Prevention of Rheumatic Fever and Heart Disease: Nepalese Experience

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ABSTRACT

Rheumatic heart disease (RHD) is a major public health problem in Nepal that affects young children and adolescents. Historically, many young people suffered severe valvular disease and died awaiting heart valve replacement. For some years, the Nepal Heart Foundation (NHF) advocated for a more comprehensive program to reduce the burden of RHD. In 2007, the government of Nepal announced funding for an RHD control program to be implemented by the NHF. The core focus of the program was to deliver antibiotics for the secondary prophylaxis of RHD. The NHF has developed a program of community awareness, free medication, RHD register development, health worker training, guideline development, and clinical audit. These services are being implemented with expanding geographic scope. This paper provides a narrative overview of the Nepalese experience designing, implementing, and beginning to evaluate this program. Challenges and successes relevant to register-based programs are highlighted.

Acute rheumatic fever (RF) is an immunologically mediated sequel of group A beta hemolytic streptococcal (GAS) tonsillopharyngitis [1]. The most common cardiac manifestations are valvulitis and myocarditis, which can lead to the chronic valve damage of rheumatic heart disease (RHD). RHD is estimated to affect more than 15.6 million people worldwide, cause 233,000 deaths every year, and contribute to significant morbidity in young people [2,3]. The vast majority of cases of RF and RHD occur in developing countries, including Nepal [4].

The burden of RF and RHD can be controlled through a program of primary, secondary, and tertiary interventions. RF can be prevented by treating GAS tonsillopharyngitis with antibiotics (primary prevention) or valve damage can be minimized by administration of prophylactic antibiotics (secondary prevention). Treatment of symptomatic RHD—including medical therapy and operative intervention—is considered tertiary intervention. This paper provides a narrative overview of the Nepalese experience designing, implementing, and beginning to evaluate a register-based RHD control program to deliver secondary prevention.

NEPAL

Nepal is a developing nation in South Asia with a population of 30.49 million people [5]. Rural inhabitants make up 80% of the population; life expectancy at birth is 69.1 years; and 34% of the population are aged 0 to 14 years [5,6]. Government health spending on health is about 7% of gross domestic product and more than half of the costs of health care are paid out of pocket by consumers [7]. Human resources for health are limited and concentrated in urban settings [8]. Although these challenges are considerable, there is growing momentum for enhancing a robust primary care system throughout Nepal [9].

BURDEN OF RF AND RHD

Data on the burden of RF and RHD in Nepal is limited. Most of the studies are school-based and are from the capital city, Kathmandu. The prevalence of RHD among schoolchildren of the 5 to 16 years age group is reported to be 1.0 to 1.35 per 1,000 in different studies [10–13]. Extrapolating throughout Nepal, the Nepal Heart Foundation (NHF) has made an expert estimate of prevalence of RHD at 2 per 1,000 schoolchildren. On this basis, the NHF estimates approximately 75,000 RHD patients live throughout the country [14]. The incidence of RF is estimated to be 15,000 per year [15]. RHD is among the leading causes of admission to cardiology services and cardiothoracic surgery [16].

THE NEPAL RF/RHD PREVENTION AND CONTROL PROGRAM

Historically, the government of Nepal funded heart valve replacements for low-income RHD patients. Over 300 valve replacements were provided each year, at a cost of approximately US$3,000 per operation. This tertiary approach generated lengthy waiting lists and many patients with end-stage disease died awaiting surgery. The government of Nepal became interested in developing a control program, which could decrease the morbidity and mortality in children and represent a more cost-effective strategy. Advocacy for a comprehensive approach to disease control was led by the NHF. The NHF was founded in 1988 and now has 37 district offices throughout the country [17]. The NHF is a member of the World Heart

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Federation and supports the World Heart Federation's mission "to unite members and lead the global fight against RHD through aligning around the WHO-related target of 25 percent reduction in RF/RHD mortality by 2025 in under 25 year olds" [18]. The Nepal government announced approximately US$30,000 of funding for an RHD control program in 2006 [19]. The NHF was contracted to design and implement this program in 2007.

