10 Final discussion

Introduction:

There is a long standing experience of preventive programmes at the national level in many Mediterranean countries. This is illustrated in the Cyprus thalassaemia prevention programme that has been highly cost effective and has resulted in almost complete control of thalassaemia. In principle, a programme on similar lines could be applied in any country where haemoglobin disorders are common (Alwan and Modell 1997). This would involve improvement of treatment facilities through adoption of a common management protocol, awareness and involvement of the community, population screening and counselling, and availability of prenatal diagnosis. The success of the Cyprus programme is attributed to low infant mortality, small size and small population, high standard of living and health care, high literacy and low birth rate, existence of a national health infrastructure and Government's involvement (Angastiniotis et al, 1986).

Haemoglobin disorders in Pakistan are of sufficient public health importance to justify a disease-oriented control programme (WHO 1993). However, development of a prevention programme on the lines of a Mediterranean programme is largely precluded at present in a developing country like Pakistan by a large population, high birth rate, low rate of literacy, limited resources, and lack of organization of health services. Another issue of fundamental importance is the attitude of a Muslim community towards various options for prevention.

At least five "policies" for thalassaemia exist in different countries of the Eastern Mediterranean Region (EMR) including Pakistan (Alwan and Modell 1997). These include:

1. No treatment, counselling or prevention.
2. Best possible patient care, plus retrospective genetic counselling after the birth of

an affected child.

3. Same as 2 plus the option for prenatal diagnosis in subsequent pregnancies.
4. Same as 2 plus prospective screening and counselling but no prenatal diagnosis.
5. Same as 2 plus prospective screening, genetic counselling with prenatal diagnosis.

An ideal "policy" for thalassaemia should include measures to provide adequate treatment facilities, genetic counselling and prospective identification of at risk couples before they give birth to an affected child. Until recently, the "policy" of no treatment, counselling or prevention was widely prevalent in the EMR including Pakistan. At present in many countries of the region treatment facilities are more widely available and retrospective counselling is also being provided to many families. Prenatal diagnosis is available to only a limited number of the families. The response of most of the affected families to prenatal diagnosis is therefore mostly unknown. The ideal "policy" for Pakistan is a long way in the future because of the general low level of development in the country and the limited resources available. Therefore, a basic question at present is where and how to start?

Keeping in view the infant mortality of around 90/1000 in Pakistan (Burney 1993) the Government's priority is to reduce it with basic programmes of primary health care, immunization and nutrition etc. (Annual report of health services in Pakistan 1995-96). Effective implementation of such programmes has caused a very rapid fall in infant mortality in many countries. As a result chronic disorders including thalassaemia very rapidly became more important and even in some countries the health priorities also changed e.g. Iran, Maldives and Thailand. This tends to happen when infant mortality falls to below 40/1000 because (a) more vulnerable children survive (b) they become conspicuous, get diagnosed and their management can be very costly (Prof B. Modell personal communication). Pakistan is far away from a situation where mortality due to genetic disorders will become conspicuous. But the problem is important and will emerge in due course of time (Fig: 10.1). Therefore, some form of planning must begin now.

The population of Pakistan is very diverse because a small urban section with better

education is more developed as compared to a large rural and mostly uneducated section (Fig: 10.2). Most thalassaemic children are diagnosed and get treated in the developed section of the population whereas affected children born in the less developed section usually die undiagnosed and parents often replace them with healthy children. A demographic transition would occur when people have better education and fewer children who survive. With this the problem which is emergent only in the developed section would also become prominent in rest of the population. Since the problem is only emerging the Government is unlikely to become interested at present. The important questions at present are:

What level of Government interest should realistically be promoted at present?

It should include:

a. An awareness of the problem and its scale and the awareness that it will become a major problem when the present health policies succeed.
b. Support (at least moral) for research and appropriate approaches for treatment and prevention of thalassaemia in Pakistan.
c. Encouragement for formation of nuclei and centres from which appropriate services can spread in due course when needed.
d. Willingness to have a dialogue with the NGOs and others to ensure progress.
e. Ensuring that the programme enters into planning at Government level.

How to achieve political will?

The usual route for achievement of political will is through increasing the Government interest in the problem (Fig 10.3). National experts, leading clinicians and thalassaemia support associations of the parents and patients can positively influence the Government authorities (Alwan and Modell 1997). The availability of epidemiological data collected through reliable sources can be effective in presenting the problem to the health authorities. The NGOs could write a report on the state of thalassaemia in Pakistan every year and send it to the ministry of health. An increasing number of patients who would survive with the availability of treatment facilities can also attract Government's attention. Collaboration of all interested parties is a key element. As long as different people tell the Government different things they will never listen.

Pakistan at present is in the earliest stage of developing a programme for thalassaemia. The work carried out in this pilot study is essential for forward planning. The results have brought forward guidelines to formulate a realistic future policy for thalassaemia in Pakistan.

