A Pilot Study for the Primary Prevention of Rheumatic Fever in Kosrae, Federated States of Micronesia

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Abstract

Rheumatic fever (RF) and its sequel, Rheumatic Heart Disease (RHD) is a disease of significant medical and public health concern in the Federated States of Micronesia. In this preliminary study the feasibility of a rheumatic heart disease primary prevention strategy was examined.

Throat swabs were taken from 667 school-aged children and tested for group A streptococci (GAS) by a rapid antigen detection test (RADT): a subset was also tested by conventional culture, so as to compare the RADT with the reference (conventional culture) test. GAS was detected in 12.4% of the children tested by either rapid antigen test or conventional culture; for RADT alone the detection rate was 11.5% and for culture alone the detection rate was 9.4%. Detection rate of GAS was analyzed in symptomatic and asymptomatic subgroups. The subgroups were compared using Fisher's exact method.

The identification of children with GAS allows for their further examination and treatment so that the prevalence of GAS in this vulnerable population, currently with an annual incidence of rheumatic fever of 50-134/100,000, may be reduced.

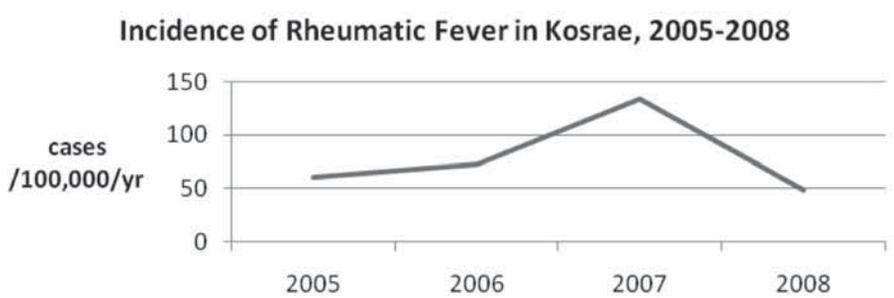
The routine testing of school-aged children appears to be possible with current resources in Kosrae and can be a cost-effective public health measure.

Introduction

It has been estimated that nearly 16 million people suffer from rheumatic heart disease (RHD) worldwide and more than 200,000 deaths occur annually due to the disease and its sequelae[1]. The incidence of RHD is highest in developing countries and for Oceania, which includes the Federated States of Micronesia; RHD remains a leading cause of cardiac related deaths[2]. The disease has been associated with overcrowding and lower socio-economic status. However, outbreaks such as that which has recently occurred in Salt Lake City in the United States from 1985 to 2002[3] have documented that RHD disease also remains an important health problem in middle class populations with ready access to medical care in developed as well.

FSM has a relatively high burden of disease for Rheumatic fever. The annual incidence of rheumatic fever in Kosrae, the eastern most state of the FSM, has ranged from 50-134/100,000 population (Kosrae RF Register). It should be noted that while every attempt is made to diagnose according to Jones criteria this was not always possible.

Figure 1: Incidence of RF in Kosrae, 2005-2008



Rheumatic fever occurs in approximately 0.3-3.0% of patients who have pharyngitis due to group A streptococcal infection (GAS)[4]. Thus primary prevention strategies rely on the identification and treatment of pharyngitis caused by group A streptococcus. An issue with this prevention strategy is that streptococcal infections may not be clinically apparent or mild and thus patients do not seek medical care[5].

Prevention of streptococcal infections and their sequelae via vaccination against group A beta hemolytic streptococci remains unavailable at the present time despite considerable effort being put into this endeavor[6]. Therefore, medical and public health approaches to control RF will have to depend on appropriate diagnosis and adequate antibiotic therapy of streptococcal pharyngitis. Because of this we have initiated a trial program in Kosrae, where cardiac sequelae of RF are important problems as indicated by relatively high rates of referral of patients to a tertiary referral center in 1998 - 2006[2].