PROGRAM DESIGN

The NHF investigated a number of models for delivering disease-specific health care while developing the national program for control of RF and RHD. In particular, decisions were required about the relative contribution of independent disease-specific activities (vertical) and integration of RHD care delivery into the broader health system (horizontal) [20]. The NHF identified that a purely vertical approach was prohibitively costly and a purely horizontal approach lacked the urgent focus needed for reducing RF/RHD morbidity and mortality. A combination (diagonal approach) was chosen in order to focus on RHD within the framework of the existing healthcare system. The RHD control program is a diagonal partnership between the government of Nepal and the NHF. As part of this partnership, the government of Nepal has included RHD in the national health program and provides the key antibiotic for the program free of charge to consumers. The NHF continues to advocate for including RHD in noncommunicable disease planning, on the recommendation of the World Heart Federation [21].

The national RF/RHD prevention and control program in Nepal has 3 objectives and 8 elements, outlined in Tables 1 and 2. Activities in some of these elements are addressed to illustrate some of the successes and challenges of implementing RHD control activities in a very low resource setting.

EPIDEMIOLOGICAL STUDIES

The NHF has developed an RF/RHD register and used this as a resource for improving local descriptive epidemiology. NHF conducted a retrospective analysis of 4 years of register data, including 6,028 patients (June 2007 to October 2011). Of these, 5,356 (88%) had been diagnosed with RHD and 672 (12%) with RF. Manifestations of RF were described as arthritis (82%), carditis (60%), Sydenham chorea (2.8%), subcutaneous nodules (1.8%), and erythema marginatum (1.1%) [22]. This is the only data available on manifestations of acute RF in Nepalese patients.

TABLE 1. Core program objectives

1. Early detection and registration of RF/RHD patients.
2. Establishment of centers for safe administration of BPG injection for secondary prophylaxis.
3. Establishment of a national strategy for RF/RHD prevention and control with development of RHD control toolkit.

BPG, benzathine penicillin G; RF, rheumatic fever; RHD, rheumatic heart disease.

TABLE 2. Elements of the program

1. Epidemiological studies.
2. Awareness activities.
3. Training of health workers.
4. Case detection (heart screening).
5. Registry of RF/RHD patients.
6. Delivery of medicines for secondary prophylaxis.
7. Surveillance system.
8. Evaluation and monitoring.

Abbreviations as in Table 1.

AWARENESS FOR RHD CONTROL

Community awareness activities are essential for a successful RHD program [23]. Health literacy at baseline in Nepal has been limited; few schoolchildren, parents, or teachers were aware that untreated streptococcal throat infection could lead to RHD [24]. The NHF has conducted a range of activities to improve awareness about RHD: putting large hoarding boards throughout the cities; mobilizing the media; including RHD materials in school curriculums; showing street dramas; distributing pamphlets, posters, and calendars [24]. A telecast of a documentary film on RHD on the national TV channel was instrumental in raising public awareness about the disease. Mobilization of celebrities in awareness campaigns was also applied with good effect. As a result of these activities, the awareness on RHD increased by 40% (from 8% to 48%) in schoolchildren and teachers of Nepal [24].

TRAINING FOR RHD CONTROL

Health care in Nepal is mainly delivered by paramedics, who are responsible for overseeing small clinics. Paramedics are responsible for delivering benzathine penicillin G (BPG) injections for secondary prevention of RF. However, many paramedics were unfamiliar with this process and unwilling to deliver intramuscular injections for prophylaxis. The major goal of paramedic training was to support paramedics and enable them to provide secondary prophylaxis at a primary care level. After completing the training, more than 90% of paramedics who had earlier refused to inject BPG agreed to do it under the guidance and supervision of the NHF. Training and support was critical for achieving the support and engagement of paramedics. Future NHF training programs are being considered for community health workers, teachers, adolescents, and mother groups. Education that encourages people to seek help for a streptococcal throat infection and treat it with a suitable antibiotic is the next step.

ECHOCARDIOGRAPHIC SCREENING OF SCHOOLCHILDREN

World Health Organization (WHO) guidelines recommend screening for RHD in high prevalence settings [25]. Screening for RHD in schoolchildren has been an important part of the RHD prevention program in Nepal. The NHF has screened more than 100,000 schoolchildren between 2007 and 2012. A 2-stage method has been used: brief clinical examination and auscultation, followed by confirmation of the suspected cases with echocardiography. NHF have just completed screening 30,000 schoolchildren in 38 government schools of the Lalitpur district in Nepal. In this district, the prevalence of RHD was found to be 1.8 per 1,000 schoolchildren of ages 5 to 16 years (NHF, unpublished data, May 2013).

