Since the 1950's intramuscular Benzathine Penicillin G (BPG) has been the recommended treatment choice for rheumatic fever (RF). Rheumatic fever is thought to be linked to socioeconomic status, poor nutrition and crowded living condition. Even though RF has declined in New Zealand since the 1970's, New Zealand rates of rheumatic fever remain high particularly among Pacific Island and NZ Maori communities (New Zealand Health Strategy, 2003). This assignment will look at pre-disposing factors, and why this disease is prevalent in developing countries. The pathophysiology of rheumatic fever; biological action of Benthazine Penicillin G as an effective treatment, and its effect on recurrent rates of rheumatic fever will be discussed. Three studies that support its use will be discussed and analyzed.

Several Studies have shown environmental factors to play a role in spreading the disease (McNicholas, et al, 2000: steer et al, 2002). Overcrowding enhances transmission as oral or respiratory secretions transmit the organism by direct contact. Some individuals can be carriers even after pharyngitis symptoms are resolved, and continue the cycle of infecting others (Chin, 2003). Socio-economic status is another factor in the incidence of rheumatic fever where prevalence of rheumatic heart disease increased with decreasing socio-economic status (Steer et al, 2002).

Urbanization has also lead to crowded inner city living and higher incidence of rheumatic heart disease. Over crowding seemed to be the predominant factor where there was a high rate of rheumatic heart disease (Steer et al, 2002) regardless of socio-economic factors (McNicholas et al,2000).

Poor nutrition in early childhood was identified in some studies as increasing susceptibility to acute rheumatic fever (Steer et al, 2002). Lack of access to medical care is another factor in perpetuating the disease (Lenon, 2004). According to Steer et al, (2002) suggest that increased access to medical care

with the introduction of primary prophylaxis programmes to treat pharyngitis, and prevent rheumatic heart disease sequelae decreases rheumatic fever incidence.

In response to the 1978 World Health Oragnization promotion of disease registered to coordinate prevention of acute rheumatic fever, New Zealand began register based prevention programmes in the mid 1970's to monitor and manage acute rheumatic fever (ARHF) case in the community. During 1995-2000, the annual rate of notified acute rheumatic fever was 2.8 per 100,000, a 12% increase from 1990-1995. period. While register based programmes may be better for monitoring ad management of acute rheumatic fever rates compared to general practitioners or hospitals, there is a need for uniformity between registers and protection of collected data from health sector restructuring (Thornley, McNcholas, Baker,& Lennon, 2001).

The Pacific region continues to have higher rates of rheumatic heart disease as seen in New Zealand's Maori and Pacific Island children. There is a need for well-designed studies and more reliable data to analyzed the trend. NZ Maori and Pacific Island people made up just over 20% of the total NZ population in 1996 and represented 74.6% of people living in crowded homes (McNicholas, Lennon, Crampton, Howden_Chapman, 2000). Baker, Goodyear, & Howden-Chapman () found from the 1998-2002 NZ census that low-incomes families with children, households containing NZ Maori and Pacific Island people and recent migrants were more likely to experience crowding. Auckland leads as the highest affected region for crowding and acute rheumatic fever rates I children up to 14 years old.

In New Zealand during the early 1980's rheumatic heart disease in the Hamilton district was 6.5 percent in 1000 in Maori and 0.9 per 1000 in non-Maori (Talbot,1984). Baker Chakraborty (1996) found that during the 1970-1995 period, in New Zealand , rheumatic fever admission had declined

markedly, and have remained stable since 1984. According to Carapetis, Curries& Mathews(2000) high rates in Pacific populations are due to Streptococcal exposure and treatment rather than differences in their genetic susceptibility. The genetic link remains unclear.

Rheumatic fever is a multi system inflammatory disease that occurs as a delayed sequel to pharyngeal infection by group A beta-hemolytic streptococci (GABHS) or Streptococcus pyogenes. Not all group A strains (GAS) are rheumatogenic. However " throat strain" can colonize the throat rapidly and stubbornly (Rullan& Leonard, 2001). Streptococccus pyogenes owes its major success as a pathogen to its ability to colonize and rapidly multiply and spread in its host while evading phagocytosis and confusing the immune system (Todar, 2002).

