CHAPTER 4

EXPECTED RESULTS

4.1 Clinical Criteria

Clinical criteria for diagnosing malaria were developed using a logistic regression analysis. The dependent variable was blood slide positivity and the independent variables were as shown in Table 3.2. Rainy season, temperature equal to or higher than 38° C and enlargement of the spleen were found to be significant and retained in the model. The summary of the results is shown in Table 4.1(a). The probability of blood slide positivity given the temperature equal to or higher than 38° C and enlargement of the spleen was 0.36 in the rainy season and 0.19 if not in the rainy season, Tables 4.1(b) and (c). The slide positive rate was taken to be 0.15 in this study according to the annual report of VBDC, Myanmar (1993). The probability of blood slide positivity in both circumstances were greater than 0.15 and these clinical criteria (i.e. temperature $\geq 38^{\circ}$ C and splenic enlargement) can thus be regarded as predictors of blood slide positivity. Based on these clinical criteria comprising temperature $\geq 38^{\circ}$ C and splenic enlargement, and their specificity and sensitivity when compared to gold standard further calculations for benefits and costs were done. There were 200 cases in the rainy season and 107 in the nonrainy season.

Calculations necessary for valuing benefits and costs were done separately for the cases coming in the rainy season and for those coming in nonrainy season. Specificity and sensitivity of the clinical criteria when compared to the gold standard (microscopy) were calculated by cross tabulating results of blood slide positives to the clinical malaria cases as diagnosed by the clinical criteria (i.e. those having temperature equal to or higher than 38° C and enlargement of the spleen), Figures 4.1 and 4.2.

Table 4.1(a) Results of Logistic Regression

Variables	Coefficients	P
Rainy season	.8736	.0287
Enlarged spleen	.8254	.0129
Temperature ≥ 38° C	.7484	.0267
Constant	-3.1044	.0000

Table 4.1 (b) Probability of Slide Positivity in Rainy Season Given Temperature and Enlarged Spleen

Constant	Coef*Rain	Coef*Spleen	Coef*Temp.	Z	ExpZ	Probability
-3.1044	.8736(1)	.8254(1)	.7484(1)	-.567	1.763	0.36

Table 4.1 (c) Probability of Slide Positivity in Nonainy Season Given Temperature and Enlarged Spleen

Constant	Coef*Rain	Coef*Spln	Coef*Temp.	Z	ExpZ	Probability
-3.1044	.8736(0)	.8254(1)	7484(1)	-1 4406	4 223	0.19

Coef = Coefficient
Rain = Rainy season
Spln = Enlarged spleen
Temp = Temperature ≥ 38° C
Z = Constant + (Coef*Rain) + (Coef*Spleen) + (Coef*Temp)

ExpZ = e^{-z}

Probability = $1/1+e^{-z}$

Figure 4.1: Determining Specificity and Sensitivity of the Clinical Criteria in the Rainy Season

Diagnosis using clinical criteria		Microscopy (Gold standard) (+)	(-)	
	(+)	9	19	28
	(-)	28	144	172
		37	163	200

Using fever as a sole criterion for selecting cases for presumptive treatment

Figure 4.2: Determining Specificity and Sensitivity of the Clinical Criteria in the Nonrainy Season

Diagnosis using clinical criteria		Microscopy (Gold standard) (+)	(-)	
	(+)	3	9	12
	(-)	6	89	95
		9	98	107

Using fever as a sole criterion for selecting cases for presumptive treatment

Referring to section 3.4.3 and Tables 3.5 and 3.6 in chapter 3 specificity and sensitivity when using clinical criteria in selecting cases for presumptive treatment and slide positive rate (SPR) in rainy and nonrainy season can be calculated from the corresponding values in Figures 4.1 and 4.2 respectively. These figures were derived from cross tabulating number of cases identified by the clinical criteria as malaria and number of cases identified by microscopy as malaria (blood slide positives). In the rainy season out of 200 cases 28 cases were identified by the clinical criteria as malaria because they had both temperature $\geq$ 38° C and splenic enlargement. Those without one of these clinical features were identified by the clinical criteria as nonmalaria and there were 172 cases. When compared to gold standard (microscopy) only 9 cases out of 28 cases identified by the clinical criteria were found to be slide positive and the remaining 19 cases were blood slide negative. Similarly out of 172 cases identified by the clinical criteria as nonmalaria only 144 cases were identified by microscopy as blood slide negative, Appendices III A, C and IV. Similar procedure was undertaken for those cases coming in nonrainy season, Appendices III B, C and IV. In rainy season the SPR will be 0.185(37/200), sensitivity 0.24(9/37) and specificity 0.88 (144/163). In nonrainy season SPR will be 0.08(9/107), sensitivity 0.33(3/9) and specificity 0.91(89/98).

From the results thus obtained, evaluation of benefits and costs was undertaken by substituting values of the specificity, sensitivity, slide positive rate (SPR) in the equations developed earlier and described in section 3.4.3 of chapter 3.

4.2 Valuing Benefits and Costs.

4.2.1 Valuing Benefits

Benefits were defined in this study as costs of giving presumptive treatment unnecessarily to the false positive cases that can be saved by using the clinical criteria to diagnose malaria before giving presumptive treatment. The benefits were calculated by substituting values of sensitivity, specificity of clinical criteria and SPR in each season (Figures 4.1 and 4.2) in equation 3.4.3(c). Calculation and results are described here. First, drug costs (Z) must be determined before proceeding to the calculations.

Drug costs for giving presumptive treatment

Single dose/presumptive treatment consists in some countries of chloroquine, while in other countries primaquine may be added. Radical treatment of sensitive strains of malaria consists of chloroquine and primaquine. In areas *P. falciparum* resistance to the 4-aminoquinolines is well established, the second line (sulfadoxin/pyrimethamine) or (sulfalene/pyrimethamine) or even third line drugs (e.g. mefloquine are used. Assuming malaria parasites are sensitive to chloroquine calculation for drug cost is based on chloroquine in this study. As the cases include both adults and children and the doses are different the drug dosage needed and the costs were calculated on the average for all the cases to be treated. Based on the annual report of VBDC (1993) and report of Arbani (1991) average drug costs in giving presumptive treatment is 3.5 Kyats (Table 4.2).

