8 Cost and benefit of thalassaemia prevention

Introduction:

An important element in programme development is analysis of the cost and benefit of different approaches. There is good evidence that implementing policies for prevention of genetic disorders leads to significant financial savings and that these are particularly marked in case of thalassaemia (Cao 1987). Alwan and Modell (1997) have worked out the minimum cost of treatment per patient per year and the cost of prevention of thalassaemia in the Eastern Mediterranean Region. However, as far as Pakistan is concerned these estimates are a theoretical exercise. The aim of this chapter is to illustrate the cost of treatment and compare it with the cost of prevention and to show how such analysis can contribute towards the development of appropriate policies in Pakistan.

Methods:

In order to analyze the cost effectiveness of thalassaemia prevention the following parameters were evaluated: (1) estimated number of new births of thalassaemia major per year (N), (2) cost of treatment (3) cost of carrier screening and (4) cost of prenatal diagnosis. The costs were calculated in Pak Rupees. Equivalent cost in US dollars, at the rate of Rs. 40.00 per $ was also calculated.

Results:

Estimated number of thalassaemia major births per year (N):

Calculation of the annual number of thalassaemia major patients in Pakistan are discussed in Chapter: 4. The annual birth rate of thalassaemia major is estimated at approximately 4550. In addition births of 550 patients of a clinically significant abnormal haemoglobin with or without thalassaemia are also expected. This number also includes approximately 200 patients of Hb-S and Hb-E homozygotes who do not normally require blood transfusions. The total number of

patients (N), who would require transfusions, is estimated at 4900. However, for the sake of calculations a round figure of 5000 new cases per year is used.

Cost of treatment:

Each year a patient of thalassaemia major on an average requires 26 units of blood and approximately 364 grams of desferal (Table: 8.1). The cost of one bag of blood (Table: 8.2) is calculated at Rs. 1540 and the average annual cost on blood transfusions alone is estimated at Rs. 40,000. The cost of desferal therapy per year is estimated at Rs. 116,000 (Table: 8.1). The annual cost of investigations per patient (Table: 8.3) is estimated at Rs. 2000. The total cost of management per patient per year (Table: 8.4) is estimated at Rs. 160,000 ($ 4000).

Cost of screening:

The cost of screening for β-thalassaemia includes the cost of sample collection tube, disposable syringe, testing the sample on red cell analyzer, Hb-A_2 estimation by cellulose acetate electrophoresis, multiplex ARMS PCR and the labour. In Chapter: 5 it was shown that all cases do not require every investigation and the number of individuals requiring Hb-A_2 estimation or DNA analysis are also different in the two groups of people studied i.e. the pregnant women and the index families. Therefore the cost per individual would also be different in these groups. The cost of screening 1000 pregnant women (Table: 8.5) is calculated at Rs. 60,000 ($ 1500) and that of screening 1000 individuals from thalassaemic families is Rs. 78,000 ($ 1950).

Table: 8.6 compares the cost of antenatal versus family screening in terms of cost per person screened, cost per carrier detected and cost per at risk couple detected. In the antenatal set up 50 carriers per 1000 (5%) and in the families 300 carriers per 1000 (30%) are expected. The expected number of at risk couples in the antenatal set up would be 2.5/1000 (0.25%) whereas in the family screening it would be 6/1000 (Chapter 5 & 9). The cost per carrier as well as per at risk couple detected is markedly different between the two groups.

Table: 8.1. Basic annual requirement for treating one patient with thalassaemia major, related to age. The figures for donor blood consumption are adopted from Alwan and Modell (1997). An average dose of desferal (35 mg/kg/day) has been used for all calculations (Cao et al, 1992).

Age group (years)	**Mean weight (kg)**	**Units of donor blood/year ***	**Desferal @35 mg/kg/day X 5 days a week.**	**Cost @ Rs. 320 per gram.**
1-5	15	10	130 g	42,000
6-10	25	17	230 g	74,000
11-15	40	27	390 g	125,000
16-21	55	37	520 g	167,000
21-25	60	40	550 g	176,000
All ages:	39	26	364 g	116,000 ($ 2900)

* at about 300 ml/kg/years: 1 unit = 450ml donor blood

Table: 8.2. An estimate of the expenditure on preparation of one bag of blood. The prices are based on calculation by the Armed Forces Institute of Pathology, and the Armed Forces Institute of Transfusion, Rawalpindi, Pakistan.