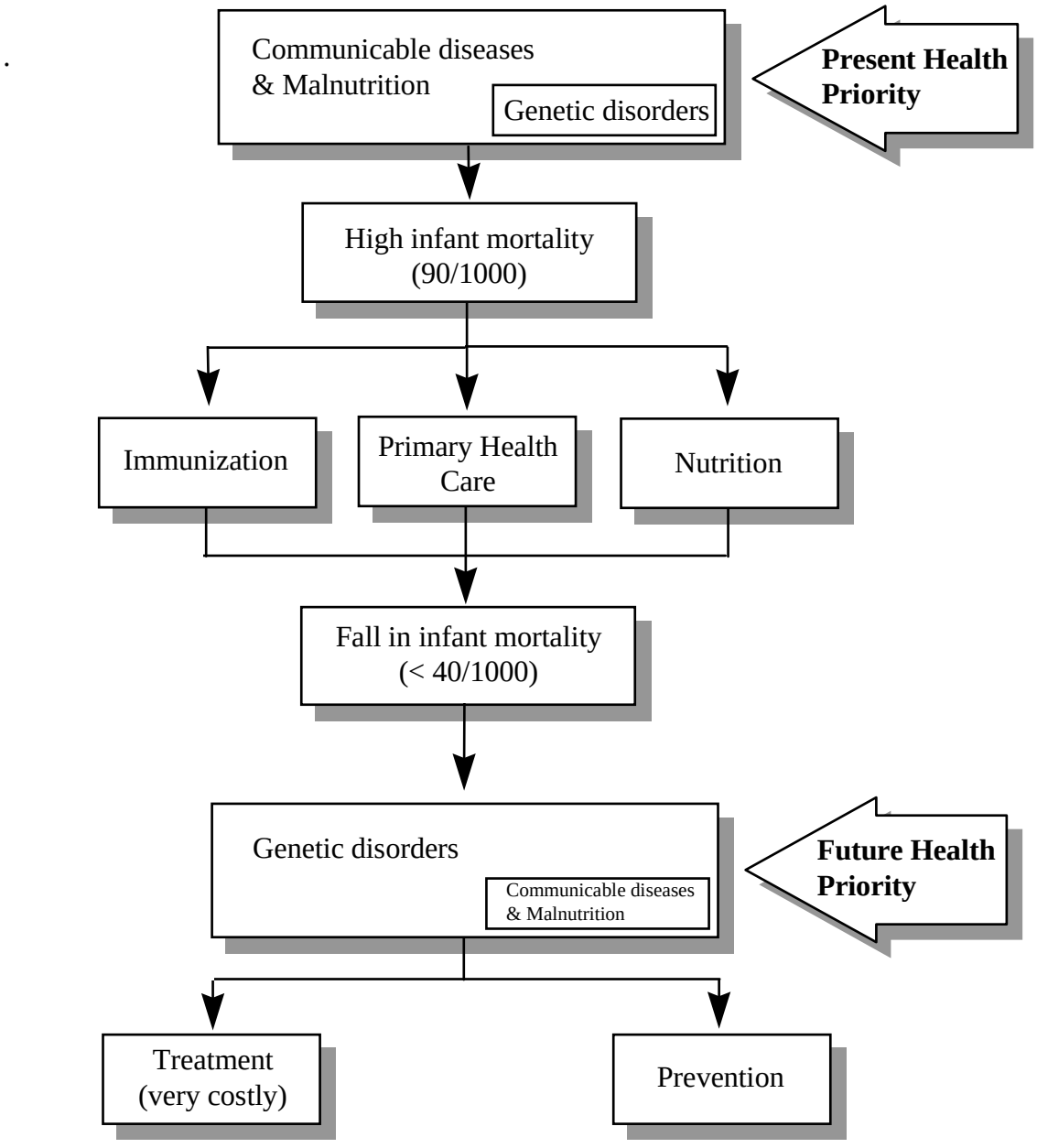

Fig: 10.1. The usual route of creating Government's interest in genetic disorders. The present health priority of the Government is to reduce the infant mortality by preventive health policies. With the success of these measures, genetic disorders will emerge as an important health priority. Therefore some planning must begin now.

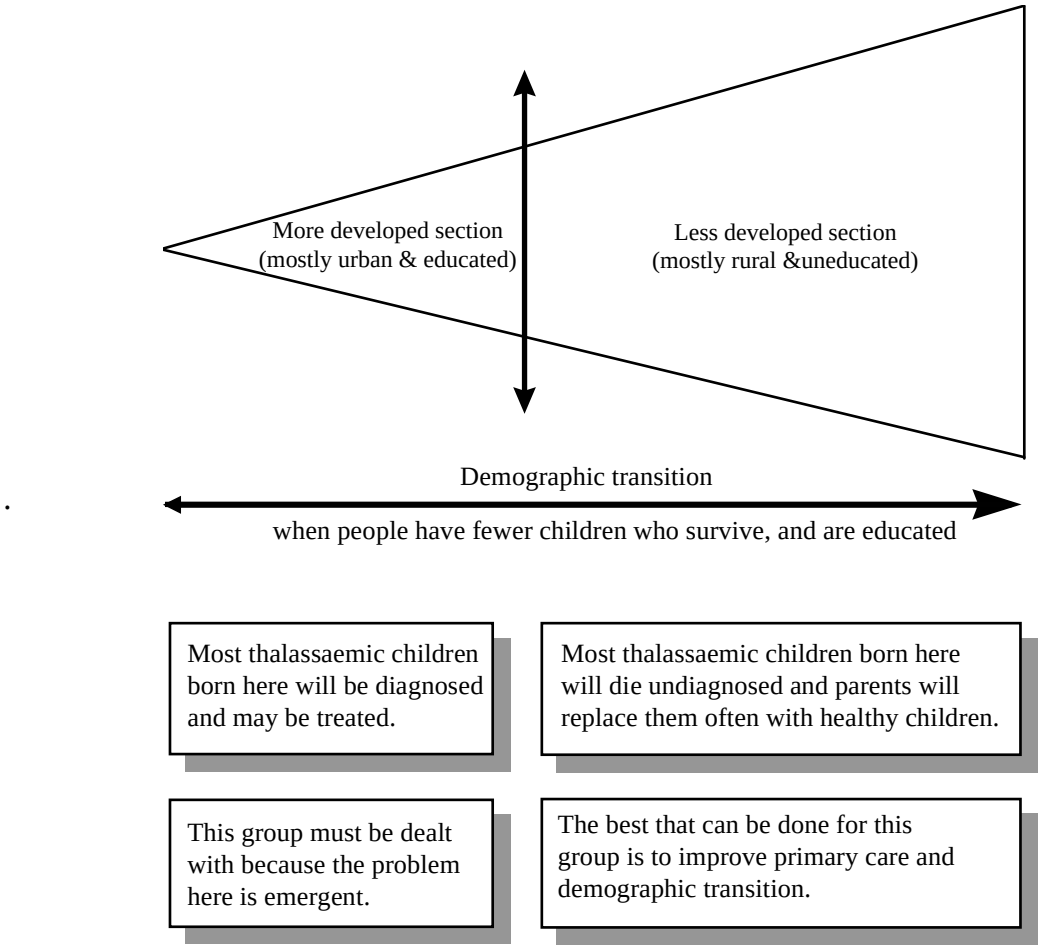

Fig: 10.2. The population of Pakistan is diverse which has a small more developed and a large under developed section. At present most thalassaemics are seen in a smaller section of the population that is mostly urban and has better education. With demographic transition the problem is likely to become more and more obvious (Prof. B. Modell personal communication).

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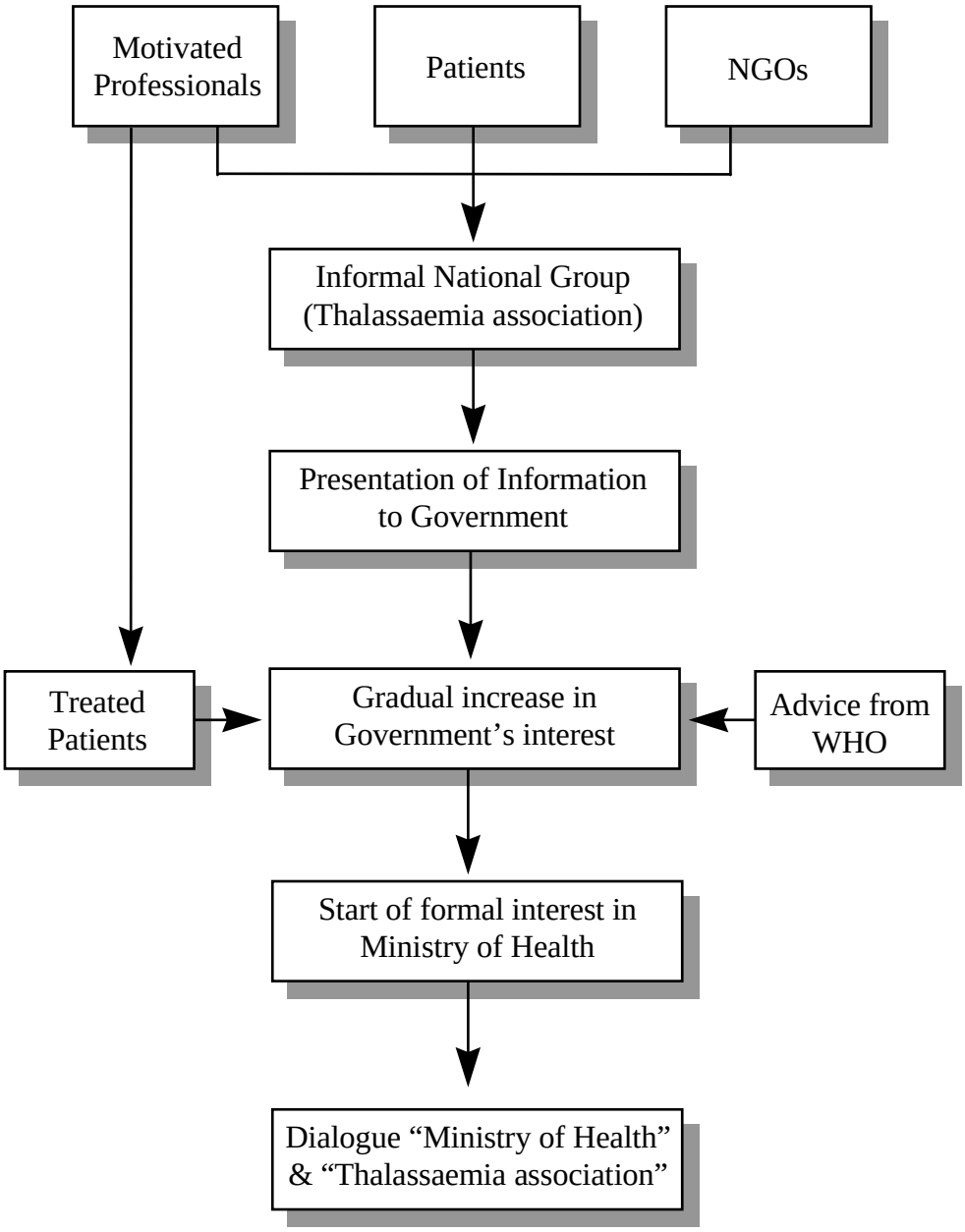

Fig: 10.3. The usual route for achievement of political will. Pakistan at present is in the earliest stage of developing a programme for thalassaemia (Prof. B. Modell personal communication).