Calculating benefits (Costs saved)

In the rainy season

It is assumed that 65% of the cases are coming in the rainy season and T (total cases) will thus be:

739,682 * .65 = 480,793.3
= 480,793

Specificity = 0.88 .... (Figure 4.1)

(1-SPR) = 0.815 .... (Figure 4.1)

Z = 3.5 Kyats .... (Table 4.2)

Substituting these values in equation 3.4.3(c) benefits (costs saved) by using clinical criteria to select cases before giving presumptive treatment in rainy season can be calculated as follows:

Benefits
(Costs saved) = ZT(1-SPR)ξ .... [eqn. 3.4.3 (c)]

= 3.5* 480,793*0.815*0.88

= 1,206,886.6 Kyats .... [4.1.1(a)]

Table 4.2 Average Drug (Chloroquine) Costs for Presumptive Treatment

Age Group	# Treated	# of Tablets for one person	Total tablets	Price per Tablet (Kyats)	Total Costs
0-1	6,864	1/2	3,242	1	3,242
1-2	18,042	1	18,042	1	18,042
2-9	75,717	2	151,434	1	151,434
9-14	94,288	3	282,864	1	282,864
14+	551,635	4	2,206,540	1	2,206,540
Total	746,166		2,662,122	1	2,662,122

Source : Vector Borne Diseases Control Program, Annual Report (1993)

Average drug costs = 2,662,122/746,166

= 3.5 Kyats

As age group (0-1) are not included in the study calculation of drug costs is based on (746,166 - 6484) = 739682 persons

In Nonrainy season

It is assumed that 35% of the cases are coming in nonrainy season and T (total cases) will thus be:

739,682 * .35 = 258,888.7
= 258,889 cases

Specificity = 0.91 .... (Figure 4.2)

(1-SPR) = 0.92 .... (Figure 4.2)

Z = 3.5 Kyats .... (Table 4.2)

Substituting these values in equation 3.4.3(c) benefits (costs saved) by using clinical criteria to select cases before giving presumptive treatment in nonrainy season can be calculated as follows:

Benefits
(Costs saved) = $ZT(1-SPR)\xi$ .... [eqn.3.4.3(c)]

= 3.5* 258889*0.92*0.91

= 758,596.55 Kyats .... [4.1.1(b)]

4.2.2 Valuing Costs

Costs in this study were taken as additional costs for introducing the clinical criteria. Valuing the costs was done after identifying their components and the levels incurred by the health care sector.

(i) Direct Costs

They are the additional costs within the health care sector for developing and using the clinical criteria, comprising 3 components which are:

(a) costs for developing the clinical criteria (i.e. costs for conducting the field survey)

(b) cost for training health workers

(c) costs resulting from false negative cases
- costs for treating new cases arising as a result of transmission by the false negative cases

Costs for training health workers

Costs for developing clinical criteria are protocol driven costs and are not considered in the analysis. Determination of costs for training health workers are shown in Table 4.3. and found to be 258,520 kyats.

These costs are to be considered as fixed costs to be borne the whole year. As there are two seasons under consideration the costs are to be apportioned into two parts one for each season. These costs will have to be borne according to the proportion of cases coming in each season.

Costs (X) for each season would thus be:

For rainy season = 258,520 * 0.65
= 168,038.00 Kyats .... 4.1.2(a)

For nonrainy season = 258,520 * 0.35
= 90,482.00 Kyats .... 4.1.2(b)

Table 4.3: Costs for Training Health Workers

Central level

Training of trainers (from States and Divisions)

Perdium

	Amount	Number	Days	Total
Trainers (central)	100 Kyats	2	3	600.00
Trainees (State & Divisions)	80 kyats	14	3	3,360.00
Traveling Allowances (For trainees)	300 kyats	14	2	8,400.00
			Subtotal ----	12,360.00

State and Divisional Level

Perdium

	Amount	Number	Days	Total
Trainers (State & Divisions)	80 Kyats	14	3	3,360.00
Trainees (Township Medical Officers)	80 Kyats	320	3	76,800.00
Traveling Allowances (For trainees)	150 Kyats	320	2	96,000.00
			Subtotal ----	176,160.00

Training materials 5000.00 Kyats for each State and Division ---------------------------------- 70,000.00

Grand Total 258,520.00 Kyats

Exchange Rate 1 US$ = 6 kyats

Costs resulting from false negative cases

In calculating costs resulting from false negative cases the following components are considered:

(i) Drug costs for presumptive treatment of new cases infected by the false negative cases

(ii) Costs for diagnosis (microscopy) of these new cases

(iii) Drug costs for radical treatment of these new cases

Referring to equation 3.4.4(c), the notations that follows and equation 3.4.4(f), δ, Z and ρ must be determined first. Value of ''Z'' has already been determined in Table 4.2. Value of ''δ'' is determined in Table 4.4 and that of ''ρ'' in Tables 4.5 and 4.6.

