

Evaluation of the national health policy of thalassaemia screening in the Islamic Republic of Iran

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تقييم السياسة الصحية الوطنية لتحريّ التلاسيميا في جمهورية إيران الإسلامية

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الخلاصة: استعرضَ الباحثان العبء الطبي والاقتصادي الذي تخلفه حالات الإصابة بداء التلاسيميا الكبرى، مع التأكيد على أهمية تشخيص المرض قبل الحمل للوقاية من الإصابة، بوصفه الأسلوب الأمثل لتحقيق سياسة رعاية صحية اقتصادية وغير مكلفة. ويتم بموجب البرنامج الحالي المطبق في جمهورية إيران الإسلامية فحص الزوجين قبل الزواج مباشرة للتعرف على حاملي المرض، ومن ثمّ إحالتهم لتلقي النصيحة الجينية المناسبة. ولقد راجع الباحثان ما هو منشور حالياً للبحث عن نموذج أكثر تحديداً وتحريراً الأمور الخاصة بالامتنال للتعليمات الصحية، وذلك من خلال مقابلات أجريت مع الأطباء والأزواج والعائلات التي لديها أطفال مصابون بهذا المرض. ولم تكن نتائج البرنامج مُرضية عند المقارنة مع برامج أخرى مشابهة أجريت في إقليم البحر المتوسط. وعلى هذا صمّم الباحثان شجرة قرار مبسّطة تشتمل على مردودية التكاليف والأمور الفنية والمنهجية والاجتماعية التي تؤثر على الامتنال. ومع أن إجراء تعديلات على السياسة الصحية يمكن أن يؤدي إلى تحسين الفعالية والمصدقية في هذا الشأن، بل قد يقلل من تكاليف الفحص، إلا أن الحاجة لاتزال قائمة لمتابعة هذه المسألة عن كثب، ولاسيما الجانب المتعلق بتوفير الفحوص التشخيصية للأزواج الحاملين لهذا المرض.

ABSTRACT We reviewed the medical and economic burden of thalassaemia major with emphasis on prenatal diagnosis for disease prevention as the most economic health care policy approach. The current programme in the Islamic Republic of Iran screens couples just before marriage, identifies carriers and refers them for genetic counselling. We searched the current literature for a refined model and enquired into compliance issues in interviews with physicians, couples and families with affected children. The programme was unsatisfactory in comparison with comparable programmes in the Mediterranean region. We devised a simple decision tree that incorporates cost-effectiveness and technical, methodological and social issues that affect compliance. While revisions to the policy could improve efficiency, follow-up is needed, especially to provide prenatal diagnosis for carrier couples.

Évaluation de la politique nationale de santé en matière de dépistage de la thalassémie en République islamique d'Iran

RÉSUMÉ Nous avons examiné le fardeau médical et économique de la thalassémie majeure en s'intéressant plus particulièrement au diagnostic prénatal pour la prévention de la maladie en tant qu'approche la plus économique de la politique de soins de santé. Le programme actuel en République islamique d'Iran effectue le dépistage des couples juste avant le mariage, identifie les porteurs et les oriente vers un service de conseil génétique. Nous avons effectué une recherche dans la littérature actuelle pour trouver un modèle amélioré et avons enquêté sur les questions de compliance dans des entretiens avec des médecins, des couples et des familles ayant des enfants affectés par cette maladie. Le programme n'était pas satisfaisant par rapport à des programmes comparables dans la Région de la Méditerranée orientale. Nous avons mis au point un arbre décisionnel simple incorporant le rapport coût-efficacité et des points techniques, méthodologiques et sociaux qui affectent la compliance. Alors que les révisions de la politique pourraient améliorer l'efficacité, un suivi est nécessaire, notamment pour assurer le diagnostic anténatal pour les couples porteurs.

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Introduction

Every year approximately 60 000 thalassaemic babies are born worldwide. Optimal management of thalassaemia major requires specialized medical services in equipped centres, and over the lifetime of a patient the cost of care is extremely expensive [1]. In countries where the incidence of thalassaemia is high with a big burden of the disease to the population and the economy, intensive preventive programmes have been established and have been very successful [2–4]. This disease is a prime example in which prevention has primary importance and priority over treatment, thus prenatal diagnosis has been the mainstay of most control programmes thus far.