Patients

Our aim in this initial phase of a rheumatic fever prevention program was to identify and treat all children identified as harboring group A streptococci in their upper respiratory tract, by performing throat swabs on all children in the age group 5 to 15 years regardless of symptoms. This approach has been shown to reduce

the incidence of streptococcal pharyngitis in school children[7]. In this study pyoderma was not cultured. Based on school registers it was estimated that approximately 1,000 children were included in this target group.

Methods and Materials

Throat swabs were taken from 667 children, who presented to the community centers with parental consent, from September 14-18, 2009. The swabs were tested for group A streptococci by a rapid antigen detection test kit (RT) following the manufacturer's printed instructions (Quidel Quick Vue Dipstick Strep A test, Quidel Corporation, San Diego, CA). Dual swabs were collected from the first 40 children presenting to the clinic on days one, two and three of the collection period. One swab was tested by the rapid test method; the second was tested by standard culture methods. Culture was performed on swabs from 117 patients. This represents 17% of the study population. There was no significant difference in age distribution or symptoms for the group tested by culture, compared to the group tested by RADT. Data not shown.

In the culture procedure, throat swabs were plated onto tryptic soy agar with 5% sheep blood and incubated in CO_2 for 18-24hours at 35-37°C. Colonies showing beta hemolysis were subcultured and a bacitracin disc, 0.04U (Taxo A) was placed at the junction of the primary and secondary streaks. Presumptive group A streptococci were reported for beta hemolytic colonies with typical colony characteristics that were sensitive to bacitracin.

Results

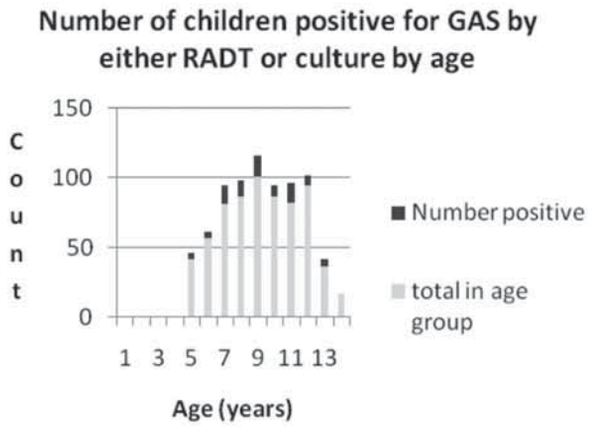
Group A: streptococci were found in throat swabs from 83 of 667 children (12.4%) by either rapid antigen detection test or culture. For RADT alone, GAS was found in 77/667 (11.5%), and for culture alone the detection rate was 11/117 (9.4%).

Most of the children who tested positive for group A: streptococci were asymptomatic, or had other respiratory symptoms other than pharyngitis.

Fifteen children had sore throat; of these 2 tested positive for group A streptococci. One child tested positive by RT and did not have a culture performed; the second child was negative by RT and positive by culture.

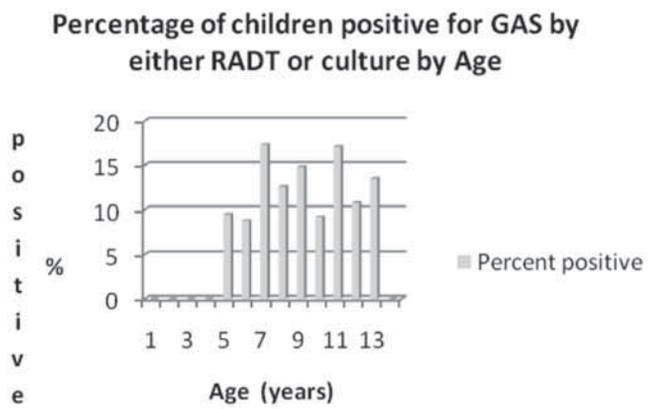
Two hundred and forty six children had cough, of these 24 tested positive for GAS by RADT (9.7%). Of the children with cough, 38 were tested for GAS by culture. Of these 38 children, 9 were positive for GAS (18.4%). One hundred and twenty eight children had runny nose, of these 15 (15/128, 11.7%) tested positive for GAS by RT. Of the children with runny nose only three were tested for GAS by culture. Two out of three tested positive for GAS. There was no correlation between these respiratory symptoms and detection rate of GAS by Fisher's exact method.