Table 4.4: Determining Costs for Diagnosis (Microscopy) of New Cases

Items	Annual Costs (Kyats)	Costs for Diagnosis
Equipment	600,000	120,000(20%)
Personnel	2,145,000	214,500(10%)
Supplies	1699,000	424,750(25%)
Total	4,444,000	759,250

Source: VBDC, Department of Health, Myanmar, 1994 (cited by Naing, 1996)

Total number of cases examined (T) = 739682

Average cost for diagnosis (δ) = 759,250/739682

= 1.03 Kyats

Table 4.5: Determining Drug Costs for Radical Treatment of New Cases (*P. falciparum*)

Age Group	Numbers	Chloroquine			Primaquine		
		Dose Tablets	Total	Costs	Dose Tablets	Total	Costs
0-1	779	1.25	973.75	973.75	-	-	-
1-2	2,458	2.50	6145.00	6145.00	0.75	1,843.5	921.75
2-9	10,883	5.00	54,415.00	54,415.00	1.50	16,324.5	8,162.25
9-14	20,249	7.50	151,867.50	151,867.50	2.00	40,498.0	20,249.00
14+	64,819	10.00	648,190.00	648,190.00	3.00	194,457.0	97,228.50
Total	99,215		861,591.25	861,591.25		253,123.0	126,561.50

Source: (1) Vector Borne Diseases Control Program, <u>Annual Report, 1993</u>.
(2) Arbani, 1991.

Note: One tablet of cloroquine was estimated to be 1 Kyat and that for primaquine to be 0.5 Kyat

Total drug costs = 988152.75 Kyats(861,591.25+126,561.5)

Average costs (ρ_f) = 988220.25/99215

= 9.96 Kyats

Table 4.6: Determining Drug Costs for Radical Treatment of New Cases (*P. vivax* and others)

Age Group	Numbers	Chloroquine			Primaquine		
		Dose Tablets	Total	Costs	Dose Tablets	Total	Costs
0-1	137	1.25	171.25	171.25	-	-	-
1-2	439	2.50	1,097.50	1,097.50	1.25	548.75	274.375
2-9	1,921	5.00	9,605.00	9,605.00	2.50	4,802.50	2,401.250
9-14	3,573	7.5	26,797.50	26,797.50	3.75	13,398.75	6,699.375
14+	11,439	10.00	114,390.00	114,390.00	5.00	57,195.00	28,597.500
Total	17,509		152,061.25	152,061.25		75,945.00	37,972.500

Source: (1) Vector Borne Diseases Control Program, <u>Annual Report, 1993</u>.
(2) Arbani, 1991.

Note: One tablet of cloroquine was estimated to be 1 Kyat and that for primaquine to be 0.5 Kyat

Total drug costs = 190033.75 Kyats

Average costs (ρ_{v+}) = 190033.75/17509

= 10.85 Kyats

Average drug costs for radical treatment "ρ" will then be;

$$\rho = (F_f * \rho_f) + (F_{v+} * \rho_{v+})$$

$$= 0.85\rho_f + 0.15\rho_{v+} \quad \ldots\ldots\ldots\ldots\ldots \quad [\text{eqn } 3.4.4(g)]$$

Notations,

ρ_f = Average drug costs of radical treatment for cases with *P. falciparum* infection

F_f = Proportion of cases with *P. falciparum* infection

ρ_{v+} = Average drug costs of radical treatment for cases infected with *P. vivax* or other parasites

F_{v+} = Proportion of cases with *P. vivax* or other parasites

Then,

ρ = 0.85*9.96 +0.15*10.85
= 10.09 kyats

P = δ + Z + ρ
= 1.03 + 3.5 + 10.09
= 14.62 Kyats

In calculating costs resulting from false negative cases, the number of new cases infected by each false negative case (i.e. ''η'') will have to be estimated. Additional costs will grow with the number of newly infected cases. Under best circumstances number of new cases infected by false negative cases will be small and under worst circumstances number will be large. The number of new cases that can be infected by false negative cases depend on many factors relating to host, parasite and the vector. Each new case before being detected and adequately treated can infect more new cases and this is also taken into consideration in calculating costs resulting from false negative cases. As definite number of new cases is not known costs resulting from false negative cases are calculated under three different scenarios; best, intermediate and worst with regards to the number of cases that can be infected by one cohort of false negative cases. It is assumed that under the best circumstances transmission will be minimum and number of new cases will be small. Under the worst circumstances the reverse will be true. In between is the intermediate condition where transmission is not high nor low. Some false negative cases can infect large number of cases while some may not infect anyone at all. Average number of new cases that can be infected by each false negative under each scenario is arbitrarily designated as below:

Best scenario	= 0.1 case
Intermediate scenario	= 0.2 case
Worst scenario	= 0.3 case

On the basis of each scenario additional costs in rainy season and in nonrainy season are calculated. Referring back to equation 3.4.4(f) Additional costs (Y) would thus be:

Y_r = 168,038 + C_{FN} in the rainy season .... 4.1.4(a)

Y_{nr} = 90,482 + C_{FN} in nonrainy season .... 4.1.4(b)

<u>Additional costs incurred in the rainy season</u>

Referring to equations 3.4.4(a), 3.4.4(e), 3.4.4(f), 4.1.2 (a) and 4.1.4(a) additional costs in the rainy season will thus be;

$$Y_r = X_r + \sigma_r(1-\sigma_r)(SPR)_r T_r \eta_s(\delta+Z+\rho)\left[\frac{1}{1-(1-\sigma_r)(1+\eta_s)}\right] \quad \ldots\ldots \quad 4.1.5(a)$$

Notations,

Y_r = Additional costs in rainy season

X_r = 168,038 .... [eqn. 4.1.2(a)]

η_s = Average number of new case infected by one false negative case in a particular scenario

σ_r = sensitivity of the clinical criteria in rainy season

SPR_r = SPR in rainy season

T_r = total cases coming in the rainy season

Substituting corresponding values in equation 4.1.5(a), additional costs under each scenario in the rainy season will be:

(1) <u>Best scenario</u>

$$Y_r = 168038 + (0.24*0.76*0.185*480793*0.1*14.62)\left[\frac{1}{(1-(0.76*1.1)}\right]$$

= 168038 + 144,629.95

= 312,667.95 Kyats

(2) <u>Intermediate scenario</u>

$$Y_r = 168,038 + (0.24*0.76*0.185*480793*0.2*14.62)\left[\frac{1}{(1-(0.76*1.2)}\right]$$