Epidemiology of haemoglobin disorders in Pakistan:

WHO (1985) has estimated that the carrier rate for β-thalassaemia in Pakistan is around 5%. The study of haemoglobin disorders by Khattak and Saleem (1992a) gave the first indication that the carrier rates for β-thalassaemia may be different in various ethnic groups. It is important to investigate carrier rate in the ethnic groups because β-thalassaemia genes have an uneven distribution. Moreover, the frequency of consanguineous marriage is also different in the ethnic groups of Pakistan (Bittles 1994; Wahab and Ahmad 1996). This would affect the calculation of annual birth rate of thalassaemia major in each group. The overall carrier rate for β-thalassaemia in this study was found to be 5.3% (95% confidence limits: 4.1-6.5%). The carrier rate also varied in the ethnic groups (Table: 10.1). The abnormal haemoglobins could not be screened in this study. However, other published reports on abnormal haemoglobins indicate that they are not significant as compared to β-thalassaemia. The largest study of 5000 Pakistani individuals by Sharma et al, (1976) showed that 0.78% had an abnormal haemoglobin including Hb-D (0.42%), Hb-E (0.18%), and Hb-S (0.18%).

The carrier rate of thalassaemia is used to calculate the annual number of births of affected children. This information is essential for planning a national programme for control and prevention of the disorder (Alwan and Modell 1997). The estimated annual number of thalassaemia major births in Pakistan, based on the carrier rate and the frequency of consanguineous marriages in each ethnic group, would be approximately 4550 (1.2/1000 new births) (Table: 10.1). Maximum affected births are expected in Punjabis (1.12/1000) which also is the largest ethnic group (80 million). The highest birth rate, however, is expected in Baluchis (4.3/1000). This is due to a high carrier rate combined with a high frequency of consanguineous marriage. The affected birth rate amongst Sindhis (0.324/1000) is low because of a low carrier rate (1.3%) in this group.

The annual births of children with an abnormal haemoglobin, based on the figures of Sharma et al, (1976), are estimated at 99 new cases each of homozygous Hb-S and Hb-E. An additional 181 cases each of Hb-S/β-thalassaemia and Hb-E/β-thalassaemia are also expected every year. Therefore the overall annual number of children born with a clinically significant haemoglobin disorder is estimated at 5116 (approximately 1.35 per

1000 births) and its major portion (89%) is represented by β-thalassaemia. The total number of pregnancies at risk would be approximately 20500. The estimated total number of births of children affected with a clinically significant haemoglobin disorder and the number of at risk pregnancies in Pakistan (Fig: 2.2 and 2.6) is the highest in the Eastern Mediterranean Region (Alwan and Modell 1997).

Table: 10.1. Carrier rates for β-thalassaemia and the estimated number of births with thalassaemia major in the five major ethnic groups of Pakistan.

Ethnic group:	**Population:**	**Carrier rate:**	***F*:**	**Estimated births/1000:**	**Annual cases:**
Punjabi	80 million	4.5%	0.0280	1.12	2454
Pathan	20 million	5.2%	0.0164	2.09	610
Sindhi	15 million	1.3%	0.0437	0.32	136
Baluchi	7 million	9.0%	0.0532	4.31	844
Mohajir	15 million	5.2%	0.0209	1.21	506
Total:	137 million	5.3%	0.0287	1.35	4550

Awareness campaign:

An essential prerequisite of a thalassaemia prevention programme would be to educate the public as well as the health professionals about the basic concept of thalassaemia prevention. The adult literacy rate in Pakistan is 35% and the rates for the urban and rural areas are 58% and 28% respectively (Economic survey 1995-96). In a predominantly illiterate community special means of educating the public would be required. This study shows that treating physicians are the most important source of information for the affected families. Therefore, the first and the most important aspect of educating the population would be to educate the doctors. At present very little genetics is taught in the undergraduate medical colleges in Pakistan (Hassan et al, 1997). Even at the postgraduate level genetics is a neglected speciality. Physicians, nurses, and social workers in practice need to be informed of new technologies and approaches. Special courses in genetics may be arranged. Medical genetics newsletter may be a good idea for the busy medical professionals where selected topics may be regularly discussed.

Education for the young population can be achieved through education in schools. It is also worth noting that because of the young age structure of the population, education efforts focused on schools can have a relatively greater impact than in most developed societies (Alwan and Modell 1997). Regular programmes about thalassaemia on radio and television can also be useful.

A simple and effective first step would be to focus on informing the families reporting at the treatment centres. Experience has shown that most of the affected families have very little information about the disease and they readily lend their ears to any advise that could be useful for them. The use of television for disseminating information on thalassaemia was quite effective. Easy to understand booklets on thalassaemia, although not as effective as television due to low rate of literacy, were also useful. The experience of the couples who have used prenatal diagnosis was also an important medium of information for other families.

Provision of improved treatment facilities:

The affected parents are unlikely to become attracted to prevention unless they are assured about the health of the sick child. An essential step before prevention can be offered, would be to improve the treatment facilities. Since thalassaemia is not the Government's health priority at present the treatment is mostly left to Non-Governmental Organizations (NGOs) who are looking after over 7500 registered thalassaemics in the country. Unfortunately, there is no uniformity in management protocols at the centres run by the NGOs. There is also no audit on the quality of treatment being offered (Saleem 1996). Till such time that thalassaemia becomes Government's health priority the NGOs would be required to improve the standard of treatment at their centres. It can be improved substantially by agreement amongst the health professionals involved, adoption of a common management protocol, and their audit at frequent intervals (Angastiniotis et al, 1986).

National co-ordination committee for thalassaemia:

The National co-ordination committee may be required when the importance of thalassaemia is recognized. This may be a long time in the future. Since the problem is emergent some planning must start now. Competent leadership and effective co-

ordination between various governmental and non- governmental organizations is essential. A national co-ordination committee is required for planning, monitoring, and evaluation of the progress of the work. The responsibilities of the committee should be to focus on formulation of policies, preparation of a national plan and mechanisms for co-ordination. The committee should include a programme co-ordinator, specialists in medical genetics, haematology, paediatrics, community medicine, public health and health education. The programme co-ordinator should be a highly motivated and knowledgeable person. He or she should either be based in the Ministry of health or work in co-ordination with the responsible health officers (Alwan and Modell 1997).