Chorionic villus sampling (CVS) and amniocentesis have been used to obtain samples for genetic analysis. Prenatal diagnosis of thalassaemia major is made using molecular techniques to test these samples, but accurate characterization of the molecular abnormality depends upon knowledge of the abnormal genetic forms, or thalassaemia variants, in each community [5–7]. Prenatal diagnosis as the preventive strategy theoretically requires the termination of 25% of such pregnancies by abortion; therapeutic abortion is the final tool of prevention in standard control programmes.

Thalassaemia in the Islamic Republic of Iran

Beta thalassaemia is the most common hereditary disease in the Islamic Republic of Iran. All patients with thalassaemia major are registered by regional health care centres. The country has about 26 000 thalassaemia major patients and an estimated 3 million thalassaemia carriers. The latter figure is easily calculated as the beta thalassaemia carrier frequency in the country has

been estimated to be 4%–5% in screening studies and the July 2000 census reported a population of 65 619 636. This gives us an estimated 2 620 000–3 280 000 carriers (mean 2 950 000). Furthermore, it has been estimated that about 8000 pregnancies are at risk each year.

The prevalence of thalassaemia major varies throughout the country with the highest incidence in regions near the Caspian Sea and the Gulf. The provinces of Mazandaran, Gilan, Hormozgan, Khuzestan, Kohkiluyeh-Boyerahmad, Fars, Bushehr, Sistan-Baluchestan, Kerman and Isfahan are the 10 provinces most afflicted.

In 1995–1996, the Blood Transfusion Organization of Iran and the Iran Thalassaemic Patients Supporting Society mass screened 8300 students from 114 high schools in Tehran for the beta thalassaemia trait. The project lasted for 2 months. Based on the results of that study, the government included beta-thalassaemia screening laboratory tests in the compulsory package of medical tests for all couples prior to marriage [8]. This standard control programme for thalassaemia, however, has not been practical because of religious uncertainties about issuing permits for legal therapeutic abortions. Instead, identifying “both carrier” fiancés and providing counselling to dissuade them from marriage, or not allowing them to marry, has been emphasized. Even those not ethically opposed to therapeutic abortion have recommended this alternative method, because access to fetal sampling techniques and laboratory diagnosis are very expensive.

The cost issue is especially important in the Islamic Republic of Iran because the dominant public insurance systems do not cover expenses not in line with well-defined government policies. A few couples have tried sending the samples to countries with high-tech facilities for laboratory di-

agnosis like the United Kingdom, but incomplete knowledge of the variety of the diseased genes in Iranian communities, the lengthy wait for the results and the high costs have interfered.

Screening for beta thalassaemia trait

Approximately 3% of the world population are carriers of a beta thalassaemia mutation. Mass screening and genetic counselling programmes have been carried out in many countries with high carrier states, but some factors have undermined the effectiveness of antenatal screening for prevention of thalassaemia [9–11]. For example, many medical practitioners and the general public are still unaware of screening procedures or do not comply and so new patients are still diagnosed in areas where the disease has been locally preventable by antenatal screening [12,13]. Defining national health policies to mass screen for carriers could be a solution and forms the basis of thalassaemia control programmes.

In an economic sense, there is a trade-off between the costs of diagnosis and prevention and the treatment of undiagnosed cases. The system must consider the cost of acceptable, although suboptimal, care for all thalassaemia cases including those births that could have been avoided. The cost of care for other health care problems more common in thalassaemics, the time lost by parents caring for their children and the emotional burden for families dealing with this health problem should be considered too. In ideal circumstances the benefit to cost ratio is larger than 1. This supports the notion of community-based screening for prevention; therefore, choosing a suitable economic tool for mass screening is an important step.

The gold standard for diagnosis of the carrier state is haemoglobin electrophoresis, but because of its high cost, it is unsuitable for mass screening in developing countries with large populations like the Islamic Republic of Iran [14]. Most screening programmes use an initial simple but sensitive test, such as red cell mean corpuscular volume (MCV), or an osmotic fragility test [15]. The Naked Eye Single Tube Red Cell Osmotic Fragility Test (Nestroft) is a sensitive, cost-effective, rapid and reliable screening test for detection of beta thalassaemia trait, or the carrier state, in a population. A positive predictive value and specificity of 85%–100%, a negative predictive value of 83%–99% and a sensitivity of about 95% have been reported for Nestroft [16,17]. Nestroft as a single screening parameter is superior to any other simple tests like MCV and is more cost-effective [18]. As a result, Nestroft has emerged as the single most effective, inexpensive and easily reproducible test of population screening for beta thalassaemia trait. Nestroft in combination with MCV with the cut-off at < 80 fL has been proven to be 100% sensitive, but the combination is not cost-effective.