= 168,038 + 539,075.26

= 707,113.26 Kyats

(3) Worst scenario

$$Y_r = 168,038 + (0.24*0.76*0.185*480793*0.3*14.62)\left[\frac{1}{(1-(0.76*1.3)}\right]$$

$$= 168,038 + 5,929,827.8$$

$$= 6,097,865.8 \text{ Kyats}$$

Additional costs incurred in the nonrainy season

Referring to equations 3.4.4(a), 3.4.4(e), 3.4.4(f), 4.1.2 (b) and 4.1.4(b) additional costs in nonrainy season will be;

$$Y_{nr} = X_{nr} + \sigma_{nr}(1-\sigma_{nr})(SPR)_{nr}T_{nr}\eta_s(\delta+Z+\rho)\left[\frac{1}{1-(1-\sigma_{nr})(1+\eta_s)}\right] \quad \ldots \quad 4.1.5(b)$$

Notations,

Y_{nr} = Additional cost in nonrainy season

X_{nr} = 90,482 .... [eqn.4.1.2(b)]

η_s = Average number of new case infected by one false negative case in a particular scenario

σ_{nr} = Sensitivity of clinical criteria in nonrainy season

SPR_{nr} = SPR in nonrainy season

T_{nr} = total number of cases coming in nonrainy season

Substituting corresponding values in equation 4.1.5(b)

(1) Best scenario

$$Y_{nr} = 90482 + 0.33*0.67*0.08*258,889*0.1*14.62\left[\frac{1}{(1-.67*1.1)}\right]$$

$$= 90482 + 25,455.634$$

$$= 115,937.63 \text{ Kyats}$$

(2) Intermediate scenario

$$Y_{nr} = 90,482 + 0.33*0.67*0.08*258,889*0.2*14.62\left[\frac{1}{(1-.67*1.2)}\right]$$

$$= 90,482 + 68,314.618$$

$$= 158,796.62 \text{ Kyats}$$

(3) Worst scenario

$$Y_{nr} = 90,482 + 0.33*0.67*0.08*258,889*0.3*14.62\left[\frac{1}{(1-.67*1.3)}\right]$$

$$= 90,482 + 155,693.77$$

$$= 246,175.77 \text{ Kyats}$$

4.2.3 Determining Benefit Cost Ratio

From the benefits and costs calculated for each season for each scenario the resulting benefit cost ratios are shown in Table 4.7.

Table 4.7: Benefit Cost Ratios for Each Season under Different Scenarios

Season	Scenario	η	Benefits	Costs	Benefit Cost Ratio
Rain	Best	.1	1,206,886.60	312,667.95	3.859
Rain	Intermediate	.2	1,206,886.60	707,113.26	1.707
Rain	Worst	.3	1,206,886.60	6,097,865.80	0.197
Nonrain	Best	.1	758,596.55	115,937.63	6.543
Nonrain	Intermediate	.2	758,596.55	158,796.62	4.777
Nonrain	Worst	.3	758,596.55	246,175.77	3.081

It is found that in the rainy season benefit cost ratios are more than one in all but worst scenarios. In nonrainy season benefit cost ratios in all scenarios are more than one. For the benefit cost ratio to be more than one sensitivity must be high, SPR must be low and ''η'' must also be low.

From the Table 4.7 it can be said the model is useful in the following situations;

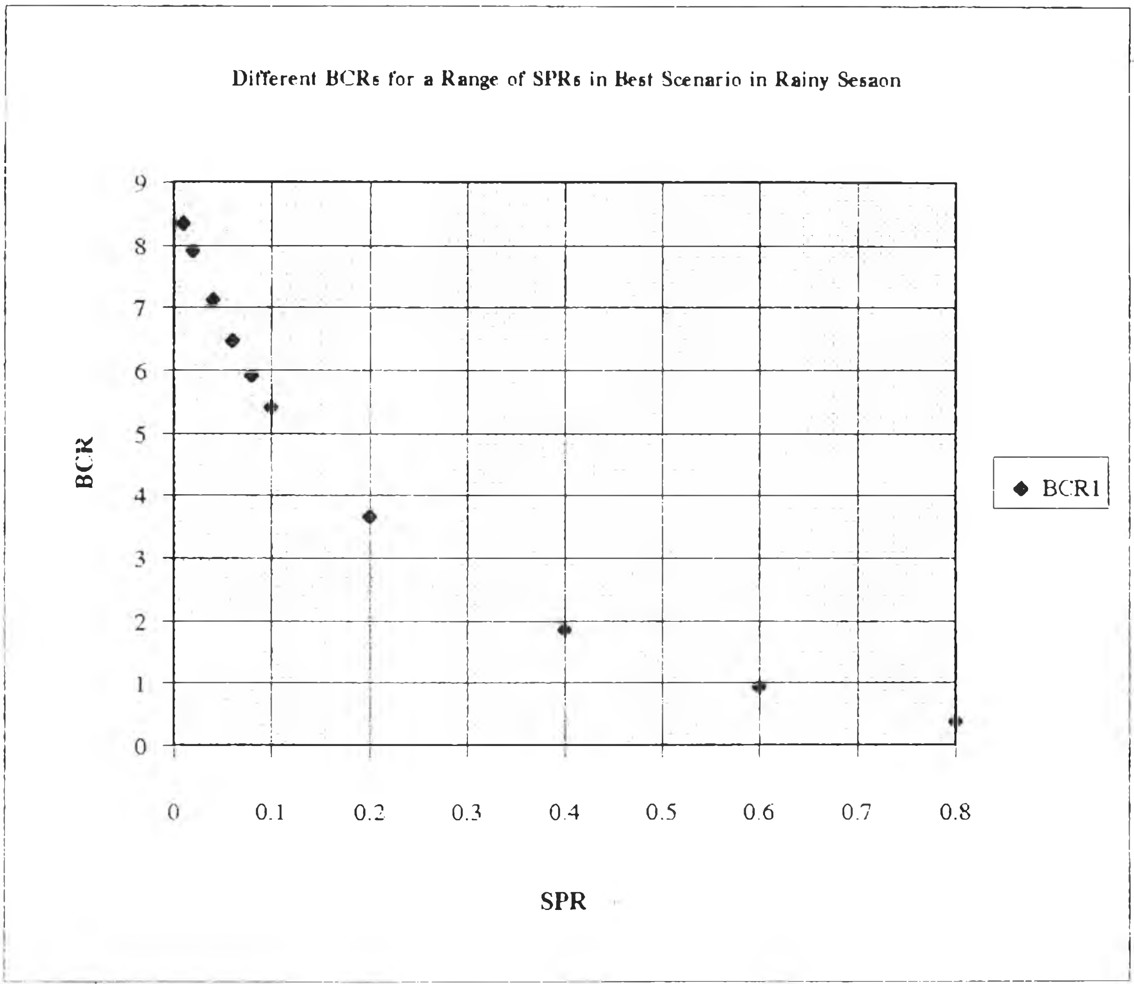
(1) when the sensitivity of the clinical criteria is high,