REGISTERS OF RF/RHD PATIENTS

Register-based programs have been shown to improve the rates of secondary prophylaxis and decrease the prevalence of RHD [25–28]. The RHD program in Nepal maintains registers as a core component of the disease control efforts [29]. The RHD control program has enrolled hospitals and health centers at different levels, with progressive implementation from central, regional, zonal, and district areas. Gradual expansion to the periphery has made the program accessible to more and more rural people. Initially, 22 government hospitals participated in the program, but by the end of April 2013, 35 hospitals were delivering secondary prophylaxis. These hospitals maintain registers of the RF/RHD patients and deliver the BPG injections free of cost. Patients allergic to penicillin receive oral erythromycin, and patients unable to receive BPG injections receive oral penicillin V. The WHO recommendations for dose and duration of secondary prophylaxis are applied [25].

Nepal has adopted a 3-tiered system for maintaining the RF/RHD registry:

1. **Hospital register**
   This is a paper register with details of the RF/RHD patients: name; age; sex; contacts; diagnosis; clinical manifestations; echo findings; medicines delivered; dose; batch number; results of allergy test; and dates of BPG injection delivery. All participating hospitals have a separate register for RF/RHD patients receiving secondary prophylaxis. These hospitals forward the data to the national register.

2. **National (central) register**
   All the patients registered in this program and receiving penicillin nationwide are entered into the National RF/RHD register, which is maintained at the program office of the NHF. This is paper and database register.

3. **Penicillin injection card**
   A penicillin injection card is issued to all the patients receiving secondary prophylaxis. This card contains patient information, diagnosis, batch number, and expiry date of BPG injection that the patient is receiving, dates of injections given, due date, and signature of health personnel delivering the injection.

SECONDARY PROPHYLAXIS OF RHD

Secondary prophylaxis requires regular administration of a long acting antibiotic—generally BPG—to prevent recurrent GAS infections and RF in patients with a history of RF or RHD. WHO recommends 1,200,000 IU of BPG every 4 weeks to those with weight ≥30 kg in most circumstances [25]. Individuals who have an RF recurrence on this regime—or in settings where the incidence of RF is particularly high—should be considered for 3 weekly BPG injections. Three weekly regimes reflect concerns that serum drug levels may fall below a protective level before the fourth week after administration in some cases [30,31]. Given the very high burden of RF in Nepal, secondary prophylaxis with penicillin once every 3 weeks is recommended by the NHF. An alternative but less effective method is the use of daily oral penicillin V. Even with optimal patient adherence, the risk of recurrence is higher in individuals receiving oral prophylaxis than in those receiving intramuscular benzathine penicillin G [32].

The NHF recently conducted an audit of patients receiving secondary prophylaxis from the RF/RHD registers. In a period from June 2007 to February 2010 in 35 hospitals, there were 4,712 patients receiving 3 weekly injections of BPG: 2,540 (53.9%) female patients and 2,172 (46.1%) male. Diagnosis was RF in 665 (14.1%) and RHD in 4,047 (85.9%). Of those, 1,728 (36.7%) were younger than 18 years age and 2,994 (63.3%) were older than 18 years. Out of 4,712 patients, there were 286 (6.0%) defaulters who had missed more than 2 consecutive doses of BPG injections. Reasons for dropout were reported as injection phobia (4.9%), prohibitive distance (0.8%), prohibitive cost (0.2%), and other (0.3%). Compliance to secondary prophylaxis was calculated to be 89.3% (NHF, unpublished data, March 2012).

HURDLES TO SECONDARY PROPHYLAXIS

The NHF has identified a number of specific challenges in the early days of the secondary prophylaxis program implementation.

Reluctance to administer BPG

The predominant challenge of the program has been the reluctance of paramedics to administer BPG for fear of anaphylaxis. Paramedics were particularly concerned about community reaction following adverse drug reactions; anecdotal reports suggested some health workers had suffered physical assault, claims for financial compensation, and jail sentences following deaths. Overcoming these concerns was the most difficult part of the program. Paramedics involved in the RHD prevention program were provided with training on penicillin skin testing and safe penicillin delivery, which increased their knowledge and

confidence. The NHF developed recommendations on penicillin skin testing (Table 3) and safe penicillin injection delivery (Table 4). This was of great practical use to the paramedics. It also became apparent that paramedics were also struggling to differentiate between anaphylactic reactions and vasovagal reactions. Providing training about the difference of these conditions and management approach was considered very helpful (Table 5).

Pain of injection

Another major issue that affected the compliance to penicillin injection was the injection pain. Nearly 5% of patients on secondary prophylaxis stopped taking BPG injections due to pain (NHF, unpublished data). The NHF developed recommendations for pain reduction (Table 6).