Carrier screening for haemoglobin disorders:

Carrier screening has played a major role in thalassaemia prevention programmes in the Mediterranean (Cao 1987). The Mediterranean experience clearly demonstrates the value of incorporating a community based control programme into the primary health care system to ensure effective delivery to the population (Angastiniotis et al, 1986). Since the primary health care system is not well developed in Pakistan (Burney 1993) thalassaemia prevention through this would be unrealistic. Screening of the whole population is also not reasonable due to administrative and financial constraints. A common approach for identifying at risk couples in Europe is the screening in pregnancy (Cao 1987). A major limitation of this approach in a developing country like Pakistan is that the vast majority of the pregnant women, especially in the rural areas, cannot be screened because they do not report to an antenatal clinic. According to a survey, trained personnel attend only 26% of pregnant women in Pakistan (Burney 1993). Under these circumstances it is very unlikely for antenatal screening to be practically feasible. The approach may be suitable for countries like the UK where most women attend antenatal care in early pregnancy (Modell and Berdoukas 1984). Another important aspect of screening during pregnancy is the gestation at which the risk is discovered. If it is discovered late it is unlikely that it would lead to abortion even if the fetus were affected.

Clearly, an alternative approach for Pakistan is needed. It may be appropriate to have a selective approach for (a) more developed part of the population within reach of the services (b) families who already know about thalassaemia. The idea of targeting a selective population of index families is attractive (Alwan and Modell 1997). However,

there are no reports on the success this approach. In this pilot study, that is the first of its kind in which the families affected by thalassaemia were targeted, many points of interest were highlighted. The study is not big enough to lead to a real conclusion as yet and further research e.g. long-term follow-up of the families is required.

Identification of at risk couples:

One of the objectives of thalassaemia screening is the identification of at risk couples. The majority of thalassaemic couples in Pakistan are identified retrospectively when they already have one or more affected children. In communities where family size is small retrospective identification of the couples and offering them prenatal diagnosis is unlikely to reduce the incidence of new births of thalassaemia major (Cao 1987). By contrast, when the final family size is large, retrospective counselling may lead to either cessation of reproduction or prenatal diagnosis. This can reduce the affected birth rate in the community by up to 50% (Alwan and Modell 1997). However, further reduction in the birth rate of the affected children would require prospective identification of at risk couples. In this study the alternative approaches of screening in pregnancy and screening the index families were investigated.

Antenatal screening:

In this study screening of 350 pregnant women could not identify any at risk couple as compared to a theoretical possibility of 1 in 200. This could be due to the small numbers studied. But there is a clear indication that screening of a large number of individuals would be required to identify only a few at risk couples. Another difficulty may arise due to late identification of at risk couples when prenatal diagnosis or termination of pregnancy may not be acceptable to the couples. Only 18% of the pregnant women screened were in the first trimester. The late discovery of risk may also produce dramatic emotional stress on the families (Petrou et al, 1990).

Screening in the index families:

The results of screening in several small to large families show that the approach is technically feasible and acceptable to almost 2/3rd of the families. Screening the index families on an average identified 31% carriers per family. By contrast, there was not a single carrier amongst 397 members of the five families without a known history of a

haemoglobin disorder. Screening in a similar number from the general population would have identified at least 20 (5%) carriers. This suggests that very frequent marriages between close relatives or Biradri/Tribe members "traps" normal as well as abnormal genes within the family. These results strongly support that screening in the affected families would be the most rewarding in this setting. Interestingly, the carrier rate amongst consanguineous Pakistani families is not higher compared to a non-consanguineous Cypriot family with history of thalassaemia (Mouzouras et al, 1980). This is because approximately 50% of the 1st degree relatives of a carrier would be carriers whether the marriage pattern is consanguineous or non-consanguineous. Consanguineous marriage as such would have little effect on the carrier rate of an abnormal recessive gene in the family. However, in a family with predominant consanguineous marriages the key factor is the general high risk of relatives who may marry each other.

There were approximately 29% unmarried carriers in a family. If all marriages in a family are consanguineous then at 29% carrier rate 8.4% of the carriers would be married to another carrier. The frequency of consanguineous marriages in these families was around 45%. At this rate 13% (29% of 45%) of the carriers would be married to 13% of the related carriers while the remaining 16% of the carriers would be married to 5% of the unrelated carriers in the general population. This would mean a total of 2.5% (1.7% plus 0.8%) of the couples in a family would be at risk. On an average there were 22.5 couples per family. It is estimated that 2.5% of the 22.5 couples (0.56 couples per family) would be at risk. The observed number of at risk couples per family, however, was higher (1.7 per family). The difference is because the study families are selected and all but one had at least one affected child. In the family without an affected child the index person was a thalassaemia carrier. It means that all families that are targeted because of a history of haemoglobin disorder may not have at risk couples. This may be especially true when the index person is a carrier rather than an affected child.

Effect of screening on the marriage choices:

The main objective of population screening for thalassaemia is the identification of carriers early enough for marriage choices to be affected. Experience from a research study in Greece shows that premarital screening has had very little effect on the choice of

partner (Loukopoulos 1996). Studies from Cyprus also show that discouraging marriages between carriers had proved unacceptable and was abandoned (Angastiniotis Hadjiminas, 1981). The follow-up for one year after screening in the index families studied shows that there was some impact on the marriage choices. However, this is too short a period to draw firm conclusion and clearly further research on this subject is needed. Preliminary results suggest that premarital screening and preventing marriages between carriers may present itself as an acceptable approach in a Pakistani setting. This may be particularly important for the families who do not accept prenatal diagnosis on religious ethical or cultural grounds. Premarital screening may be expected to have a long term benefit if the carriers are suitably informed. Premarital screening is being considered in a number of countries of the Eastern Mediterranean Region and has already been mandated in Iran (Alwan and Modell 1997).

Other advantages of screening the index families:

There are several other advantages in screening the index families. For example, the screening can be initiated by counselling of one or a few individuals in a family. The rest of the family members are likely to follow the guidance of the leading members. A critical step would be to identify the right person as the starting point. The key person in a family can be identified by asking others to whom they go for advice. Some of the families who refused the offer for screening mostly did so because of the lack of a key person. The social set up in most Pakistani families, particularly in the rural areas, is such that a few family elders handle most of the important affairs (Punjabi 1976). The obedience of the younger generations is considered obligatory. Therefore it would be appropriate to involve the family elders in the screening exercise. Marriage in a Pakistani set up is mostly planned by women, but the final decision whether to accept or to reject the proposal may lie with the men. While carrying out screening inclusion of both men and women would be essential.

There also are technical advantages in carrying out a targeted screening. For example it can be started from the eldest available members. The children may be screened only when one or both of their parents are found to be carriers. A practical problem may arise, because in a field trip to a rural area it may be difficult to screen the elders first and sample the children at a later stage. One tube osmotic fragility test (Kattamis et al, 1981)

can be very useful for guiding on the spot whether to include or exclude a person from screening. This may substantially reduce the number of individuals requiring screening.

Genetic counselling:

At present most of the couples who seek genetic counselling in the Eastern Mediterranean Region, including Pakistan, are already married and have one or more affected children (Alwan and Modell 1997). Once the genetic diagnosis is made the couples learn that the treatment of the child is complex and life long and there are chances of recurrence of the disorder in future pregnancies. A choice to have no further children may be relatively simple for couples who have several healthy children. The choice may be difficult for the young couples. The study shows that prenatal diagnosis is technically feasible and is also accepted by the majority of the retrospectively identified couples. This may reduce stress within the families by broadening choices away from focus on choice of partner. It therefore would reduce stigma, stress and fear. Continuing and sustained efforts are needed for counselling the affected couples who report to the treatment centres. This is not only important for the couple itself but it also provides an opportunity to access a large number of other family relatives who may be at risk. Alwan and Modell (1997) have suggested that retrospective counselling of the affected couples where the final family size is large may reduce the birth incidence of thalassaemia major to almost 50%. The offer of prenatal diagnosis to such couples can further reduce the birth rate of affected children. The response of the prospectively identified at risk couples to genetic counselling could not be assessed in this study as this is a long term undertaking. Clearly more research is needed to investigate this aspect.