Diagnosis of acute rheumatic fever is by throat swabs and throat cultures and use of the Jones criteria guidelines (Stollerman, 2003). If a streptococcal throat infection is undetected or not treated adequately, this can progress in susceptible individuals to rheumatic heart disease where the valves of the heart become damaged or scarred resulting in inadequate functioning of the heart (Rush Univresity Medical Center website, 2005).

This inflammatory disease affects the connective tissues of the heart, joints, skin and central nervous system. Children aged 5-15 years and those with frequent streptococcal throat infections are more susceptible to developing rheumatic fever. Symptoms start about one to five weeks after infection with streptococcus bacteria. Symptoms range from joint inflammation, especially the larger ankle and knee joints, and can be migratory; change in neuromuscular movements eg: chorea; anorexia; rash on trunk, limbs; fever; and fatigue (Lennon, 2004).

Streptococcus pyogenes a genus of Group A streptococci usually reside in the respiratory tract (Todar,2002). They are gram-positive cocci, and penicillin G benzathine is effective for this as it prevents with cell wall replication of susceptible in streptococcus pyogenes, causing the cell walls to swell and burst from osmotic pressure, destroy the cell (Skidmore-Roth, 2005).

Group A streptococci strain are highly sensitive to the action of penicillin. Intramuscular Benzathine Penicillin G remains the drug of choice in preventing rheumatic fever and recurrences, due to its proven effectiveness, low cost and narrow antibacterial spectrum (Stollerman,2003). According to Manyemba & Bongani (2003), two or three weekly intramuscular penicillin injections were more effective than four weekly injections, in reducing the recurrence rates of rheumatic fever and associated streptococcal throat infections. Similar studies carried out by Kassem et al., (1996) and Lue et al., (1996) have shown similar results.

Continuous Benzathine Penicillin prophylaxis prevents recurrent attacks, and the risk of rheumatic fever rises by 25-275% with each subsequent recurrence of a streptococcal throat infection. New Zealand prophylaxis recommendation is for 10 years after presenting episode of acute rheumatic fever or until 21 years of age, whichever is longer (Lennon, 2004).
The following selected three key studies will be assessing the effectiveness of intramuscular Benzathine Penicillin G, and providing support for its use against rheumatic fever infections and in reducing recurrence rates.

Kassem et al from Alexandria, Egypt (1996) compared the effectiveness of biweekly schedule of 1.2 million units of intramuscular Benzathine PenicillinG and four weekly schedules in the prevention of upper respiratory Group A beta- hemolytic streptococcal infections and rheumatic fever recurrences. The study was over 2 years and involved 360 subjects in a

Randomized Clinical Trial (Kassem, Zaher, Shleib, El-Kholy, Madhour & Kaplan, 1996).

In this study, 360 subjects with documented rheumatic fever were followed up over 2 years. Their age ranged from 4-20 years (mean age 11.4yrs+/- 4), ethnicity was Egyptian.

Group A beta-hemolytic streptococcal infection rate showed no difference between biweekly and four weekly schedule, with infection rates of 0.2% and 0.3% respectively, with a p value> 0.005. However, rheumatic fever recurrence rate in subjects on the biweekly schedule was half that in subjects on the four weekly schedule. Non-compliance resulted a four-fold increase in rheumatic fever recurrence rate. There was no significant difference in compliance between subjects of both study groups.

The p value> 0.5 indicated no significant difference in group A beta-hemolytic streptococcal infection rates, between the biweekly and four weekly prophylaxis schedule. However the significant difference in rheumatic fever recurrence rate, of the subjects on the biweekly schedule and those on the four weekly schedule indicated that the biweekly schedule reduced the sequelae of upper respiratory group A beta-hemolytic streptococcal infection. The finding that rheumatic fever recurrence rate increased four-fold with non-compliance was consistent with the results of the study that intramuscular Benzathine Penicillin G injections reduce rheumatic fever recurrences. It is important to note that the authors have not elaborated on what criteria determined compliance, or the non-compliance figures for both groups, however it is assumed that non-compliance meant that the subjects did not complete the prophylaxis regime. Moreover, increased costs associated with the increased frequency of injections and compliance could be an issue with the pain and discomfort related to intramuscular Benzathine Penicillin G injections, with the biweekly schedule versus the four-weekly regime.