(2) when SPR in that place at the time of using the clinical criteria is low.

Effects of a range of slide positive rates on benefit cost ratios in different scenarios given the present sensitivity and specificity of the clinical criteria in the rainy season are shown in Figures 4.3 (a), (b) and (c). In Figure 4.3(a) it can be seen that when the number of new cases infected is low, benefit cost ratio higher than one can be expected if the slide positive rate is less than 0.6 or 60%. Benefit cost ratios higher than one can also be expected when the slide positive rates are less than 0.3 and 0.05 in the intermediate and worst scenarios respectively, Figures 4.3 (b) and (c).

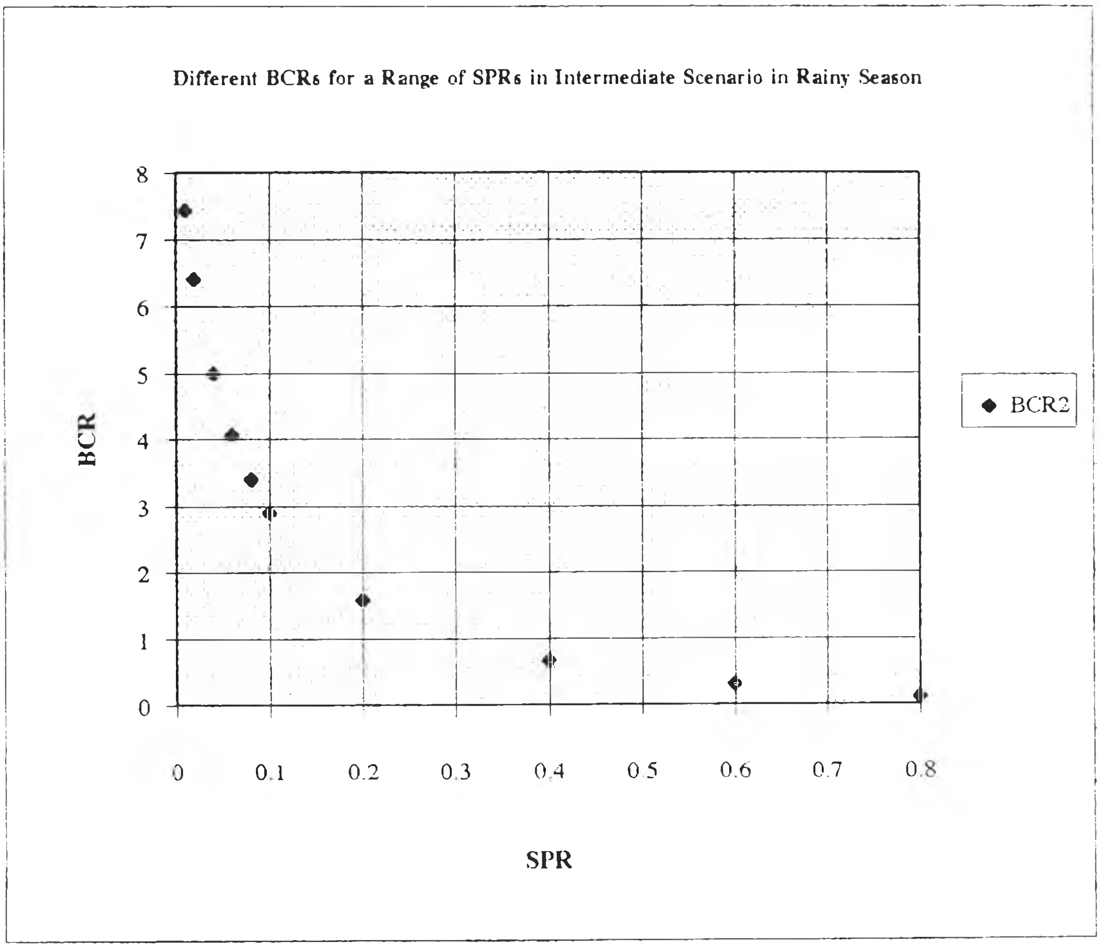
In nonrainy season high benefit cost ratios can be expected if the slide positive rate is lesser than 0.7 provided the number of new cases infected is low (i.e. best scenario), Figure 4.4 (a). In intermediate and worst scenarios slide positive rates should be less than 0.5 (50%) and 0.3 (30%) respectively to have higher benefit cost ratios, Figures 4.4 (b) and (c). Maximum slide positive rates for higher benefit cost ratio in different scenarios and seasons are summarized in Table 4.8. It implies that given other things being equal, benefit cost ratios can be higher than one if the slide positive rates are low as mentioned earlier. These findings may be helpful in determining conditions in which the clinical criteria are useful.

