qué factores influyen en la decisión referente a la elección de la marca de BPG que utiliza su institución? (marque todos los que correspondan):

- ☐ Es decidido por una organización externa
- ☐ Disponibilidad en el mercado
- ☐ Asequibilidad en costo
- ☐ Calidad
- ☐ Embalaje
- ☐ Requisitos de almacenamiento

☐ Otros:

r) ¿Su institución tiene alternativas de antibióticos si las existencias de BPG no fueran suficientes?

☐ No

☐ Sí:

- ☐ Penicilina oral
- ☐ Aminopenicilinas (por ej. Amoxicilina, amoxicilina-clavulanato, etc.)
- ☐ Cefalosporinas (por ej. cefdinir, cefpodoxima, cefalotina, etc.)
- ☐ Macrólidos (por ej. azitromicina, eritromicina, etc.)
- ☐ Lincosamidas (por ej. clindamicina, etc.)
- ☐ Sulfonamidas
- ☐ Otros:

s) Por favor realice comentarios generales sobre la cantidad de BPG que su institución puede adquirir:

8. Referente a la calidad de las existencias de BPG en su institución:

j) ¿Cómo calificaría la calidad de la existencia actual de BPG?

☐ Excelente

☐ Muy buena

☐ Buena

☐ Regular

☐ Mala

k) ¿Ha experimentado alguna dificultad al reconstituir algún lote en especial de BPG?

☐ No

☐ Sí. Por favor diga qué marca estaban usando en ese momento:

l) ¿Ha experimentado alguna dificultad al llenar la jeringa con BPG reconstituido?

☐ No

☐ Sí. Por favor diga qué marca estaban usando en ese momento:

m) ¿Ha habido evidencia de irrupción de fiebre reumática con algún lote en especial de BPG?

☐ No

☐ Sí. Por favor diga qué marca estaban usando en ese momento:

n) ¿Es común en su clínica que se produzca una erupción como efecto colateral con la formulación de BPG que se usa actualmente?

☐ No

☐ Sí. Por favor estime la incidencia de erupciones debido al uso de BPG:

o) ¿Alguno de sus pacientes han experimentado anafilaxis luego de ser inyectados con BPG?

☐ No

☐ Sí

- **i.** Si respondió sí, por favor diga qué marca estaban usando en ese momento:
- **ii.** Si respondió sí, ¿cómo afectó esto el modo en el que se lleva a cabo la profilaxis secundaria?

p) ¿Alguno de sus pacientes ha fallecido de anafilaxis luego de ser inyectado con BPG?

☐ No
☐ Sí

i. Si respondió sí, por favor diga qué marca estaban usando en ese momento:

ii. Si respondió sí, ¿cómo afectó esto el modo en el que se lleva a cabo la profilaxis secundaria?

q) ¿Inyecta BPG después de su fecha de vencimiento?

☐ No
☐ Sí

r) ¿Se realizan pruebas cutáneas de alergia a la penicilina en su clínica?

☐ No
☐ Sí

ii. Si respondió sí, ¿cuál es el porcentaje de pacientes que pueden testear antes de iniciar tratamiento?

t) Por favor realice cualquier comentario general sobre la calidad del BPG que su institución puede adquirir:

9. Referente a directivas nacionales e internacionales sobre profilaxis de RF/RHD:

i) ¿Hay algún programa nacional estructurado de prevención y control de RF/RHD en su país?

☐ No
☐ No sé
☐ Sí

j) ¿Su país tiene un registro nacional de RF/RHD?

☐ No
☐ No sé
☐ Sí

i. Si respondió sí, ¿su organización le informa al mismo?

☐ No
☐ Sí

k) ¿Qué directivas de prevención de RF/RHD están siendo utilizadas actualmente por su organización?