• Blood bag and transfusion set:	Rs. 80.00
• Screening for Hepatitis B:	Rs. 150.00
• Screening for Hepatitis C:	Rs. 600.00
• Screening for HIV:	Rs. 400.00
• Blood grouping:	Rs. 60.00
• Cross match:	Rs: 250.00
• Total cost:	Rs: 1540.00 ($ 38.00)

Table: 8.3. Estimated cost of investigations per patient of thalassaemia major per year. The investigations include those recommended by Cao et al (1992) and the prices are based on those calculation by the Armed Forces Institute of Pathology, Rawalpindi, Pakistan.

• Haemoglobin estimation (X 24):	Rs. 480.00
• Liver function tests (X 2):	Rs. 570.00
• Serum ferritin (X 2):	Rs: 350.00
• Miscellaneous investigations:*	Rs. 600.00
• Total:	Rs. 2000.00 ($ 50)

* Miscellaneous investigations: thyroid function tests, growth hormone, blood sugar, ECG and Muga-I scan of heart etc.

Table: 8.4. Total cost of treatment for thalassaemia per patient per year.

Blood transfusions X 26 units per year (Table: 8.1 & 8.2):	Rs. 40,000 ($ 1000)
Desferal (Table: 8.1):	Rs. 116,000 ($ 2900)
Investigations (Table: 8.3):	Rs. 2000 ($ 50)
Miscellaneous expenditures:*	Rs. 2000 ($ 50)
Total cost:	Rs. 160,000 ($ 4000)

* Miscellaneous expenditures include cost of labour, antibiotics, occasional hospital admissions, and splenectomy if required.

Table: 8.5. Estimated cost of screening for β-thalassaemia in pregnant women and index families.

Investigations consumable items and manpower:	**Cost X 1: (Rs)**	**Cost per 1000 individuals screened (Rs):**			
		Antenatal screening:		**Family screening:**	
		Requirement:	**Cost:**	**Requirement:**	**Cost:**
Sample tube	5	100%	5,000	100%	5,000
Disposable syringe	3	100%	3,000	100%	3,000
Haematology	20	100%	20,000	100%	20,000
Hb-A_2 estimation	35	20%	6,650	50%	17,500
DNA analysis	350	3.5%	12,250	5%	17,500
Technicians	3000 pm	X 2	6,000	X 2	6,000
Phlebotomist	2000 pm	X 1	2,000	X 2	4,000
Doctor:	5000 pm	X 1	5,000	X 1	5,000
Total	-	-	59,900 ($ 1500)	-	78,000 ($ 1950)

pm: per month salary

Table: 8.6. Comparison of the cost of antenatal versus family screening in terms of cost per person screened, cost per carrier detected and cost per at risk couple detected.

Cost of screening (Rs.):		
	Antenatal:	**Index families:**
Per person:	60	78
Per carrier detected:	1200	260
Per at risk couple detected:	24000	13000

Cost of prenatal diagnosis:

Chorionic villus sampling (CVS):

All of the CVS in this study were done free of cost. It is therefore difficult to calculate the cost of each CVS. The cost of a CVS aspiration needle is Rs. 4000 and the cost of a biopsy forceps is Rs. 22000. However, the needles as well as the forceps can be reused. Therefore the cost of a CVS is equivalent to the salary of the obstetrician and the ultrasound operator (approximately Rs. 20,000 per month). If approximately 100 CVSs are done every month then the cost per procedure will be Rs. 200.

Laboratory diagnosis:

The cost of mutation analysis (Table: 8.7) by the standard ARMS PCR per person is calculated at Rs. 800 ($ 20) and by multiplex PCR is Rs. 500 ($ 12.5).

Cost of termination of pregnancy:

Cost of termination involves the cost of the procedure and the cost of hospital admission for 2-3 days. The total cost is calculated at approximately Rs. 4000 ($ 100). Since only about 25% of women who request prenatal diagnosis would require termination, the actual cost per diagnosis will be Rs. 1000 ($ 25).