Genetic counselling aims at replacing misunderstandings with correct information about the cause of genetic disease and resources available for its diagnosis, treatment and prevention. It is usually done according to the internationally accepted guidelines (Harper 1993). The approach however may be modified according to the local cultural, social and religious beliefs (Alwan and Modell 1997). The issues that need consideration while formulating an approach for counselling Pakistani families include (1) illiteracy (2) confidentiality (3) stigmatisation and (4) consanguineous marriages.

Illiteracy:

Comprehension of the genetic concepts correlates with the level of education (Yuen et al, 1988). However, even in well educated communities the effect of counselling on the knowledge of carrier state and its implications may be small (Barrai and Vullo 1980b). The situation may be worse in a predominantly uneducated community as in Pakistan where it may be difficult to grasp even the basic concept of a genetic disorder. The aim of providing an informed choice can be achieved only if the parents understand the implications of the choices. Therefore the genetic counsellor in addition to providing information and giving an informed choice, may have to help in making the right choice. The counsellor should not be over-directive or the individuals may feel guilty about their choice. Counselling may be made more effective by using visual aids and illustrated booklets.

Counselling would be easier if the person has already seen affected children. While screening the index families most members would have at least some knowledge about the affected child's illness. This is a significant advantage when the literacy rate is very low. It would be unrealistic to expect an illiterate Pakistani lay person to understand or believe they carry a very severe disease, which they have never seen or heard about previously. Counselling therefore would be easier and more effective when delivered to members of a thalassaemic family.

Confidentiality:

Confidentiality of results would be a key factor in counselling of individuals in a family. During screening in the families it was observed that some individuals had reservations about screening because they thought it might cause difficulties in arranging marriages of their children. The marriage in a traditional Pakistani family is arranged by agreement between the parents of the spouses. The parents try their best to find a match within the family or the Biradri (Punjabi 1976). Therefore if the carrier status of a boy or a girl was known within the family, then these individuals may be rejected as spouses. In one of the families, the mother of a thalassaemic child, who herself was under considerable stress due to the illness of her child, preferred to hide the carrier status of her younger brother while arranging his marriage with another close relative. The targeted screening is attractive but its actual impact on making decisions about marriage preferences in a family may be complicated. In cases where rejection of a carrier is feared, prenatal

diagnosis may work as an acceptable solution. Rejection of heterozygotes does not happen in Cyprus because the population is educated and prenatal diagnosis is freely available (Prof. B. Modell personal communication).

Stigma:

Thalassaemia carrier status may be taken as a stigma for the affected person or families. The counselling of carriers should also include efforts to reduce the element of stigmatisation. It may help to inform the carriers of the benefits associated with the disease. The knowledge that the carriers have a natural resistance to falciparum malaria (Weatherall et al, 1989) or ischaemic heart disease (Crowley et al, 1987; Gallerani et al, 1991; Wang and Schilling 1995) may be helpful to reduce stigmatisation.

Consanguineous marriage and implications for counselling:

In populations where consanguineous marriage is customary, an understanding of its genetic implications is essential for developing appropriate genetic services. Numerous studies provide supporting evidence that consanguineous marriage is associated with increased risk of genetic disorders (Bittles 1980). However, the data supports some harm but clearly shows it is far less than generally believed. It is important to understand that the outcome of consanguineous marriage should not be assessed solely in terms of the restricted horizon of medical audit (Bittles 1995). There are numerous social and economic benefits associated with this practice (Alwan and Modell 1997). Our current state of knowledge tends to be overly focused on the undesirable clinical outcome of close kin marriage, which affect only a minority of families and individuals (Panter-Brick 1991). There is a much larger proportion of couples whose children do not show identifiable deleterious biological effects and to whom the social and economic benefits of a consanguineous marriage appear obvious and natural (Bittles 1995).

This leaves a dilemma for the medical geneticists and others, whether to discourage the practice on medical grounds or not. Attempts to discourage the practice on genetic grounds alone can do more harm than good (Modell and Kuliev 1992). A more appropriate and acceptable solution would be the establishment of educational programmes and to provide counselling and carrier screening if available for the families who already have a child with a recognizable genetic disorder or where there is an

unfavourable family history. In Pakistan the progress in developing screening programmes for genetic disorders may be slow because of the limited resources available. A strategy to identify and diagnose genetic risk may be required, that can be gradually developed over time. Haemoglobin disorders are a good group to pilot and develop the approach.

Prenatal diagnosis:

Molecular genetics of haemoglobin disorders:

Plenty of data are available on thalassaemia mutations in people from the Indian subcontinent (Kazazian et al, 1990). But most of the studies have been done on selected individuals settled in the Western countries. Varawalla et al (1991a; 1991b) have studied β-thalassaemia mutations in British Pakistanis from the northern parts of Pakistan. But this study is inadequate for epidemiological purposes because of a small sample size and lack of representation of all ethnic groups. The present study of over 1200 mutant alleles provides a comprehensive picture of β-thalassaemia mutations in the major ethnic groups of Pakistan.

A total of 19 different mutations were identified. The five common mutations, IVSI-5 (G-C) (37%), Fr 8-9 (+G) (25%), del 619bp (7%), Fr 41-42 (-TTCT) (7%), and IVSI-1 (G-T) (5%) account for 81% of the alleles. In each ethnic group four or five common mutations account for over 80% of the alleles (Fig: 10.4).