The screening method in the Islamic Republic of Iran is unclear and is sometimes confusing as usually only a complete blood count (CBC) is requested and many variables in the report are evaluated without specific measures or standard criteria. Nonetheless, as reported in our interviews, MCV seems to be the most important item to informed physicians who judge the results of the tests. They usually provide counselling as a simple explanation of the inheritance mechanism and prognosis of thalassaemia major, thereby keeping counselling expenses to just the doctor's visit

fees, especially in small cities where genetics counselling by specialists is unavailable.

Our study was a search of the current literature for information pertaining to the cost-effectiveness of the Iranian national screening programme in comparison to programmes in other countries. We also interviewed physicians, laboratory doctors and individuals personally affected by thalassaemia major. Our aim was to devise a simple decision tree that could be used to improve cost efficiency.

Methods

We searched electronic databases (including Medline, PubMed, EMBASE and CINAHL), information gathered by international and domestic thalassaemia support organizations, Iranian national health databases, collections of university periodicals and theses, research projects, presentations and reports of seminars and government reports with the following queries: "screening and thalassaemia", "Iran and thalassaemia" and "economics and thalassaemia". We sorted the retrieved data by abstracts and then we studied the full texts.

For more detailed information on the Iranian control programme and to examine its medical, laboratory and technical, social, ethical and patient group perspectives, a series of interviews were performed. We visited 5 health centres regularly providing services for thalassaemic patients, including clinics in Bahrami Hospital, Imam Khomeini Hospital and Amir-Kabir Hospital, and we interviewed 18 medical doctors, including 2 haematologists, 2 medical laboratory doctors (PhDs), 3 paediatricians, 4 obstetric-gynaecologists and 7 general physicians working in the screening system; 27 families (at least 2 members from any one family) of thalassaemic patients; and 9 couples referred for haemoglobin

electrophoresis tests (because of suspicious CBC test results). These visits served as a problem finding stage in which we identified commonly reported issues. We then further searched the literature for options with higher success rates and fewer problems, especially in other Mediterranean countries.

Finally, by looking at the programme's pitfalls with cost-effectiveness concerns and at the reviewed articles for potential methodological and technical improvements, a refined model was designed as a simple decision analysis tree.

Results

Thalassaemia control programme

Fars Province, in the south-eastern part of the country, is home to 5% of the population and nearly 10% of the thalassaemic patients of the Islamic Republic of Iran. In 1997–1998, a study evaluated thalassaemia in Fars. Ten years prior to the study, it had been estimated that the beta thalassaemia carriage rate was 7% in the province and a prevention programme had been initiated [19]. The 1997–1998 programme evaluated the prevalence of beta thalassaemia minor by examining 24 485 boys in their final year of high school. The frequency of beta thalassaemia minor in 1997–1998 was then estimated at 6.88% [19]; there were 2193 thalassaemia major patients (1263 boys and 930 girls) and the frequency of thalassaemia major was 7.2 in 10 000 population. The mean age of patients was 10.1 years with a SD of 6.6 years. A large part of the decrease in prevalence of thalassaemia major was among those under age 10 years and was less significant after adjustment for population age distribution. The slight decrease was determined to be the result of a birth control programme, rather than the programme for the prevention of beta

thalassaemia. Studying the reasons for the relative failure of the programme and setting up new strategies were recommended as the programme had been operating for 10 years and was only moderately successful.

Other studies found that the number of children born annually with congenital disorders in the country had fallen by 38% and potential births of children with thalassaemia major had fallen from over 1200 to about 860 per year while the overall population had increased [20,21]. More recent evidence from population surveys, however, indicates that the Islamic Republic of Iran has actually reduced its population growth to 1.2%, a rate only slightly higher than that of the United States of America. The country's population growth rate dropped from an all-time high of 3.2% in 1986 to 1.2% in 2001, one of the fastest drops ever recorded. The results of the former study [19] explained much of the success claimed in the latter studies [20,21]. The claimed decrease in thalassaemic births is not as great as in some endemic areas in the Mediterranean where long-established control programmes have achieved 80%–100% prevention of newly affected births [22].