Figure 4.3(a): Different Benefit : Cost Ratios for a Range of Slide Positive Rates in Best Scenario in Rainy Season



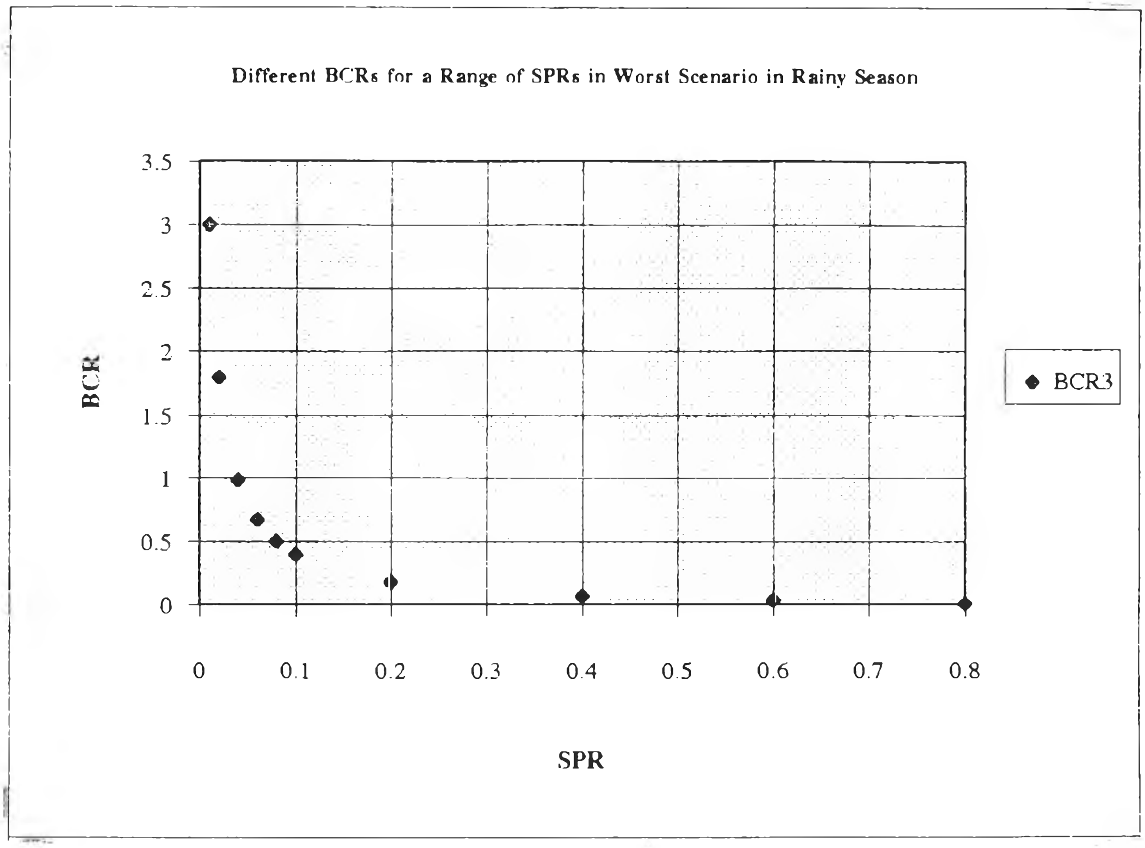
It can be seen that given other things being equal benefit cost ratio will be higher than one when the slide positive rate becomes smaller than 0.6. In rainy season when the number of new cases that can be infected on the average by false negative cases is small benefit cost ratio higher than one can be expected when slide positive rate is less than 60%.

Figure 4.3(b): Different Benefit : Cost Ratios for a Range of Slide Positive Rates in Intermediate Scenario in Rainy Season



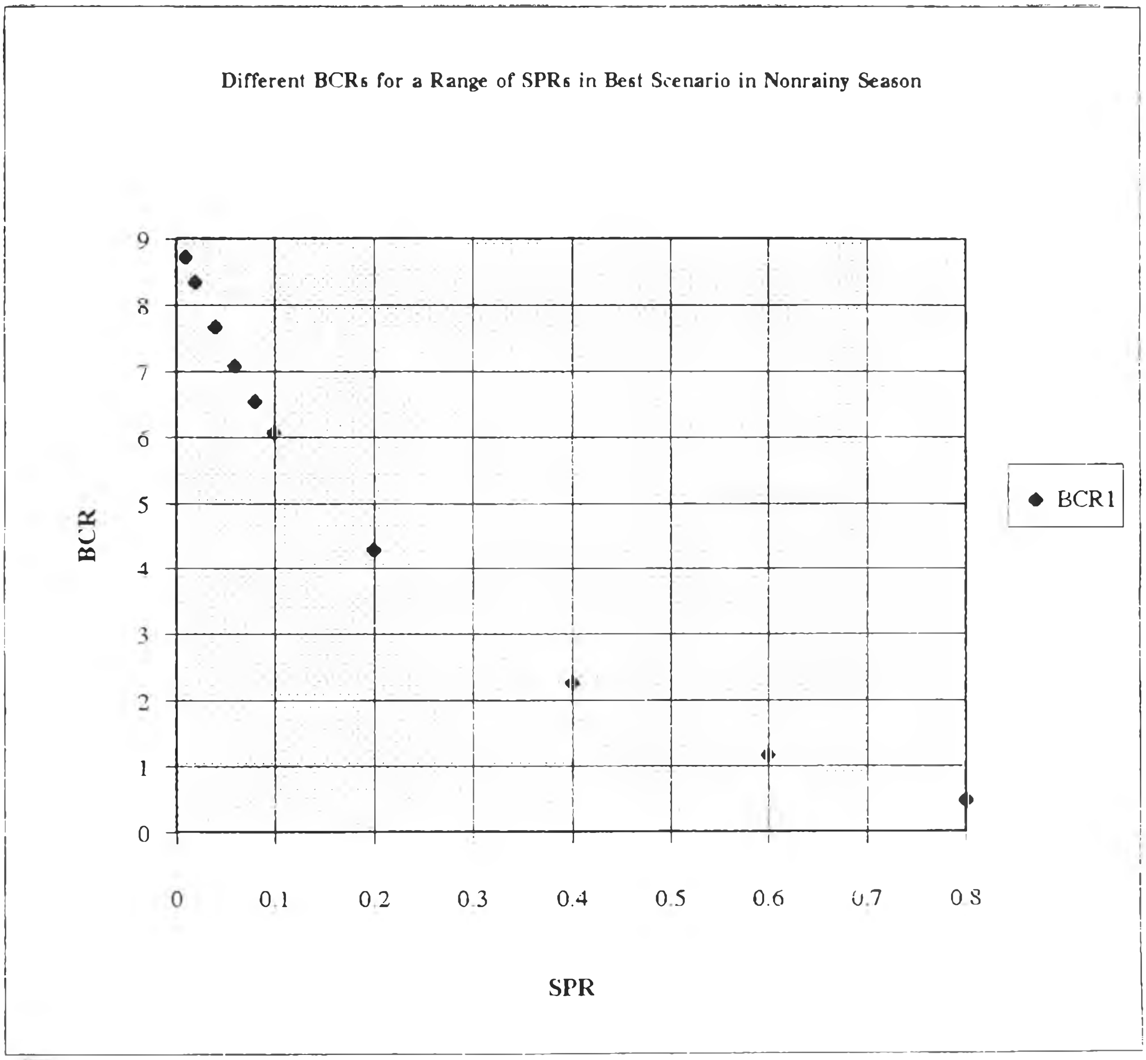
Other things being equal benefit cost ratio will be higher than one when the slide positive rate becomes smaller than 0.3. In rainy season when the number of new cases that can be infected on the average by false negative cases is moderate benefit cost ratio higher than one can be expected when slide positive rate is less than 30%.