Concerns about BPG quality

BPG appears on the WHO essential medicines list and on the Nepal national list [33,34]. Supplies for the national RHD control program are provided by the government of Nepal. There are no local manufacturers and all BPG supplies are imported from India. Three brands of BPG are available in Nepal: Penidure LA (Wyeth, Madison, New Jersey); Pencom (Alembic, Gujarat, India); and Longacillin (Hindusthan Antibiotic, Pimpri, India). Anecdotal concerns about quality have been reported for all manufacturers. Of the 3 options, paramedics were most satisfied with Penidure LA, because they felt it was easy to reconstitute, had less clogging, and fewer allergic reactions. More quality concerns were reported during the period when Wyeth discontinued manufacturing Penidure LA and Pencom was substituted [35]. This appeared to be associated with more minor allergic reactions and blocking of the needle during injection [35]. The association between brand and frequency of adverse drug reaction is concerning for the manufacturing process of BPG. A safe, reliable, and high-quality supply of BPG is critical for the continued confidence of patients, paramedics, and the community. Research to support this goal is urgently needed.

TABLE 3. NHF recommendations on penicillin skin testing

1. Perform penicillin allergy skin test in the following situations:
   a. Before first penicillin injection.
   b. With change in batch number.
   c. With change in brand name.
2. Steps for penicillin skin test:
   a. Use 23-G needle.
   b. Clean the middle of forearm with spirit swab.
   c. Inject 0.1 ml of diluted BPG intradermal on the forearm.
   d. Wait for 15 to 20 min.
   e. Look for local signs and symptoms of allergy (e.g., redness, inflammation, itching, erythema, swelling, blistering).
   f. If any of the local signs are present and if the swelling is >10 mm, the test is considered positive.

BPG, benzathine penicillin G.

TABLE 4. NHF recommendations on safe benzathine penicillin injection delivery

1. Take consent from the patient or his/her relative before the first penicillin injection, with change in batch number and brand.
2. Record the brand name and batch number of the BPG.
3. Reconstitute the BPG powder with 3.5 ml of sterile distilled water.
4. Use 2 separate needles: 1 for pricking the vial and the other for injecting into the patient.
5. Use 10 ml syringe and 21-G needle for deep intramuscular injection.
6. Patient should lie down on trolley or bed on abdomen with head resting on pillow in a comfortable and relaxed position. In hospital settings, bed should be portable to rush the patient to the intensive care unit in case of emergency.
7. Inject BPG deep intramuscularly in the upper outer quadrant of the buttock.
8. Stay prepared for the treatment of possible anaphylaxis. The following medicines and instruments should be ready for emergency use:
   a. Adrenaline injection: l ampoule pre-loaded into the syringe.
   b. Atropine injection.
   c. Dexamethasone or antihistamine injection.
   d. Intubation set.
   e. Suction machine.

STRATEGIES FOR ADDRESSING BARRIERS

Penicillin injection delivery rooms

One of the objectives of the NFH program was to establish centers for safe delivery of injection BPG. Hospitals with large numbers of patients receiving secondary prophylaxis

TABLE 5. Signs, symptoms, and treatment of anaphylactic reaction and vasovagal reaction

Anaphylactic reaction	a. Low blood pressure b. Tachycardia c. Sweating d. Dizziness e. Dyspnea f. Syncope	If not treated immediately, it may lead to death. Treat anaphylaxis with adrenaline injection. Repeat injection after 2 to 3 min if necessary.
Vasovagal reaction	a. Low blood pressure b. Bradycardia c. Syncope	Treat vasovagal reaction with atropine injection.

TABLE 6. NHF recommendations for minimizing pain of BPG injections

1. Shake the powdered BPG vial after adding 3.5 ml of distilled water until the powder dissolves and an opaque, viscous, suspension is formed with a final volume of ~5.0 ml. The penicillin crystal can easily pass through a 21- to 23-G needle. If the crystals are attached to each other, they form large particles that get clogged inside the needle. To avoid this situation, reconstitution of the powder with 3.5 ml of distilled water rather than 3 ml is advised.
2. Use 21-G taper cut needle for intramuscular injection.
3. Properly select the injection site and apply finger pressure for 10 s.
4. Stretch the skin at the injection site with the thumb and index finger.
5. Inject the liquid medicine at 90° angle with taper cut needle tip facing downward in vertical plane, which will cause minimum nerve end damage.
6. Never double prick with the same needle.
7. Push the syringe slowly, applying sufficient pressure in a gradually increasing manner to allow the crystals in the viscous medicine to flow smoothly. It may take up to 1 min to push 5.0 ml of solution.
8. Distract the attention of the patient away from the injection.
9. Maintain the injection delivery room temperature below 30°C. In hot air and moist skin, the injections are more painful.
10. Apply ice pack in case of pain immediately after injection.
11. Mix 0.5 to 1.0 ml of 1% lignocaine with the BPG solution for reducing pain if all other techniques fail.