Figure 2: Number of children positive for GAS by either RT or culture by age.



Nota bene: A meaningful comparison of culture versus RT could not be made for each age group, as the number of children in each sub-group was too small.

Figure 3: Percentage of children positive for GAS by either RT or culture by age



A comparison was made with data from a pilot study carried out in January 2009 (data not published). In our January pilot study 103 children were tested for carriage of group A; streptococci from throat swabs by culture. Carriage of group A streptococci was found in 11 (10.7%) of the children tested. From this original cohort, 39 children were retested in the September survey. Four children that were positive for group A streptococci in January, were retested in September and found to be negative for GAS. These four children had not received antibiotics. Of the 35 children who tested negative for GAS in January, 6/35 (17%) were demonstrated to harbor GAS in their upper respiratory tract by either RADT or culture in September.

Comparison of Rapid Antigen Detection Test with culture

The sensitivity and specificity of the rapid test kit was compared to the culture method. The comparison data is summarized in the table below.

	Culture +	Culture -	Total
Rapid Test +	5	9	14
Rapid Test -	6	97	103
Total	**11**	**106**	**117**

The sensitivity of the rapid test was only 45.4% when tested against our culture method. (See discussion). The specificity of the rapid test was 91.5% when compared to our culture method.

Discussion

Our finding of 12.4% of tested children in Kosrae with GAS in their upper respiratory tract is somewhat lower than that of other studies. Other studies have reported that carriage rate in asymptomatic children reaches 15-20%, while the rate in adults is generally lower[8]; however, these studies were not performed on populations from tropical countries. Why our carriage rate is slightly lower is unclear, but it is consistent with our early pilot study, where a carriage rate of 10.7% was found. The rates amongst various age groups in our study ranged from 8.8% to 17.3%. There were too few cases in each group, however, to determine whether these differences were significant.

The findings from the 39 children who were tested in January and September suggest that a primary prevention strategy must be on-going. Some children had spontaneous clearing of bacteria, while others were found to newly harbor GAS. Long-acting penicillin is effective in eliminating GAS, but children may become re-infected, and thus screening for the presence of GAS in throat cultures should be carried out periodically.

Our capacity in FSM is not sufficient to be able to identify particular strains of GAS, and thus we cannot tell if children were re-infected with the same strain or had a new infection with a different strain, nor can we comment about the epidemiology of strains in this population.

Rationale and Strategy

There are two broad strategies for preventing RHD. **Primary prevention** is defined as adequate antibiotic therapy of group A streptococcal upper respiratory tract infections to prevent an initial attack of acute rheumatic fever. The antibiotic therapy is generally only given when there is streptococcal infection; *it is intermittent*. **Secondary prevention** involves the continuous administration of an antibiotic, most often penicillin. If the individual is allergic to penicillin, alternate agents such as a macrolide may be substituted. Secondary prophylaxis is for those individuals to individuals who have experienced a previous episode of rheumatic fever or have well-documented rheumatic heart disease in order to prevent recurrence[9].

Primary prevention strategies rely on individuals with upper respiratory infection seeking health care. GAS pharyngitis may be mild or asymptomatic, and therefore in many instances there will be no opportunity for health workers to be aware of and confirm GAS upper respiratory tract infection.

Our strategy in FSM varies from standard primary prevention strategies. Our strategy is based on regular systematic screening of all children, not just those with pharyngitis, in the most susceptible age group (5-14 years). All individuals found to be infected with or carrying GAS will be given antibiotic therapy: oral penicillin or, preferably, intramuscular benzathine penicillin G. Erythromycin will be used for those individuals allergic to penicillin. Our strategy can not differentiate between carriers and those with asymptomatic infection, nor does it provide information on the patient's immunological response which is important for documentation of bona fide GAS infection[10], however, we will attempt to determine the effect of this program on the incidence of rheumatic fever in Kosrae.

All identified children are further examined for signs and symptoms of RF and RHD.