Figure 4.3(c): Different Benefit : Cost Ratios for a Range of Slide Positive Rates in Worst Scenario in Rainy Season



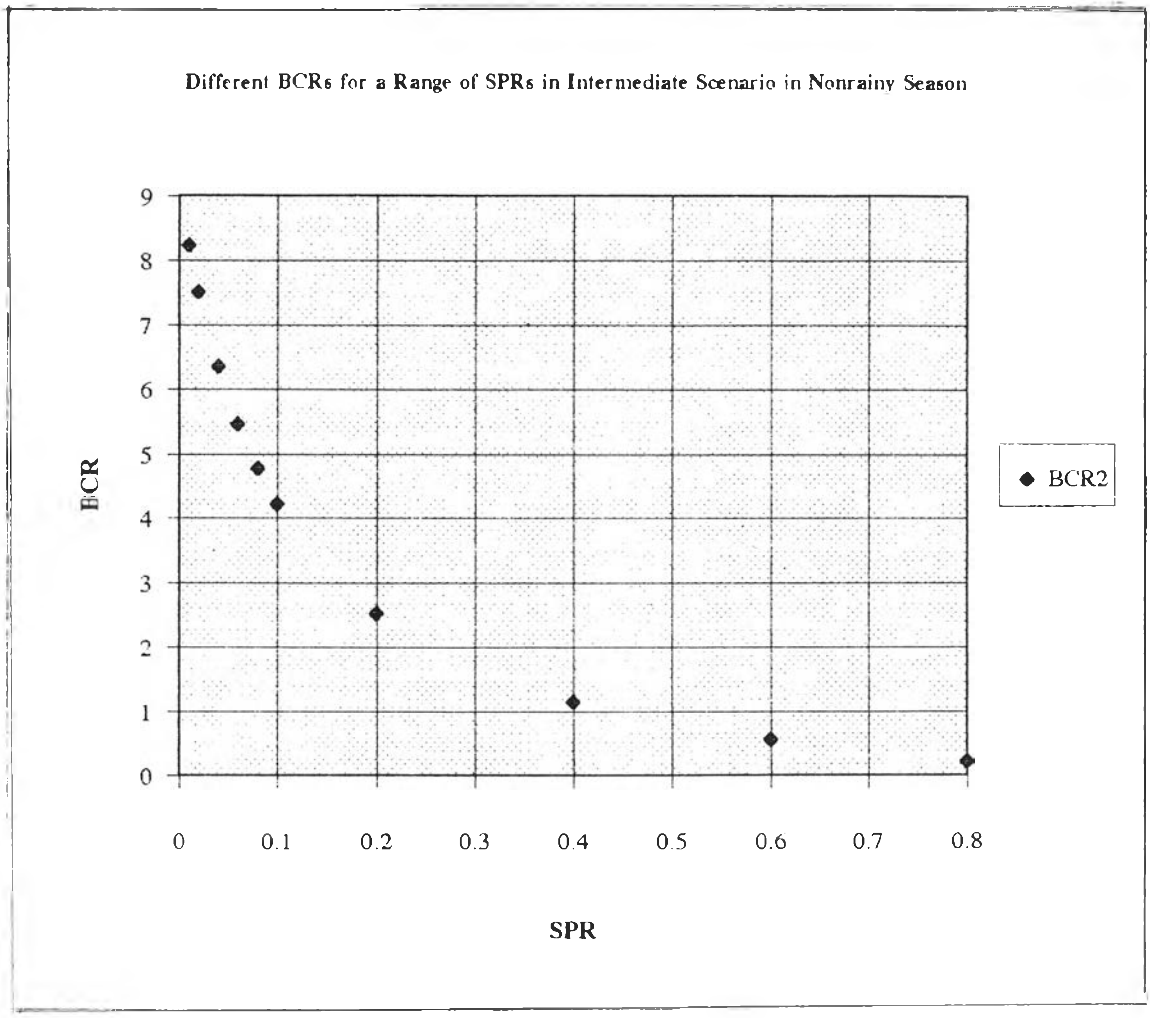
Benefit cost ratio will be higher than one when the slide positive rate becomes smaller than 0.05 provided other variables are constant. In rainy season when the number of new cases that can be infected on the average by false negative cases is large benefit cost ratio higher than one can be expected when slide positive rate is less than 5%.