Total cost:

The total cost of one prenatal diagnosis (Table: 8.8), including the cost of CVS, mutation analysis, and termination of pregnancy when required, is estimated at Rs. 3600 ($ 90) by standard ARMS PCR and Rs. 3000 ($ 75) by multiplex ARMS PCR.

Discussion:

The success of a policy depends on whether genetic counselling is provided retrospectively i.e. after the birth of an affected child or prospectively i.e. to at risk individuals and couples without an affected child (Alwan and Modell 1997). The potential effect of a policy also depends on its acceptability to the families concerned and the society as a whole.

The concept of thalassaemia prevention is new to Pakistan. This pilot study clearly shows that carrier screening as well as prenatal diagnosis are technically feasible and also accepted by the majority of affected families. Consequently, formulation of policies incorporating prenatal diagnosis is feasible for a large-scale thalassaemia prevention programme in Pakistan. In the subsequent sections the cost and benefit of three basic policies, including no prevention, retrospective counselling with prenatal diagnosis and prospective identification of at risk couples and the offer of prenatal diagnosis, will be discussed. For the purpose of discussion a hypothetical situation is assumed in which the total number of thalassaemics is equal to the number of new births of thalassaemia in one year.

Table: 8.7. Estimated cost of mutation analysis for β-thalassaemia per person.

Item:	**Cost per person (Rs.):**	
	Standard ARMS PCR:	**Multiplex ARMS PCR:**
Sample tube and Syringe	8.00	8.00
Red cell indices	20.00	20.00
DNA extraction	70.00	70.00
ARMS PCR	250.00	75.00
Electrophoresis	150.00	100.00
Photography	50.00	-
Sub total	548.00	273.00
Wastage @ 10%	55.00	27.00
Labour	200	200
Grand total	803.00 ($ 20)	500.00 ($ 12.5)

Policy-1:

Policy-1 is a situation in which all thalassaemics are provided adequate treatment facilities but no efforts are made for prevention. The cost of providing treatment to the estimated 5000 patients (N) born each year will be Rs. 800 million. The cost will increase at a rate equal to N x number of years from the start of policy. At ten years it will be Rs. 8.8 billion and at 20 years it will be Rs. 16.8 billion (Fig: 10.6).

Table: 8.8. Estimated cost of prenatal diagnosis for thalassaemia. The cost of termination is included at ¼ of the actual cost because only 1 in 4 would actually require termination.

Procedure:	**No:**	**Rate (Rs.):**		**Cost (Rs.):**	
		Standard PCR:	**Multiplex PCR:**	**Standard PCR:**	**Multiplex PCR:**
Mutation analysis	X 2	800	500	1600	1000
CVS:	X 1	-	-	200	200
Fetal testing	X 1	800	800[#]	800	800
Cost of termination:	X 1	-	-	1000	1000
Total	-	-	-	3600 ($ 90)	3000 ($ 75)

[#] Fetal DNA is tested by the standard ARMS PCR.

Policy-2:

It is based on providing treatment facilities to the affected children as in Policy-1 but at the same time it also includes counselling of the affected couples. Alwan and Modell (1997) have suggested that when the final family size is large, if parents have no more pregnancies after the birth of one affected child, the birth rate of affected children, would fall by as much as 50%. This hypothesis, however, is subject to the availability as well as to the acceptance of family planning. A more realistic option would be to offer prenatal diagnosis to such couples.

If it is assumed that Policy-2, including retrospective counselling and the offer of prenatal diagnosis, would reduce the birth incidence of thalassaemia by about 50%, the number of children requiring treatment would also be reduced to half. The cost of providing prenatal diagnosis to 2N (N/2 X 4) number of couples would, however, be added to the net annual cost for the policy. The estimated total cost for the 1st year of the policy would be Rs. 830 million that includes Rs. 30 million for carrying out 10,000 prenatal diagnoses at the rate of Rs. 3000 per procedure. At 10th year of the policy the total annual expenditure would be Rs. 4.8 billion and at 20th year it would be Rs. 8.8 billion (Fig: 8.1).