Safety of Primary Prevention

As in all public health strategies the risk benefit of the intervention must be considered. There is a very small possibility of anaphylactic reaction from the penicillin injection[11]; also with the widespread use of antibiotics there is also the possibility of bacterial resistance.

The incidence of adverse advents to chemoprophylaxis for RF is low. An incidence of 3.2% for minor allergic reactions and 0.2% for anaphylactic reactions has been reported in studies of secondary prophylaxis with penicillin[11]. The reported anaphylaxis was not in children, but in adults with advanced rheumatic heart disease. The risk for children is even smaller than the low numbers in adults.

Evaluation of Testing Strategies

Rapid antigen detection test kits have several advantages over traditional culture methods for GAS. The test employed in this study took about 10 minutes to complete and was easily performed in the community halls where the screening was done. By contrast our culture method took up to 48 hours for results to be available.

However, our analysis of the sensitivity of the rapid test method, when compared to the culture method, was disappointing. The comparison of the rapid test with conventional culture in this study proved to be different from results reported in the Quick Vue Product Insert (Quidel 1053405 10/08), i.e., that there were no statistical differences between standard culture and Quick Vue test: with a reported sensitivity of 92% and a specificity of 98%. However, this has also been reported using other rapid antigen detection tests and comparing them to classic culture techniques.

There are possible explanations for the discrepancy between the package insert and our findings: less than vigorous swabbing can reduce the amount of detectable antigen to detect (sampling error), and thus if substandard specimens are collected the available antigen may be below the level of detection of the RT. This has been noted previously in studies of rapid tests. When there are small numbers of organisms on the swab, it is more likely that there can be a false negative. A second possibility is that the majority of our study population did not have pharyngitis, while the Quidel study population all had pharyngitis. The further investigation of this discrepancy between rapid antigen detection test and culture will guide the testing strategy in subsequent population screenings and in decisions about which of the several rapid tests are selected for use.

The American Academy of Pediatrics recommends that all negative rapid diagnostic tests for *Streptococcus pyogenes* (i.e., GAS) be backed up by culture[12]. This recommendation confirms the importance of back up culture methods in confirming the presence of GAS.

Feasibility of Primary Prevention Strategy

There are many expressed concerns about primary prevention strategies, especially in developing countries. Chief among these is the ability to promptly and accurately diagnose GAS. Diagnosing GAS pharyngitis clinically is challenging and according to the American Academy of Pediatrics reliable clinical differentiation of viral and S.pyogenes pharyngitis can be difficult. Sore throat in children and adults is most often of viral origin; with about 10-20% of cases caused by streptococci[8]. Therefore laboratory diagnosis is important. While laboratory capacity in developing countries like the Federated States of Micronesia is limited, this may be the only option for diagnosis and therefore prevention, given that vaccines against GAS are currently unavailable and may remain unavailable for years to come.

In our strategy, we are screening all children in the susceptible age group irrespective of clinical signs and symptoms. This strategy can not differentiate between carriers or children with asymptomatic infection. Children may be transient carriers or may be spontaneously cured. This phenomenon is well documented[13]. While some may argue that our approach may lead to overuse of antibiotics, we believe this approach is justifiable as asymptomatic infections may lead to acute rheumatic fever[13]. This is especially true in populations with increased cases of rheumatic fever.

The capacity of small laboratories in Pacific Islands is often mentioned as an issue with this type of primary prevention strategy[15]. The laboratories in the FSM are faced with numerous challenges. Getting short expiry reagents that require refrigeration is a perennial challenge. Many remote laboratories have difficulties with purchasing pre-prepared agar plates for culture as they often arrive from the manufacturer in poor condition. The alternative is in-house preparation of blood agar plates. FSM is not unique amongst small island laboratories in being unable to have a good source of fully quality controlled agar plates. GASES are typically cultured onto tryptic soy agar containing 5% sheep blood. Sheep blood is unavailable in FSM, and therefore some laboratories often rely on human blood from outdated banked blood. Hemolytic patterns used to differentiate streptococci are not as clear on agar containing human blood as they are on agar plates containing sheep blood, making reading of primary plates problematic. Human blood agar plates are not recommended for culture of GAS.