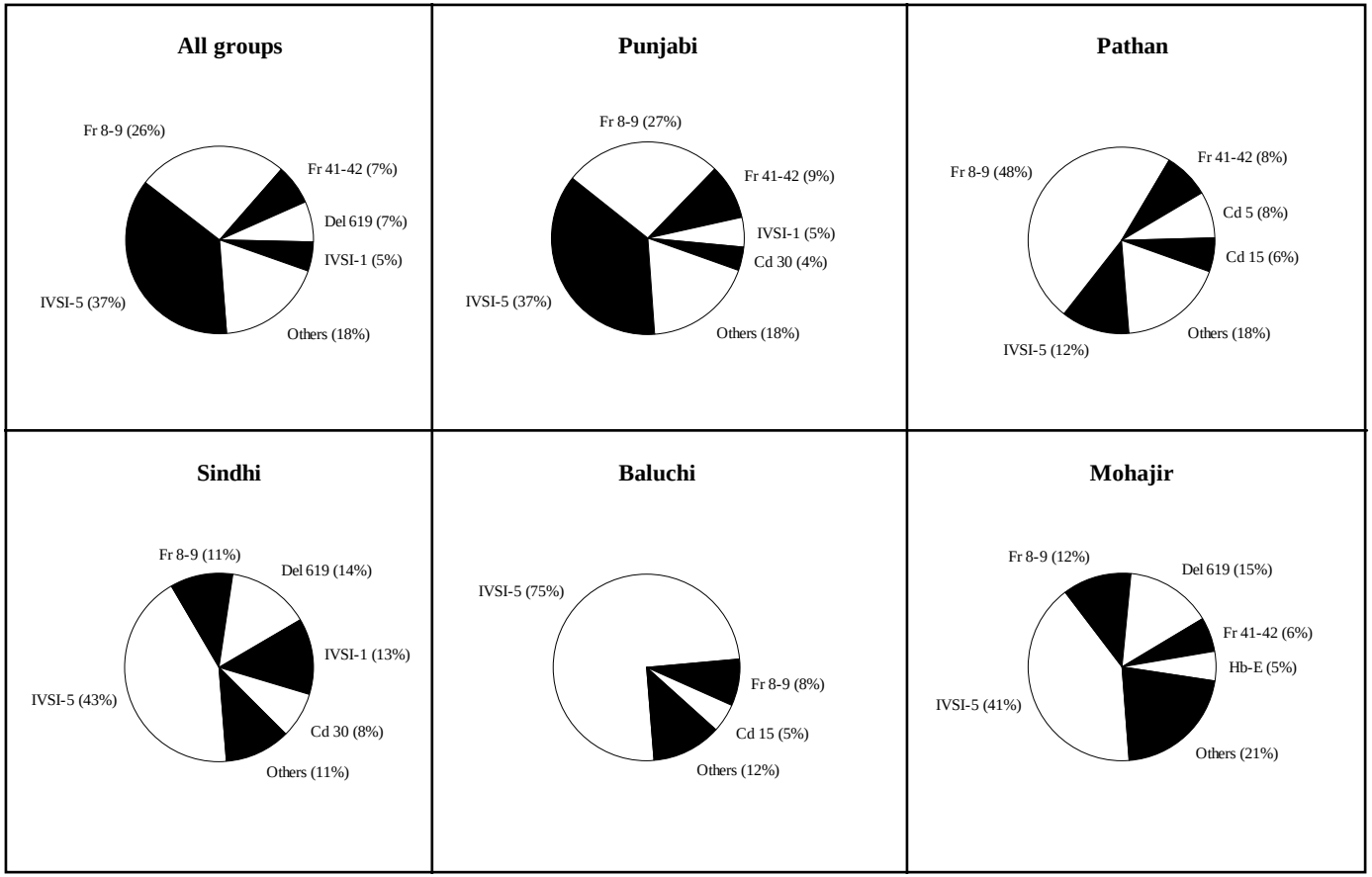

Fig: 10.4. Spectrum of thalassaemia mutations in the five major ethnic groups of Pakistan.

The spectrum of mutations is heterogenous in all of the ethnic groups except in Baluchis where IVSI-5 alone comprises 75% of the alleles. Several factors e.g. the time since appearance of a mutation, population migrations, and random genetic drift might have contributed to the genetic heterogeneity.

Technical feasibility of prenatal diagnosis:

Prenatal diagnosis by direct mutation analysis was possible in over 98% of the couples. In the remaining couples linkage analysis can be used as a backup support. The method is quick, reliable and cost effective. Mutation analysis by multiplex ARMS PCR was also technically feasible and very effective in reducing the cost.

Response of the families to prenatal diagnosis:

There is very little information about the reaction of Muslim families in general and Pakistanis in particular to prenatal diagnosis. Initial information for British Pakistanis suggested a low uptake rate of prenatal diagnosis (Modell et al, 1981). Recent results in the UK show that late referrals, inadequate counselling and a preconception amongst health professionals that Pakistanis do not terminate pregnancies because of religious reasons are the main reasons for low utilization (Petrou 1994). The data from British Pakistanis cannot be extrapolated to Pakistan as British Pakistanis mostly represent people from the Mirpur district in the north of Pakistan that migrated to the UK in the sixties and maintain limited contact with the people back home.

The vast majority of the affected couples in this study (96%) were in favour of prenatal diagnosis and said they would request it in the future pregnancies. Only 56% of the families who had a pregnancy when prenatal testing was available actually used prenatal diagnosis. This finding is not unusual because many people may not actually do what they might have thought of doing in the future (Alwan and Modell 1997). The behaviour of the couples was related to their educational level and socio-economic status. For example, in a randomly selected sample 27% of the couples said they would request prenatal diagnosis in future pregnancies only if the test were free of cost because they could not afford it otherwise. This was probably an important factor in the lower than expected uptake of the test which costs Rs. 3000 ($75). The families may not have been worried about the cost of treating a thalassaemic child as this was free of charge (blood

transfusions only).

This study clearly shows that prenatal diagnosis is accepted by most thalassaemic families in Pakistan. There are two important issues that may determine the long term outcome of prenatal diagnosis and need further discussion. These are (1) termination of pregnancy for a serious genetic disorder and (2) cost of prenatal diagnosis.

Termination of pregnancy for serious genetic disorders:

Islam is the leading religion of Pakistan and it is the faith of about 97 percent of the people. A vast majority of the population follows the Islamic rituals. The low rates of adult literacy in Pakistan make it difficult for the people to distinguish between their religious, traditional and cultural beliefs. This can easily lead to misconceptions about the permissibility or prohibition of anything in religion. In the context of prenatal diagnosis of genetic disorders the most important question is whether termination of pregnancy is permissible in Islam, if the fetus is affected by a serious genetic disorder?

Induced abortion has always been frowned upon in all human societies. As early as the dawn of medical history abortion was taboo. Its proscription was included in the Hippocratic oath and therefore it has been part of the professional heritage from generation to generation up to our own times. The semblance of unanimity on prohibition of abortion however excludes cases where a continuing pregnancy can be harmful for the mother's well being or when the fetus is seriously deformed or defective (Hathout 1974). The views of Islamic jurisprudence on the subject are unanimous in prohibiting abortion if it is carried out on the embryo after animation unless there is a valid reason or excuse justifying it. Concerning abortion before animation the views differ and range from permissibility and disfavour to prohibition (Makdur 1974). The concept of animation is explained in a Quranic verse as follows:

> *"Then We made the sperm into a clot of congealed blood; then of that clot We made a lump (fetus); then We made out of that lump bones and clothed the bones with flesh; then We developed out of it another creature" (Al-Quran, Sura Al-Momenoon verse 14).*

There is consensus of opinion that “development of another creature” means breathing of soul in to the inanimate fetus (Shafi 1980). However, a difference of opinion is found in the timing of animation. Some people think it coincides with the start of fetal heartbeat (40 days). Most Islamic scholars consider 120 days of embryonic age as the timing of animation, which is based on the following Hadith:

> *"Each one of you is put together in the womb of his mother for forty days, and then turns into a clot for an equal period (of forty days) and turns into a piece of flesh for a similar period (of forty days) and then the soul is breathed into him" (Abdullah, Sahih Al-Bukhari, 8.593).*

The community would accept the concept of prevention of thalassaemia if it were seen to be compatible with religious as well as cultural beliefs. Therefore it is important to consider the views of religious scholars, doctors, and the affected families. Two renowned religious scholars in Pakistan, when asked to give an opinion on the subject of permissibility of prenatal diagnosis for thalassaemia gave a clear verdict that it is permissible provided termination of pregnancy is carried out before 120 days (17 weeks) of pregnancy. Whether the time period specified is gestation or the embryonic age is not clear. But as a general policy we have taken the upper limit as the fetal age determined by ultrasound examination. Both the scholars had based their opinion on the above quoted Quranic verse and the Hadith.

Obstetricians have different views on termination of pregnancy. The two obstetricians who did CVSs in this study are of the opinion that termination can be done at any stage of pregnancy regardless of religious interpretations. They have in fact done CVS for couples reporting late and have also terminated pregnancies in such cases. Although there is no legislation in Pakistan defining an upper limit of permissibility of termination, it is important to work within the framework defined by consensus of opinion. We have not encountered criticism from any religious or social organization since introducing the service for prenatal diagnosis. However if a debate on this subject should arise in future, the service can be defended if it has the backing of prominent religious scholars. Leaving such sensitive issues to each individual's own judgement in the absence of consultation with religious leaders and the community can have harmful effects for the whole

programme.