The second key study was aimed at finding out the effects of three versus four-weekly intramuscular Benzathine Penicillin G on streptococcal infection and recurrences of rheumatic fever. The study was conducted by Lue et al 91996), carried out in Taipei, Taiwan over a 12-year period in a Randomized Controlled Trial (RCT) and involved 249 subjects with rheumatic fever. Ethnicity of subjects was Taiwanese (Lue, Wu, Wang,Wu & Wu,1996).

Streptococcal infections and rheumatic fever recurrences were greater in the four-week (12.7 per 100 patient-years) versus three-week (7.5 per 100 patient-years) programme with a p value<0.01 indicating a significant difference between the two groups. Lower rates of rheumatic fever recurrences were observed in the three weekly programme.

Recurrence rates per streptococcal infection showed no statistical difference (p value>0.3) between the three (13.6%) and four-weekly (15.5%) programmes. However, the rate of rheumatic fever recurrences as a result of prophylaxis failure was five times greater in the four-weekly (9.7%) than the three-weekly (3.0%) programme (p value=.015). Patient compliance was classified as complete if only one injection was missed in a year; partial, if two to three were missed; and drop out if four or more were missed in a year.

Lue et al (1996) found that three week prophylaxis treatment was more effective given that heart murmurs were significantly lessened in the three weekly (46%) versus four weekly (66%) programme, showing an increased risk of rheumatic fever recurrences in those receiving prophylaxis every four weeks.

It is surprising to find that in this study non-compliance was higher in the four-week programme. This can possibly be attributed to long intervals between rheumatic fever attacks (2-11 years) and possibly subject complacency with

prophylaxis treatment. Lue et al (1996) found that three weekly prophylaxis treatments reduced streptococcal infections and rheumatic fever recurrences significantly in comparison to the four weekly one. This finding is similar to that of Kassem et al (1996) that the increased frequency of intramuscular Benzathine Penicillin G injections had a positive effect on reducing streptococcal infections and rheumatic fever recurrence rates.

The third study investigated plasma penicillin concentrations after increased doses of Benzathine Penicillin G for prevention of secondary rheumatic fever. This study was carried out by Currie, Burt & Kaplan (1994). The subjects were rural aboriginal communities in Arnhemland, Northern Territory, Australia with rheumatic fever. The study was over a 2-month period in a Randomized Clinical Trial (RCT) involving 25 subjects (15 are female), aged 16 to 49 years (mean, 29 years) and weight 40 to 90 kg
(mean 57kg). Written informed consent was obtained. Three different doses of Benzathine Penicillin G (1.2mu, 1.8mu, and 2.4mu) were given monthly.

The result showed that mean levels of penicillin in plasma for subjects with level>25ng/ml were not significantly different between the three dosage groups. Despite higher proportion of patients with plasma penicillin levels>25ng/ml, with higher than 1.2mu traditional Benzathine Penicillin G doses, figures did not reach statistical significance> three-week penicillin levels in 8 of 16 subjects showed inadequate levels (51.8ng/ml). This study provided some preliminary evidence that Benzathine Penicillin G doses greater than 1.2 mega units may prolong the duration of penicillin plasma levels during treatment against recurrent rheumatic fever.

Limitations to the success rate of increased doses of Benzathine Penicillin G in the secondary prevention of secondary rheumatic fever might be attributed to the possibility that some injections may have been given into adipose tissue rather than muscle, quality and storage of Benzathine Penicillin G may also

have affected the results. A small sample size may have also affected figures not reaching statistical significance. There are also the practical difficulties associated with implementing such studies in rural outback communities, involving a lot of travel, associated costs, time and obtaining larger sample numbers.

In conclusion, rheumatic fever still prevail in some countries like New Zealand and this is thought to be linked to environmental factors such as socioeconomic status, overcrowding, poor nutrition, lack of access to appropriate medical care. Register based prevention programmes were set up to monitor and manage rheumatic fever in the community, however there needs to be some uniformity between registers and protection of data for continuity purposes. Intramuscular Benzyl Penicillin G (BPG) remains the drug of choice in reducing rheumatic fever and its recurrence rates. This is largely due to the fact that penicillin has proven its effectiveness, narrow antibacterial spectrum and is obtainable at low cost. The three selected key studies further support the effectiveness of penicillin through is findings that it reduces rheumatic fever recurrence rates with increased frequency of injections, and that larger doses of Benzyl Penicillin G may play a role in prolonging the effectiveness of penicillin. However, with increased frequency of injections, compared to the traditional monthly regime, and the possibility of administering larger Benzyl Penicillin G doses, associates costs need to be considered.