Policy-3:

This includes all of the features of Policy-2 and in addition it also caters for prospective identification of couples at risk and the offer of prenatal diagnosis. Table 8.9 gives a calculation of the number of individuals who may have to be screened if index thalassaemic

families are targeted. The number of individuals requiring screening in the 0.225 million index families is estimated at 22 million (average 97 individuals per family). This would identify approximately 126,500 at risk couples and about 16% of this (20,000) would also require prenatal diagnosis. The total cost of screening 22 million people would be Rs. 1.7 billion (Table: 8.11).

The expected number of women who may require screening if approached through an antenatal clinic is 31 million (Table: 8.10). This would identify 5% (1.55 million) carrier women whose husbands would also require screening. The total number of individuals who may require screening would be approximately 32.5 million and the cost of screening would be Rs. 1.95 billion (Table: 8.11).

Table: 8.9. Calculation of the total number of couples and the number of at risk couples in a targeted screening approach.

• Population of Pakistan:	135 million
• Total number of carriers (at 5% carrier rate):	6.75 million
• Average number of individuals per family:	97 (Chapter: 5)
• Total number of families:	135 / 97 = 1.39 million
• Percent of carriers per family (Chapter: 5):	31%
• Number of carriers per family:	31/100 X 97 = 30
• Number of families at risk:	6.75 million / 30 = 0.225 million
• Average number of couples per family:	22.5
• Total number of couples in families at risk:	22.5 X 0.225 = 5.0625 million
• Proportion of consanguineous couples:	45% (2nd cousins or closer)
• Estimated proportion of couples at risk at: 45% consanguineous marriages (Chapter 5 & 9):	13 X 13 / 100 + 16 X 5 / 100 = 2.5%
• Total number of at risk couples:	2.5% of 5.0625 million = 126562

Table: 8.10. Calculation of the number of couples who may require antenatal screening.

• Proportion of females in active reproductive life:	46% (31 million)*
• Number of couples in active reproductive life:	31 million
• Expected numbers where husband's screening may be required:	5% of 31 = 1.55 million
• Total numbers that may require screening:	31 + 1.55 = 32.55 million
• Total number of at risk couples identified:	5% of 1.55 = 77500

*Annual report of Health Services in Pakistan 1995-96.

Table: 8.11. The cost of family and antenatal screening for β-thalassaemia in Pakistan.

Approach:	**No. of Individuals required to be screened: (millions)**	**No of at risk Couples identified:**	**Cost of screening for β-thalassaemia (Rs):**	
			Per 1000:	**Total:**
Family:	21.8	126500	78,000	1.7 billion
Antenatal:	32.5	77,500*	60,000	1.95 billion

* The number of at risk couples identified by antenatal screening are less as compared to targeted approach because the later group also includes couples who are not in active reproductive life.

The cost of prospective identification of at risk couples, whether done by screening the index families or by antenatal screening, will be added to the net initial expenditure for the Policy-3. However, this can conveniently be spread over the first few years of the policy. The overall effect of Policy-3 is expected to reduce the number of births of affected children to approximately 90% of N (Alwan and Modell 1997). Consequently, the number of affected children requiring treatment would be reduced to 90%. But at the same time an additional cost of approximately 54 million for providing prenatal diagnosis (Rs. 3000 per diagnosis) to the at risk couples (90% of N x 4=18,000) would be added to the total cost for Policy-3. The initial cost of Policy-3 would be approximately Rs. 1.5 billion that will gradually increase over the next ten years to Rs. 2.88 billion and to Rs. 4.2 billion till the 20^{th} year of the policy.

Comparison between the three policies:

There is a clear financial benefit in adopting Policy-2 and Policy-3 as compared to Policy-1. Policy-3 is obviously more cost effective than the Policy-2. The expenditure on Policy-3 would be higher during the initial few years that would be balanced by the huge amount of savings achieved in the years to follow. A basic assumption in the three policies discussed includes provision of adequate treatment facilities to all patients. An immediate benefit in adopting either Policy-2 or Policy-3 lies in the savings achieved on treatment of the affected children. Since the Government of Pakistan is not spending anything on treatment of thalassaemia, the immediate benefits of adopting a policy cannot be appreciated. However, it would certainly result in saving of the resources of non-governmental organizations.