BPG, benzathine penicillin G.

were advised to have a separate room dedicated only for penicillin injection delivery. Hospitals with smaller numbers of RHD patients could use the same room for injections and dressings. The RHD control program had to put forth tremendous efforts to establish penicillin injection delivery rooms for safe and smooth injection administration and managing anxiety for paramedics and for patients. Recommendations were developed to standardize the process, maximize safety, and minimize pain. Staff were trained to recognize and treat adverse drug reactions. Rooms were equipped with an emergency care kit box containing medication and equipment to manage anaphylaxis. Recommendations for a model penicillin injection delivery room were developed to include patient trolley, oxygen cylinder, IV stand, suction machine, intubation set, and emergency care kit with necessary medicines.

Penicillin allergy and penicillin skin testing

The incidences of allergic and anaphylactic reactions to BPG injections are reported to be 3.2% and 0.2%, respectively, and fatal reactions are rare [36,37]. The risk of a serious reaction is reduced in children under the age of 12 years and the duration of prophylaxis does not appear to increase the risk of an allergic reaction [36]. The long-term benefits of BPG therapy in preventing RF far outweigh the risk of a serious allergic reaction [25,36].

The NHF audited adverse drug reactions to BPG over 77,300 injections delivered to 4,712 RHD patients for secondary prophylaxis during the period from June 2007 to February 2010 [35]. Sixty-five patients (1.4%) had an adverse drug reaction: 5 were anaphylactic reactions, an incidence of 0.1% (0.7/10,000 injections); 60 were minor reactions, an incidence of 1.3%. Ten patients had minor allergy while receiving new batch of benzathine penicillin (incidence of 0.2%), and 18 patients had minor allergy with new brand of injection BPG (change from Penidure LA to Pencom), an incidence of 0.4%. There were 8 vasovagal reactions (0.16%). No deaths were reported [35].

RHD patients, because of poor cardiac function, may be more susceptible to vasovagal reactions [36]. All health workers dispensing secondary prophylaxis need proper training in performing penicillin skin test and delivery of intramuscular injection. Training the health workers who deliver secondary prophylaxis helps improve survival from anaphylaxis. Mortality from anaphylaxis significantly decreased after the launch of RHD control program in Nepal.

There were no standardized guidelines about indications for skin testing in Nepal prior to the advent of the national RF/RHD control program. Some centers performed skin test before each penicillin injection, whereas others limited the test to the first penicillin injection only. The NHF has published recommendations on penicillin skin testing [35] (Table 3). In Nepal, skin testing for allergy is recommended in all patients who are to receive penicillin injections.

NEXT STEPS FOR RHD CONTROL IN NEPAL

Pilot project on primary prevention of acute RF

The NHF is collaborating with the District Public Health Office, the government of Nepal, and Rotary International district 3292 to initiate a pilot project on primary prevention of RF in the Lalitpur district. This region has a population of 400,000 of which 40% are children of 5 to 16 years of age. The program was launched in July 2013 with 42 primary health centers participating and paramedic training completed. Tonsillitis and pharyngitis registers will be maintained. Developing a protocol for diagnosing GAS has been challenging; the NHF has decided to treat children with clinical signs and symptoms, aiming for a financially viable "treat all" approach [38]. One group of patients will receive amoxicillin 3× daily for 7 days and the other group will receive azithromycin once for 5 days for sore throat.

CONCLUSIONS

The Nepalese model of a diagonal RF/RHD control program illustrates the feasibility of care delivery in very low-resource settings. The commitment from the government

and the community involvement support program sustainability. Developing an RF/RHD registry, training paramedics, publishing recommendations and guidelines, and securing a supply of BPG are significant achievements and advances in practice. The extensive involvement and coordination by the NHF has been critical for success. Improving the quality and safety of BPG supplies and piloting primary prophylaxis are the next steps for disease control. Comprehensive program evaluation is an ongoing requirement but there are early signs of enormously valuable progress.

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