Interviews

We interviewed 18 medical doctors, 27 families of thalassaemic patients, and 9 couples referred for haemoglobin electrophoresis tests because of suspicious CBC tests. This was our final problem finding stage and commonly reported issues included: the financial difficulties of the patients' families; lack of access to or lack of insurance funding for chelation therapy; unnecessary anxiety and confusion in the first round of routine screening; difficulties performing prenatal tests; and difficulties obtaining legal abortions of thalassaemic fetuses.

With this information, we charted the current programme as a simple decision tree (Figure 1). Then, using information from our literature search, we devised a decision tree that is more cost-effective (Figure 2).

Discussion

Economic aspects of thalassaemia

The economic burden of thalassaemia is determined by the birth prevalence of affected infants, their survival, the availability, cost and effectiveness of treatment,

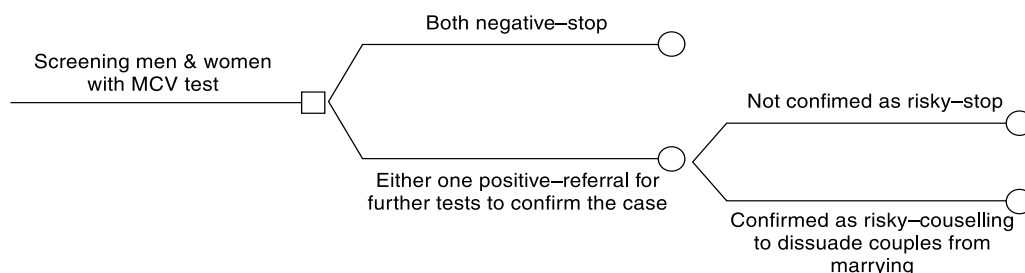


Figure 1 The flow of the screening procedure in the current thalassaemia programme presented as a simple decision tree

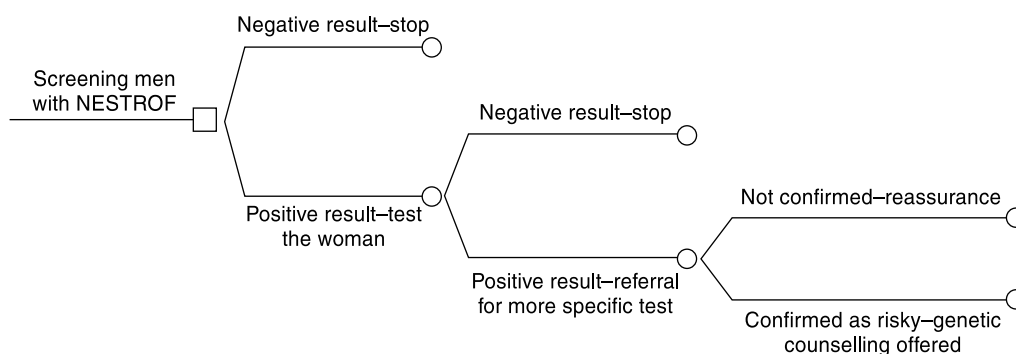


Figure 2 The flow of our proposed screening procedure, which introduces cost-effective refinements to the current programme, presented as a simple decision tree

social support and the extent to which patients can be integrated into society. The need for care and its costs at any given time depend on the number of living patients in the population. The availability of better health services leads to a cumulative increase in the number of patients needing care and also to a higher annual cost per patient because cost of care usually rises as treatment options improve. The lifetime cost of optimum treatment in developed countries has been estimated to be about US\$ 1 350 000 (undiscounted) per patient, and with a discount rate of 6%, about US\$ 370 000. In a sensitivity analysis, the discounted cost ranged from about US\$ 315 000 to US\$ 380 000 [23].

In most countries, children with thalassaemia major are easily diagnosed, and regular blood transfusion is available, is life saving and gives excellent short-term quality of life. Without more expensive therapy to remove excess iron, death from iron overload results at an early age; iron chelation therapy is needed for long-term survival.