☐ Ninguna
☐ Organización Mundial de la Salud
☐ American Heart Association [Asociación Americana de Cardiología]
☐ World Heart Federation [Federación Mundial de Cardiología]
☐ India
☐ Australia y Nueva Zelanda
☐ Otros; por favor indique a continuación el nombre de las directivas:

l) Para pacientes con bajo riesgo de recurrencia de RF, ¿con qué frecuencia les proporciona profilaxis?

m) Para pacientes con alto riesgo de recurrencia de RF o pacientes para los que hubo una irrupción de RF en una profilaxis de 4 semanas, ¿con qué frecuencia se les proporciona profilaxis?

n) Si no se programa la profilaxis, o se programa de otro modo, por favor explíquelo:

o) Para adultos y niños que pesan 30 kilos o más, ¿cuántas unidades de BPG están inyectado, si aplicable?

p) Para niños que pesan menos de 30 kilos, ¿cuántas unidades de BPG están inyectado, si aplicable?

10. Referente a proveedores de asistencia a la salud que tratan RF/RHD:

- Por favor proporcione el nombre y los detalles de contacto para cualquier otro individuo u organización que usted considere podría tener información adicional pertinente a este cuestionario:

Muchas gracias por su interés y participación

Por favor reenvíe el cuestionario completado a: Stephen.Marko@worldheart.org.

WORLD HEART FEDERATION®

et des Cardiopathies Rhumatismales

A PROPOS DE CETTE ÉTUDE:

- Le principal instigateur de cette étude est Stephen Marko, Docteur en Médecine et étudiant en Master en Santé Publique à l'Université du Connecticut, qui travaille en collaboration avec la World Heart Federation (Fédération Mondiale de Cardiologie).
- Le but de cette étude est de préciser et d'évaluer, quantitativement et qualitativement, l'administration de Pénicilline G Benzathine (BPG) dans les régions du monde présentant un taux élevé de cas de fièvre rhumatismale et de cardiopathies rhumatismales.
- Cette enquête est envoyée à des praticiens de santé dans divers pays à travers le monde
- Les participants à cette enquête doivent être des praticiens de santé qui traitent des patients atteints de RF/RHD (fièvre rhumatismale et cardiopathies rhumatismales)
- Les participants à l'enquête doivent avoir libre accès au stock de BPG du centre de soins où ils exercent, si la clinique utilise de la BPG pour prévenir les RF/RHD
- Remplir ce formulaire d'enquête ne devrait pas prendre plus de 30 mn
- La participation à cette enquête est facultative et il n'est pas obligatoire de répondre à toutes les questions
- Peut-être serez-vous le seul praticien de votre pays à répondre à cette enquête – Ne permettez pas que la voix de votre pays reste muette
- Répondez aux questions posées au meilleur de vos compétences
- Remplir ce formulaire d'enquête et le retourner implique votre consentement à ce que les informations qu'il contient soient utilisées
- Les résultats individuels seront confidentiels
- Une compilation des résultats de l'enquête sera communiquée à tous ceux qui y ont participé
- Les conclusions de l'étude seront utilisées pour la rédaction de la thèse de M. Marko
- Toute question peut être adressée à M. Marko par courriel à Stephen.Marko@worldheart.com

INSTRUCTIONS:

- Taper X avec la souris de l'ordinateur dans la case que vous avez choisie ☐
- Ecrivez dans chaque champ, celui-ci s'agrandira automatiquement
- ENREGISTRER le formulaire à chaque fois que vous fermez le document
- Merci de donner les informations les plus complètes possibles. Trop d'informations valent mieux que pas assez
- **Merci de TRANSMETTRE LE QUESTIONNAIRE DÛMENT REMPLI à**: Stephen.Marko@worldheart.org

Votre Pays:
Votre Nom:
Votre Dénomination/Titre:
Votre Organisation:
Milieu dans lequel vous exercez (ex. urbain/rural,

clinique/hôpital, etc.):
Date à laquelle vous avez rempli le questionnaire:

Merci de préciser le nom et les informations de contact de la personne à laquelle nous devons nous adresser à l'avenir au sujet de la BPG au sein de votre institution (ex. vous-même, ou un clinicien/ pharmacien responsable)

Nom:
Organisation/Adresse:
N° de Tél (+code du pays):
N° de Fax (+code du pays):
Adresse Email:

11. A propos de la marque de BPG actuellement la plus utilisée dans votre institution pour la prophylaxie primaire et secondaire des RF/RHD (information fournie sur les flacons/les emballages courants):

Marque:
Fabricant:
Adresse du fabricant:
Fournisseur:
Date de péremption:
Conditionnement
(ex. seringue pré-remplie, poudre, etc.):
S'il s'agit de poudre, volume utilisé pour la reconstitution (ml)
Type de diluant
(ex. eau stérile, lignocaïne, etc.):
Formulation des doses disponibles
(ex.1.2 millions d'unités, 2.4 millions d'unités):
Types de formulation
(ex. combinée avec de la pénicilline aqueuse, de la pénicilline procaïne, ou d'autres préparations):
Commentaires sur les formulations:
Taper X avec la souris de l'ordinateur dans la case si votre institution n'a pas accès à la BPG: ☐

12. A propos de la quantité de BPG disponible dans votre institution:

u) Merci de donner une estimation du nombre de patients actuellement soignés dans votre institution qui requièrent une prophylaxie secondaire à la BPG pour une RF/RHD :

v) Tenant compte de votre approvisionnement en BPG, merci d'estimer le nombre de patients que votre institution est actuellement en mesure de traiter à la BPG avec une prophylaxie secondaire pour une RF/RHD

w) Votre institution a-t-elle rencontré des problèmes pour assurer un approvisionnement suffisant en BPG pour la prophylaxie primaire ou secondaire des RF/RHD ?

☐ Non

☐ Oui Il y a combien de temps ?

x) Votre institution utilise-t-elle actuellement plus d'une marque de BPG?

☐ Non

☐ Oui: Merci de citer toutes les marques actuellement utilisées:

y) Y a-t-il eu un changement de marque de BPG au cours des deux dernières années?

☐ Non

☐ Oui:

i. Si oui, citez le nom de toutes les autres marques connues utilisées au cours des deux dernières années:

ii. Si oui, y a-t-il eu des changements parmi les caractéristiques suivantes de la BPG (cocher tout ce qui convient):

☐ Préparation

☐ Volume de reconstitution

☐ Type de diluant

☐ Formulation de la dose

☐ Type de formulation

☐ Autre:

iii. Si oui, quelles étaient les raisons de ce changement? (cocher tout ce qui convient):

☐ Cela a été décidé par une organisation externe

☐ Disponibilité sur le marché

☐ Accessibilité du prix

☐ Qualité

☐ Conditionnement

☐ Impératifs de stockage

☐ Autre:

z) L'approvisionnement en BPG dépend-il d'une organisation externe ? (ex. une ONG, l'UNICEF, etc.)

☐ Non

☐ Oui. Merci de citer le nom de l'organisation qui fournit votre institution en BPG:

aa) Quels sont les facteurs qui influencent la décision du choix de la marque de BPG utilisée par votre institution? (cocher tout ce qui convient):

☐ Il est déterminé par une organisation externe

☐ Disponibilité sur le marché

☐ Accessibilité du prix

☐ Qualité

☐ Conditionnement

☐ Impératifs de stockage

☐ Autre:

bb) Votre institution a-t-elle des alternatives en antibiotiques en cas d'insuffisance de stock en BPG?

☐ Non

☐ Oui:

☐ Pénicilline orale
☐ Aminopénicillines (ex., Amoxicilline-clavulanate, etc.)
☐ Céphalosporines (ex. cefdinir, cefpodoxime, cephalothin, etc.)
☐ Macrolides (ex. azithromycine, érythromycine, etc.)
☐ Lincosamides (ex. clindamycine, etc.)
☐ Sulfamidés
☐ Autre:

cc) Merci de faire tout commentaire sur la quantité de BPG que votre institution peut acquérir:

13. A propos de la qualité du stock en BPG de votre institution:

s) Quelle mention accorderiez-vous à la qualité du stock actuel en BPG de votre institution?
☐ Excellente
☐ Très bonne
☐ Bonne
☐ Passable
☐ Mauvaise

t) Avez-vous rencontré des difficultés dans la reconstitution de certains lots de BPG?
☐ Non
☐ Oui. Si oui, Merci de citer la marque utilisée alors:

u) Avez-vous rencontré des difficultés lors du remplissage de la seringue avec de la BPG reconstituée?
☐ Non
☐ Oui. Si oui, Merci de citer la marque utilisée alors:

v) Avez-vous constaté une rechute évidente de fièvre rhumatismale avec certains lots de BPG?
☐ Non
☐ Oui. Si oui, Merci de citer la marque utilisée alors:

w) La formulation de BPG actuellement utilisée dans le centre de soins où vous exercez a-t-elle pour effet secondaire courant une éruption cutanée ?
☐ Non
☐ Oui. Veuillez préciser l'incidence des éruptions cutanées que vous attribuez à l'usage de BPG

x) L'un de vos patients a-t-il été victime d'une réaction anaphylactique suite à une piqûre de BPG?
☐ Non
☐ Oui
i. Si oui, Merci de citer la marque utilisée alors:
ii. Si oui, en quoi cela a-t-il affecté la procédure de prophylaxie secondaire?

y) L'un de vos patients est-il décédé d'anaphylaxie, suite à une piqûre de BPG?
☐ Non
☐ Oui
i. Si oui, Merci de citer la marque utilisée alors:
ii. Si oui, en quoi cela a-t-il affecté la procédure de prophylaxie secondaire?

z) Injectez-vous la BPG après sa date de péremption ?

☐ Non
☐ Oui

aa) Pratique-t-on des tests cutanés d'allergie à la pénicilline dans votre clinique ?

☐ Non
☐ Oui

i. Si oui, quel est le pourcentage de patients que vous pouvez tester avant de commencer le traitement ?

j) Merci de faire tout commentaire sur la qualité de BPG que votre institution peut acquérir:

4. A propos des directives nationales et internationales sur la prophylaxie RF/RHD:

q) Existe-t-il un programme national structuré pour la prévention et le contrôle des RF/RHD dans votre pays ?

☐ Non
☐ Je ne sais pas
☐ Oui

r) Existe-t-il dans votre pays un registre national des RF/RHD?

☐ Non
☐ Je ne sais pas
☐ Oui

i. Si oui, votre organisation en reporte-t-elle à lui ?

☐ Non
☐ Oui

s) Quelles sont les directives en matière de prévention des RF/RHD qu'applique aujourd'hui votre organisation?

☐ Aucune
☐ Organisation Mondiale de la Santé
☐ American Heart Association (Association Américaine de Cardiologie)
☐ World Heart Federation (Fédération Mondiale de Cardiologie)
☐ Inde
☐ Australie et Nouvelle-Zélande
☐ Autre; Merci d'indiquer ci-après le nom des directives :

t) Pour les patients à faible risque de récurrence de RF, à quelle fréquence leur dispensez-vous un traitement prophylactique ?

u) Pour les patients à haut risque de récurrence de RF, ou pour les patients qui ont rechuté dans les 4 semaines suivant le traitement prophylactique, à quelle fréquence leur dispensez-vous un traitement prophylactique ?

v) En l'absence d'un programme, ou si un autre programme est suivi, merci d'expliquer:

w) Pour les adultes et les enfants pesant 30 kg ou plus, combien d'unités de BPG sont injectés, le cas échéant?

x) Pour les enfants pesant moins de 30 kg, combien d'unités de BPG sont injectés, le cas échéant ?

5. **A propos d'autres fournisseurs de produits de santé qui traitent les RF/RHD**
    - Merci de transmettre les noms et les coordonnées détaillées de toute personne ou organisation qui pourrait, selon vous, fournir des informations pertinentes quant à ce questionnaire.

Nous vous remercions de l'intérêt que vous nous portez et de votre participation à cette enquête.
Nous vous prions de bien vouloir envoyer le questionnaire à
Stephen.Marko@worldheart.org.