Several couples in this study who were hesitant in using prenatal diagnosis were greatly relieved to learn that Islam permits termination of pregnancy under special circumstances. During the two study years three couples requested prenatal diagnosis after the 17th week of gestation. They were counselled and informed about the Islamic view on terminating a pregnancy at this stage. All three couples were greatly disappointed to know about this, but all opted to refrain from using the test.

Most of the couples who requested prenatal diagnosis in this study had little hesitation in terminating a pregnancy. Only 3/42 (7%) couples refused termination on religious grounds. An important reason for the high rate of acceptance of termination is that the couples had already made up their minds before requesting the test. It is likely that those who had reservations about the acceptance of termination had avoided the test. Most of the prospectively interviewed couples (87%) would have a termination of pregnancy if required in future.

Cost of prenatal prenatal diagnosis:

There is no allocation for thalassaemia in the National health budget and the affected families have to bear the cost themselves. Therefore the cost of treatment and diagnostic procedures is of fundamental importance in Pakistan. It was observed that the socio-economic status of over 2/3rd of the couples whose children were receiving treatment at a centre in Lahore was low (income <Rs. 5000 per month). This is also reflected by the response of 24% of the couples who would be willing to use prenatal diagnosis only if it were done free of cost. The total cost of one prenatal diagnosis including CVS, laboratory diagnosis and possible termination in selected cases is Rs. 3600 ($90) by the standard method and it can be reduced to Rs. 3000 ($75) by the multiplex ARMS method. The cost is very low as compared to $ 900-1000 per diagnosis in the UK (Petrou et al, 1990). This is mainly because of the very cheap cost of labour in Pakistan. Our experience shows that even at such a low cost many patients are unable to afford the test. Clearly there is a need to subsidize the cost of prenatal diagnosis by the government or NGOs.

National thalassaemia prevention programme:

Short-term measures:

The "ideal" approach for thalassaemia prevention in Pakistan is a long way in the future. The most important first step would be the organization and utilization of the existing resources. The NGOs have a very important role to play. From the point of view of prevention, the most effective simple and cheap step would be to focus on informing the affected families at the treatment centres about carrier screening and prenatal diagnosis. This step alone may bring about 50% reduction of new births in the families who come to treatment centres (Alwan and Modell 1997). Offering prenatal diagnosis to the couples would further reduce the birth rate. However, the cost of prenatal diagnosis might have to be subsidized to make its full utilization.

Long-term measures:

The long term solution for thalassaemia lies in the adoption of a National policy. A suggested plan for the programme is presented in Fig: 10.5. This includes establishment of a cell for prevention and control of genetic disorders in the ministry of health and the appointment of a National programme co-ordinator who should co-ordinate the activities of the Governmental and the non-governmental organizations. A joint approach for all genetic disorders may be more appropriate to get Government support. Separate expert panels should be appointed under the supervision of the National co-ordinator to organize prevention and treatment activities of the important genetic disorders including thalassaemia.

The expert panel on treatment for thalassaemia should include paediatricians, haematologists, and psychologists. The panel should formulate and ensure adoption of a uniform protocol for thalassaemia management and do research studies on new and cheaper treatment options. For example the trial of oral iron chelators can be a useful study. Provision of screened blood for transfusion should be ensured by compulsory screening of blood for hepatitis and HIV. A regular audit of the treatment facilities at the centres run by NGOs and charity organizations should be mandated.

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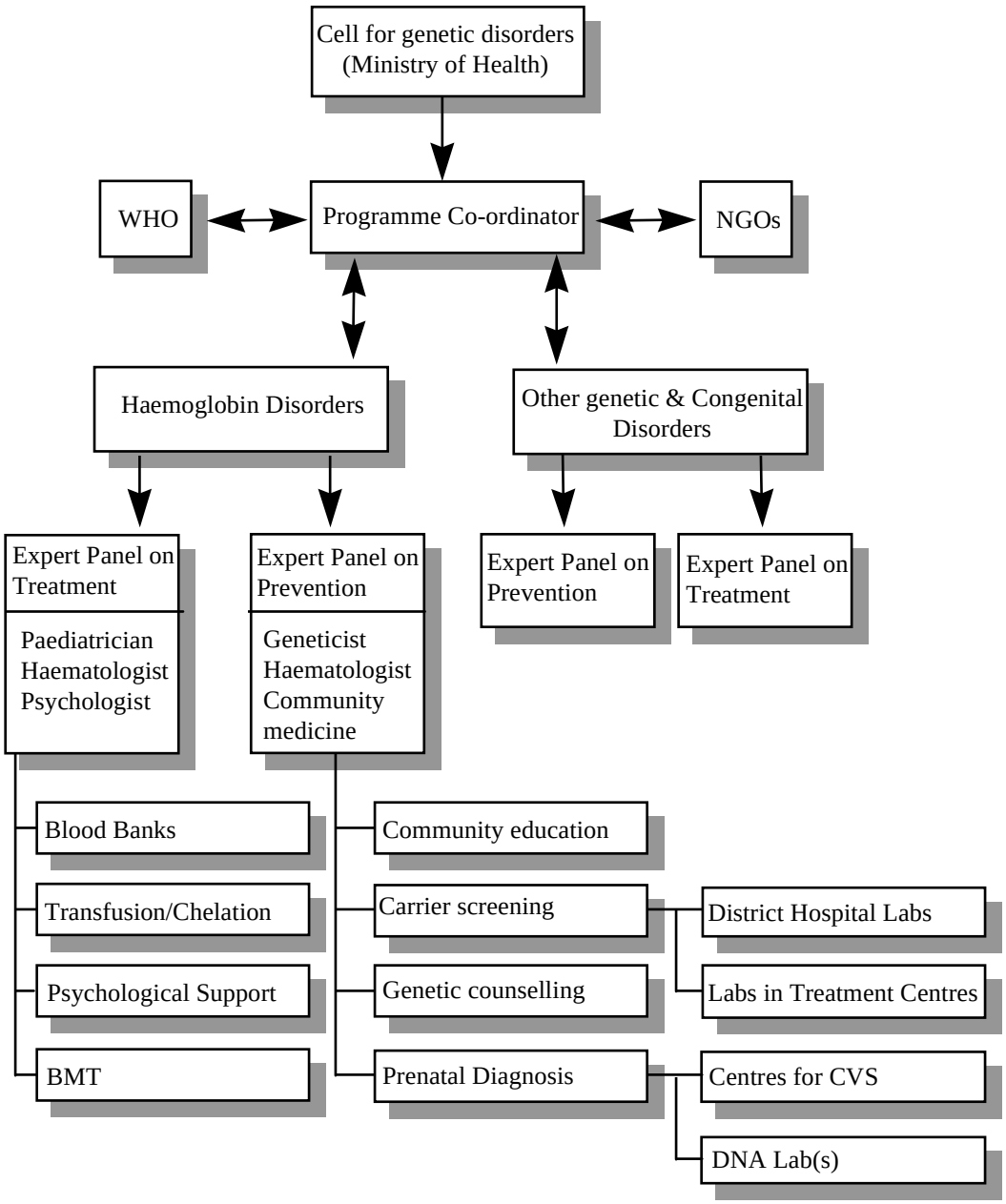

Fig: 10.5. A suggested layout of a National plan for prevention and control of genetic disorders in Pakistan.

The panel on prevention should comprise geneticists, haematologists, and experts on public health and community medicine. The National plan for prevention should include training of manpower and establishment of diagnostic centres. Basic facilities for screening of haemoglobin disorders should be established at each district hospital

laboratory. Additional units for carrying out screening of haemoglobin disorders should also be established at each treatment centre. The latter should be equipped with sufficient staff to carry out screening in the families and provide genetic counselling to the affected couples and the carriers.