Figure 4.4(a): Different Benefit : Cost Ratios for a Range of Slide Positive Rates in Best Scenario in Nonrainy Season



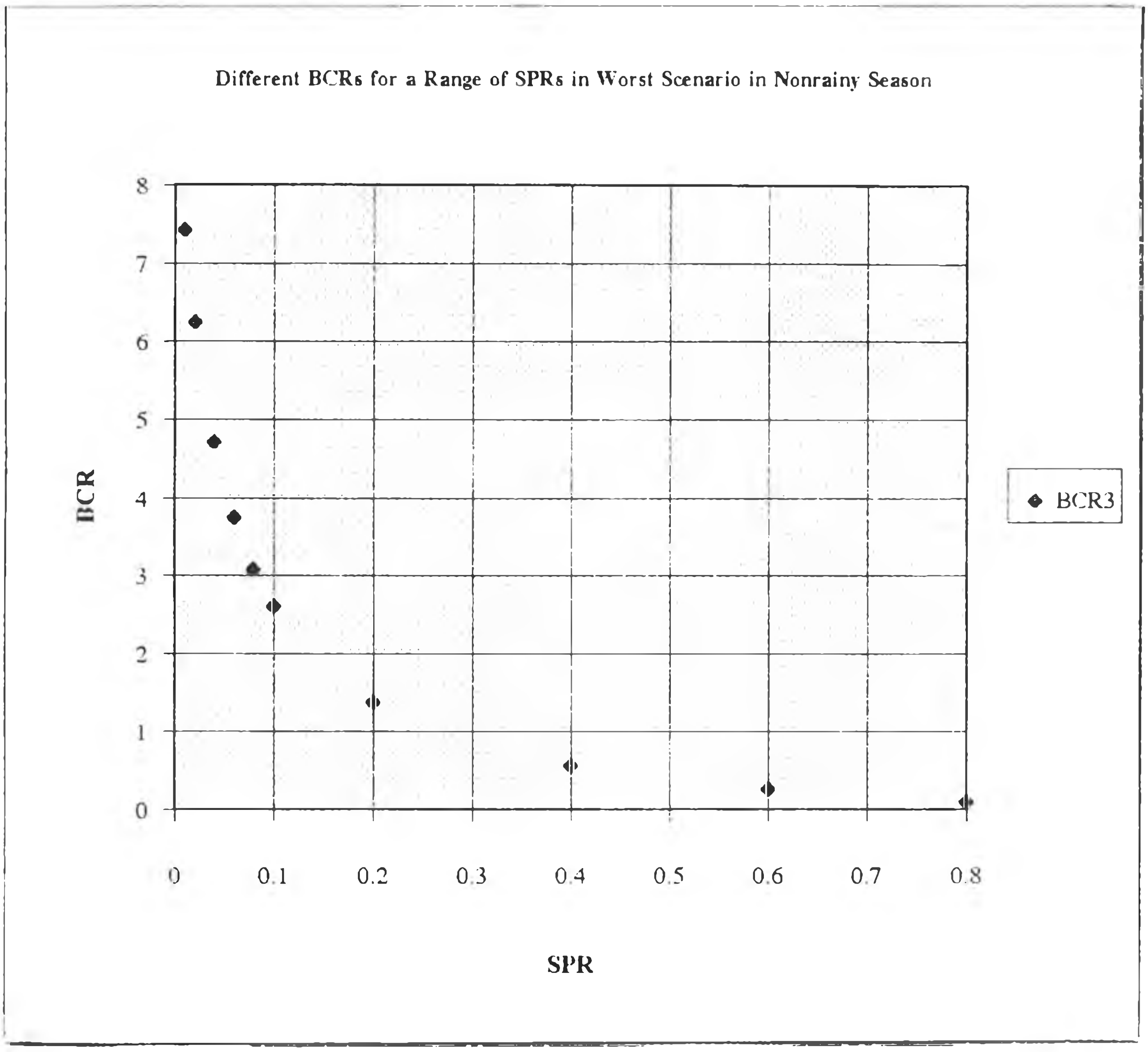
If assumption can be made that other things are equal, it can be said that benefit cost ratio will be higher than one when the slide positive rate becomes smaller than 0.7. In nonrainy season when the number of new cases that can be infected on the average by false negative cases is small benefit cost ratio higher than one can be expected when slide positive rate is less than 70%.

Figure 4.4(b): Different Benefit : Cost Ratios for a Range of Slide Positive Rates in Intermediate Scenario in Nonrainy Season



Benefit cost ratio will be higher than one when the slide positive rate becomes smaller than 0.5 assuming other variables are constant. In nonrainy season when the number of new cases that can be infected on the average by false negative cases is moderate benefit cost ratio higher than one can be expected when slide positive rate is less than 50%.

Figure 4.4(c): Different Benefit : Cost Ratios for a Range of Slide Positive Rates in Worst Scenario in Nonrainy Season



Other things being equal benefit cost ratio will be higher than one when the slide positive rate becomes smaller than 0.3. In nonrainy season when the number of new cases that can be infected on the average by false negative cases is large benefit cost ratio higher than one can be expected when slide positive rate is less than 30%.

In summary the slide positive rates at which benefit cost ratio will be higher than one for different scenarios in two seasons are presented in the following table.

Table 4.8: Maximum Slide Positive Rates for High Benefit Cost Ratio in Different Scenarios and Seasons

Season	Scenarios	Slide Positive Rates
Rainy	Best	60%
Rainy	Intermediate	30%
Rainy	Worst	5%
Nonrainy	Best	70%
Nonrainy	Intermediate	50%
Nonrainy	Worst	30%

For each scenario in different seasons the slide positive rate should be less than that shown in Table 4.8 to have benefit cost ratio higher than one.