Baker, M., chakraborty, M. (1996). Rheumatic fever in New Zealand in the 1990's: still a cause for concern. *The New Zealand Public Health Report*, 3 (3), 17-19.

Baker, M., Goodyear, R. Howden-Chapman, P. (n.d). Chapter5: *Household Crowding and Health*. Retrieved March 18, 2006 http://www.stats.govt.nz/NR?rdonlyres/96EA48CC-FF7d-4540-A290-D866F6211B0E/0/Chapter5.pdf

Carapetis, J. R., Currie, B. J., Mathews, J. D. (2000). Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? *Epidemiology ad Infection*, 124 (2) 239-44.

Chin, T. K. (2003). Rheumatic fever. Retrieved March 7, 2006, from http://www.emedicine.com/PED?topic2006.htm

Currie, B. J., Burt, T., Kaplan, E. L. (1994). Penicillin concentrations after increased doses of Benzathine Penicillin G for prevention of secondary rheumatic fever. *Antimicrobial Agents and Chemotherapy*, 38 (5), 1203-1204.

Kassem, A. S., Zaher, S. R., Shleib, H. A., El-Kholy, A. G., Madkour, A. A., Kaplan, E. L. (1996). Rheumatic fever prophylaxis using benzathine penicillin G (BPG): Two-week versus four-week regimens: Comparison of two brands of BPG. *Paediatrics*, 97, 992-995.

Lennon, D. (2004). Acute rheumatic fever in children: Recognition and treatment. *Paediatric Drugs*, 6 (6), 363-373.

Lue, H., Wu, M., Wang, J., Wu, F., Wu,Y. (1996). Three-week versus four-week administration of benzathine penicillin G: Effects on incidence of streptococcal infections and recurrences of rheumatic fever. *Paediatrics*, 97, 984-988.

McNicholas, A., Lennon, D., Crampton, P., Howden-Chapman, P. (2000). Overcrowding and infectious diseases-when will we learn the lesions of our past? *The New Zealand Medical Journal*, 113 (1121), 453-454.

Manyemba, J., Mayosi, B. (2003). Intramuscular penicillin is more effecive than oral penicillin in secondary prevention of rheumatic fever- a systematic review. *South African Medical Journal*, 93 (3), 212-8.

New Zealand Health Strategy (2003) DHB Toolkit: Cardiovascular disease, Edition 2. retrived March 18, 2006, from http://www.newhealth.govt.nz/toolkits/cardiovascular/cardiovascular.pdf

Rheumatic heart disease (2005) Rush University Medical Centre. Retrieved April 12, 2006, from http://www.rush.edu/rumc/page-P06595.html.

Rullan, E., Leonard, S. (2001). Rheumatic Fever. *Current Rheumatology Reports*,3, 445-452.

Skidmore-Roth, L. (2005). Mosby's Nursing drug Reference. St Louis, Missouri: Mosby Inc.

Steer, A. C., Carapetis, J. R., Nolan, T. M., Shann, F. (2002). Systematic review of rheumatic heart disease prevalence in children in developing countries: The role of environmental factors. *Journal Paediatrics and Child Health*, 38, 229-234.

Stollerman, G. H. (2003). Current Concepts of Rheumatic Fever. *The internet Journal of cardiology*, 2 (1). Retrieved March 23, 2006 http://www.arabmedmag.com/issue-28-02-2005/cardiology/main04.htm

Talbot, R. G. (1984) Rheumatic fever and rheumatic heart disease in the Hamilton Health district: I. An epidemiological survey. *New Zealand Medical Journal*, 97, 634-7.

Thornley, C., McNicholas, A., Baker, M., Lennon, D. (2001). Rheumatic fever registers in New Zealand. *New Zealand Public Health Report*, 8 (6), 41-44.