A centre for carrying out CVS should be established at each thalassaemia treatment centre. The samples collected at these centres can be transported to a central DNA laboratory. A DNA laboratory should also be established in the South of the country. The two laboratories should be able to handle the prenatal diagnostic work for the whole country.

Monitoring the outcome of programme:

The success of the programme can be monitored at regular intervals by evaluating the following parameters (Alwan and Modell 1997) at the treatment centres:

1. Improvement in survival of patients monitored through a central registry of the number and age distribution of patients.
2. Improvement in quality of life of the patients (e.g. growth, school attendance etc.).
3. Reduction in birth prevalence of new cases (also assessed through patient register).
4. Documenting the circumstances of the birth of new thalassaemic children.
5. Impact on the family life of the parents (assessed by measuring the number of healthy children they have relative to the population norm).

Funding for the thalassaemia prevention programme:

In view of the meagre health budget it is unlikely that a major share for funding would be provided by the Government. Therefore fund raising by voluntary donations and NGOs would be important. A National Thalassaemia Fund can be established. The help of philanthropists and the Zakat Foundation, which is already sponsoring many useful projects in the health sector, can significantly contribute towards initiating a programme as well as its recurring expenditures. Zakat is a Muslim tax of 2.5% that is levied on the total income and fixed assets of the well to do Muslims. The beneficiaries of the Zakat

fund are the poor and deserving people.

Cost and benefit of various policies for thalassaemia:

For the purpose of comparing cost effectiveness three policies for thalassaemia in Pakistan are considered. Policy-1 is based on providing only treatment facilities but no measures for prevention. Policy-2, in addition to treatment, includes retrospective genetic counselling and provision of prenatal diagnosis for all future pregnancies. Policy-3, in addition to the features of Policy-2, includes screening the index families with a view to prospectively identify at risk couples and offer prenatal diagnosis. A comparison of the cost of the three policies (Fig: 10.6) clearly demonstrate the benefits of adopting policies that include prevention.

Most of the savings in adopting preventive policies are done on the cost of treatment. Since the Government is not spending anything directly on the treatment of thalassaemics, the cost of initiating a prevention programme is likely to be an additional liability rather than a relief for the Government. Keeping in view the limited health budget and the health priorities of the Government, the role of NGOs and the private sector becomes important. A co-ordinated activity and recruitment of more NGOs working for thalassaemia would be of fundamental importance.

Application of the results to other EMR countries:

Consanguineous marriage and clinically significant haemoglobin disorders are common in most countries of the Eastern Mediterranean Region (Alwan and Modell 1997). Table 10.2 summarizes the frequency of consanguineous marriages and the annual births of children affected with haemoglobin disorders in the EMR countries. The majority population of these countries is Muslim. Prevention programmes for thalassaemia do not exist in any of these countries except Iran. Therefore the response of the population to various options of prevention is mostly unknown. The cultural social and religious background of the entire EMR has several things in common. However, the socio-economic conditions, education and organization of the health care system varies considerably in different countries of the region.

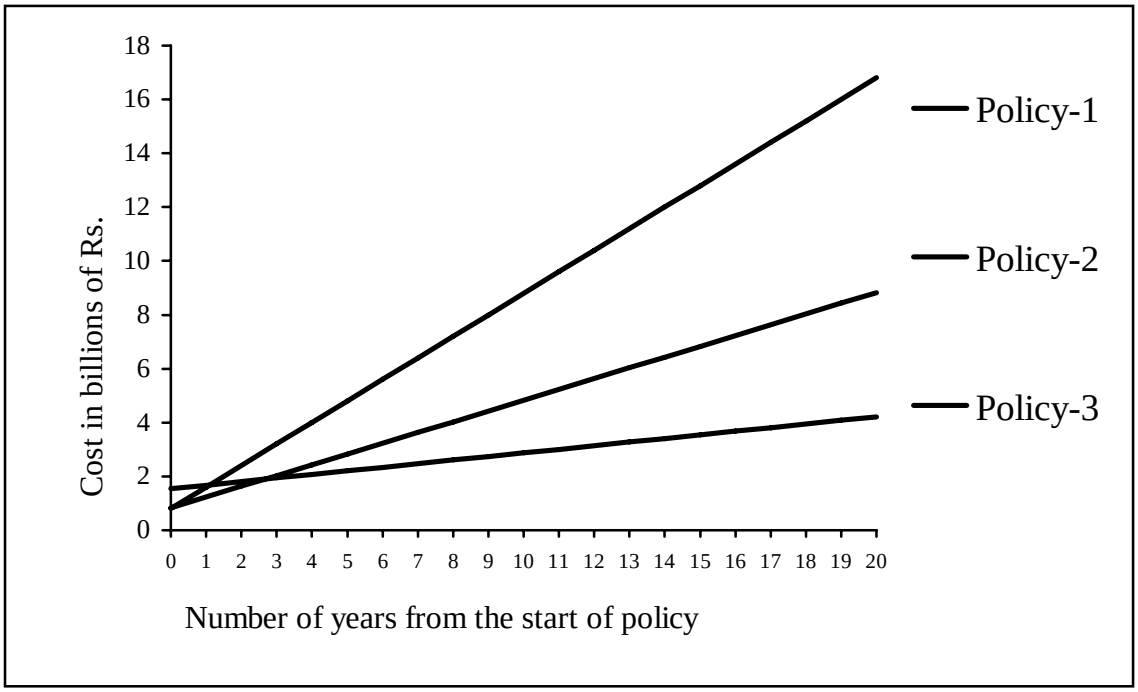

Fig: 10.6. Cost effectiveness of the three policies for thalassaemia in Pakistan. A basic feature of all policies is the provision of adequate treatment facilities to all patients. Policy-1 includes only treatment but no measures for prevention. Policy-2, in addition to treatment, includes retrospective genetic counselling and provision of prenatal diagnosis for all future pregnancies. Policy-3, in addition to the features of Policy-2, includes screening the index families with a view to prospectively identify at risk couples and offer prenatal diagnosis.

The following general guidelines based on the results of this pilot study can be helpful in formulating policies for other EMR countries:

1. Screening the index families is the most cost effective approach to identify at risk couples and unmarried carriers i.e. “premarital testing” well in advance.
2. Screening the index families provides the best opportunity for counselling of the carriers as most members of the family have at least some knowledge of the illness of the affected child.
3. Antenatal screening may be feasible if most at risk pregnancies can be monitored in the 1st trimester.
4. Prenatal diagnosis is technically feasible by cost effective methods and is also accepted by the affected families provided at risk pregnancies are identified in the 1st trimester.

5. Most religious scholars consider that termination of pregnancy is permissible for a serious genetic disorder provided it is done before 17 weeks of gestation.

Efforts to discourage consanguineous marriages on medical grounds can do more harm than good. The best approach would be to encourage carrier screening in the families at risk and take the information and availability of prenatal diagnosis into account when planning marriages.

Table: 10.2. Frequency of consanguineous marriage and annual number of children affected by haemoglobin disorders in the EMR countries (Based on Alwan and Modell 1997).

Country:	**Total consanguineous marriages:**	**Annual number of children affected with Haemoglobin disorders:**
Bahrain	39%	126
Egypt	29%	808
Iran	37%	1,896
Iraq	58%	1,501
Jordan	50%	97
Kuwait	54%	47
Lebanon (muslims)	30%	110
Libya	?	166
Moroco	?	1,824
Pakistan*	45%	5100
Saudi Arabia	54%	2,845
Sudan	?	2,314
Syria	?	1,043
UAE	54%	46
Yemen	?	1,571

? 20-50% consanguineous marriages
* this study