There are many costs associated with thalassaemia, including blood transfusions,

medicines and other essential treatment, hospital care and home visits. Thalassaemic patients receive red blood cell transfusions every 2–3 weeks, amounting to as many as 24.6 litres of blood a year. In the Islamic Republic of Iran, 50%–60% of all donated blood is transfused to thalassaemic patients. Each bag of donated blood costs at least US\$ 25 to the country's Blood Transfusion Organization (personal communication). Desferrioxamine is imported and is currently (2001) about US\$ 3 per vial of 500 mg. A 12-year-old, 30 kg patient on regular blood transfusion will require three vials daily throughout his lifetime. Including the cost of consumables like disposable syringes and scalp-vein needles, the expenditure for Desferal therapy is US\$ 280 per month. The infusion pump is also imported and costs US\$ 400. Many costs to the patients are financed by plans in the public budget, and yet most thalassaemic patients cannot afford the cost of optimum treatment and die before they reach 20 years of age.

Major public health insurance policies discontinue coverage when the child reaches the legal age. This is yet another finan-

cial problem that thalassaemic patients and their families face, as they often do not have the resources to cover the costs. This can lead to a further fall in the quality of the care they receive and can have grave consequences on the patient's longevity. A great number of patients hence rely on charity and support organizations that provide the needed assistance. The estimated annual and 10-year projected costs for treating thalassaemia and the estimated annual cost of prevention in Eastern Mediterranean countries have been compared by the World Health Organization [24,25].

In the Islamic Republic of Iran, the average birth prevalence of thalassaemia major is 0.74 per 1000, and the proportion of patients expected to survive at least into their late teens has risen from practically none 30 years ago to over 90% today based on Iranian thalassaemic registries. Over 25 000 patients are currently under care, representing a forward commitment of approximately US\$ 220 million per year for at least the next 30 years. In the absence of prevention, annual treatment costs could rise to over US\$ 700 million per year. The treatment of thalassaemic patients is a huge expense on the national health budget, and therefore we propose that government and public insurance organizations actively look for eligible resources to continue insurance coverage until patients are employed.

Spending on preventive measures is more cost-effective than treatment in the Islamic Republic of Iran. As annual prevention costs are constant but annual treatment costs rise yearly, the cost-effectiveness of prevention increases with every year that it is in place. The 10-year projection figures suggest that it is impossible for the country to finance optimal treatment for all patients who may be born, and that effective prevention is a necessary condition for those already living to be adequately treated.

Health policy aspects

National programmes of community information, carrier screening and counselling, and availability of prenatal diagnosis have greatly reduced the birth prevalence of thalassaemia major in all countries where they have been established. In the Islamic Republic of Iran, a national prevention programme has been under development and the national patient register has shown a reduction, although insufficient, in affected births [26].

The health policy aspect of the control programme has a few problems that need to be addressed. The routine prevention of the birth of thalassaemic children by prenatal diagnosis has not been practically possible. The religious regulation, *hokm*, prohibits any kind of abortion after the fourth month of pregnancy. It does allow abortions before that stage, but only when the mother's life is endangered and provided that a lengthy procedure involving a council committee documents the case. After specialists petitioned the current religious leader, or *faghih*, about thalassaemia major, they received a permit for abortion only for cases of thalassaemia major before the fourth month of pregnancy. Initially the permit seemed enough, but in practice it has not been successful, as physicians have tended to be conservative and to hesitate to issue definitive opinions. Furthermore, obtaining test results is a lengthy matter. Chances of success for the legal option have thereby become so remote that in one daily newspaper a few specialists warned of and criticized the "legal void" that makes families resort to illegal abortions for thalassaemic babies. This problem is not unique to the Islamic Republic of Iran. In the United Kingdom, only a minority of couples of Hindu, Sikh and Pakistani origin accepted fetal diagnosis; termination

of pregnancy within the second trimester and alternative methods of control were recommended when this attitude prevailed [27].

The health policy in the Islamic Republic of Iran is to use alternative means to prevent the birth of thalassaemic children by avoiding marriages of carriers to each other [20]. In a large, 3-year study of 100 000 cases in Isfahan, after identification and genetic counselling of carriers, an average of 90% of high-risk couples decided not to marry and no new cases of thalassaemia were detected in the children of the screened population. It was concluded that when both members of the couple were trait-positive their preferred choice was not to marry, rather than to marry and use other or no methods to prevent the birth of a thalassaemic child. Cultural and religious ideas seemed to have a role in these decisions and the establishment and use of a genetic counselling centre seemed to prevent most new thalassaemia cases by discouraging at-risk couples from marriage [20]. Although more studies are needed to confirm this, some have already suggested a different explanation [19]. Moreover, 10% of at-risk couples in the Isfahan study that insisted on marrying, reported trying to register the marriage in another area outside Isfahan. The study did not follow them nor did it include their offspring in its results.