To overcome this particular issue, we opted to purchase sufficient prepared agar plates for this project (Remel, Kansas). This approach may not be feasible for routine work. The volume of plates normally required for a laboratory such as Kosrae is low, and thus plates may expire before they are used. Shipping of short expiration consumables that require refrigeration is a logistical problem for remote areas like Kosrae. Flights are infrequent, and supplies may be held up in ports or customs where they remain unrefrigerated. Standing orders and close cooperation between laboratories and procurement officers may alleviate some of these issues.

The cost and logistics of primary prevention strategies is often cited as a reason that these strategies may not be sustainable, especially in developing countries. This project was generously supported by a number of people, with several volunteers supporting the public health teams. The cost of the rapid tests was generously discounted to approximately $1.54 USD per test. The blood agar plates were kindly donated. The cost of manpower in FSM is quite low and therefore the overall cost of the project was not prohibitive. If we had to pay full price for lab supplies we may expect at least double the price per test for rapid tests and

approximately $1.20 to $3.40 per pre-prepared agar plate. If we were to repeat test 1,000 children the total cost for laboratory consumables alone would be in the order of $3,000 USD.

One of the highest costs of the program is supplying benzathine penicillin G to the children found with throat swabs positive for GAS. The cost per dose is approximately $30-50 USD from local suppliers; however programs such as UNICEF can provide this antibiotic at a considerably reduced price. This cost however, must be weighed against the cost of preventing RF and subsequent RHD. It is also worth mentioning that patients with RHD are referred to major centers for treatment, generally either Hawaii or Manila. This cost is very burdensome for the FSM government, even for those who are insured. The current price for a valve replacement at the Manila Heart Center is approximately $17,000 USD, while a double valve replacement costs about $23,000 USD. Patients who have had heart valve replacement must be guaranteed long term, monitored anticoagulant therapy. The total cost for the treatment of one patient with RHD is generally well in excess of $30,000. The cost of this must be taken into consideration in cost-benefit analyses. Kathikeyan and Bongani[4] cite early studies where 1 case of RF was prevented for every 50 to 60 individuals treated, while another study[16] predicts that the at least 5.4 cases of RF can be prevented with the money spent for managing one case of RHD for one year.

Secondary prophylaxis is mandatory for patients who have had an attack of RF, or who have a well-documented RHD. Typically benzathine benzyl penicillin is given by intramuscular injection every three to four weeks. For patients without proven carditis the duration of the prophylaxis is 5 years or until the patient reaches 18 years old. For patients with carditis, the duration of prophylaxis is for a minimum of 10 years from the last attack and may be longer[8]. This prophylaxis is burdensome for developing countries, but considerably cheaper than treating RHD, and this cost must be taken into consideration when assessing the cost-effectiveness of prevention strategies.

Many questions remain to be answered. How frequently should GAS screening be carried out? How should close contacts be managed? Will there be a significant impact on the incidence of RHD in Kosrae? Can the addition of education programs in the schools and community assist in making such programs more effective? What is the contribution of pyoderma/impetigo related GAS to illness in Kosrae? The strains of GAS that cause pyoderma are associated with production of post streptococcal glomerulonephritis, however these same strains have not been linked with RHD[17].

This project was relatively easily carried out in Kosrae with the commitment and support of public health teams, physicians, laboratory personnel and health care administrators and community volunteers. The project raised healthcare worker's and community awareness about the link between sore throat and RHD, and it is hoped from this that more people will seek treatment for sore throat in children. The project will be cost-effective if at least one case of RHD can be prevented in the future.

Conclusion

A preliminary program to reduce the medical and public health impact of group A streptococcal upper respiratory tract infections and rheumatic fever was carried out in Kosrae. Although it is too early to judge long term effectiveness, the initial efforts were successful in documenting that this can be carried out. Issues to be resolved include the long term availability of laboratory reagents and penicillin, as well as financial support.

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"Examine what is said, not the person who speaks"

by: Arab proverbs, sent by Annie