Results of the 4-year premarital screening programme to reduce the incidence of thalassaemia major in the city of Denizli, Turkey, are interesting [6]. At-risk couples were counselled and offered prenatal diagnosis and termination of pregnancy in cases of an affected fetus. This study demonstrated that premarital screening in the context of offering therapeutic abortion was very useful for detecting carrier couples and was an effective way of controlling thalassaemia major. It also showed that

only a small proportion of cases were likely to face the final decision to terminate pregnancy or not. In another study, prevention programmes based on carrier screening and genetic counselling in the absence of prenatal diagnosis produced no consistent effect on the birth rate of thalassaemia major [28].

Conclusions

The pitfalls in the current thalassaemia control programme could be addressed with a simple decision tree. Figures 1 and 2 show the scheme of the current programme and our proposed revisions.

The current programme screens both members of every couple applying for marriage with MCV indexes. In the standard package of premarital tests in the Islamic Republic of Iran, men provided a sample of blood to be tested by VDRL for syphilis screening and a sample of urine to be tested for addiction. Women only provided urine samples before the current programme began. We propose limiting the use of MCV index for thalassaemia screening to only men as this has many advantages over screening both men and women. Relying on microcytosis as revealed on MCV for thalassaemia minor screening has led to a large number of false positives as the number of iron deficient women is very high. The Ministry of Health and Medical Education reported a 17% rate of iron deficiency anaemia (34% iron deficiency) in women of childbearing age in the Islamic Republic of Iran (project report to the World Bank, 2000) [29]. Iron deficiency is the most common cause of acquired microcytosis worldwide and is prevalent in developing countries like the Islamic Republic of Iran. With fewer false positives, there will be fewer referrals to doctors and less psycho-

logical trauma of a hereditary disease stigma. Moreover, performing half the number of tests would reduce current costs of screening.

The use of CBC tests in the current programme causes confusion and could be largely avoided if the first screen were for men only or if the cheaper and more accurate Nestroft were to be used for screening. At very least, the current screening tool and its criteria should be standardized with specific cut-off points for MCV and with collaboration between the marriage registration offices requesting the screen, the laboratories performing the test, and the physicians judging borderline cases.

In the current programme, carrier couples are prohibited to marry: this endangers the compliance rate and adds to the stigma of being labelled a carrier. In our analysis, providing genetic counselling and asking the couple to consider the procedures necessary to prevent the birth of a thalassaemic child and the costs and risks, including death of healthy fetuses because of sampling procedure, is enough and is more efficient.

In the long term, we could include a suitable screening test in the health check

package of schools and could provide information with results of the test as is done in the Gaza Strip [30]. The matter could then be considered before choosing a partner for marriage instead of waiting until just before the couple prepares for the ceremony as in the current policy. The current policy does not provide the necessary compliance rate and is not ethical in this respect.

Iranian scientists have been able to detect up to 85% of cases (70%–90% for different geographic and ethnic origins) [31,32]. More successful prenatal diagnosis in the Iranian population requires more studies to identify mutant genes.

Finally, the current thalassaemia control programme has ignored a prevention policy for already married couples that may or may not already have affected children. The considerable number of families with more than one affected child seen in some studies is strong proof. Provision of a working option of prenatal diagnosis and therapeutic abortion for this group of couples is necessary.

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A study of national health research systems in selected countries of the WHO Eastern Mediterranean Region

A study of national health research systems in selected countries of the WHO Eastern Mediterranean Region comes at a time of global interest in promoting the development of appropriate national health research systems in low and middle-income developing countries. It presents the findings of a detailed and systematic situation analysis of the national health research systems in five countries of WHO's Eastern Mediterranean Region: Egypt, Islamic Republic of Iran, Morocco, Pakistan and Sudan. The aim of the study was to pave the way for developing innovative and effective strategies for strengthening national health research systems in the Region. The experience gained will be shared with other countries in the Region and will provide a critical input to WHO's collaboration in the Region in the area of health research in the coming years. The publication can be obtained from: Distribution and Sales, World Health Organization Regional Office for the Eastern Mediterranean, Abdul Razzak Al Sanhoury Street, PO Box 7608, Nasr City, Cairo 11371, Egypt. Telephone: (202) 670 25 35; Fax: (202) 670 24 92/4; Email: emr:dsa@emro.who.int.