

**Human Genetics Programme  
Management of Noncommunicable Diseases  
World Health Organization**

WHO/HGN/WG/00.1  
ENGLISH ONLY  
Distr.: GENERAL

# **Primary health care approaches for prevention and control of congenital and genetic disorders**

**Report of a WHO meeting,  
Cairo, Egypt, 6-8 December 1999**



Copyright © World Health Organization, 2000

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced or translated, in part or in whole, but not for sale or for use in conjunction with commercial purposes.

The views expressed in documents by named authors are solely the responsibility of those authors.



# Executive summary

As a result of the global fall in infant mortality and birth rate, the focus of health policy development is shifting from acute problems towards management of chronic disease and disability, and from vertical programmes towards integrated primary health care systems. This change is particularly marked in the area of reproductive and child health, because an increasing proportion of infants born with potentially disabling conditions, who would previously have died undiagnosed, now survive and require medical and supportive interventions. The health burden of congenital disorders can be greatly reduced by deploying approaches for primary prevention, cure when feasible (e.g. paediatric surgery), supportive management when cure is not feasible, and availability of prenatal diagnosis and selective abortion, and in many developed countries infant mortality is now lower than the birth prevalence of potentially lethal congenital disorders.

However, no comprehensive model of these interventions is available. Services in developed countries have grown up in an ad hoc manner, and are not perceived as components of a single discipline. The time has come to develop systematic scientific approaches for the control of congenital disorders, packages of care for implementation in reproductive and primary health care services, and appropriate training programmes.

In December 1999 a group of WHO advisors met in Cairo at the WHO Meeting on Public Health Approaches for the Control of Genetically Determined Disorders and Birth Defects in Primary Health Care to review the global epidemiology of congenital and genetic disorders, identify evidence-based interventions that are effective in reducing health burden, and recommend approaches that are as simple as possible and which can be implemented in primary health care and provide a basis for further service development. It was concluded that the potential burden of congenital disorders is at least as great in developing as in developed countries, and recommended a global initiative combining prevention, services for diagnosis and best possible patient care.

Implementation of basic reproductive health approaches, including accessible family planning, a diet adequate in folate, iodine, and iron, prevention and management of maternal infections (including HIV, rubella, syphilis and toxoplasma) and avoidance of excess alcohol and smoking, can reduce the birth prevalence of infants with serious congenital disorders to a baseline level. Further reduction depends on population screening programmes aiming to identify individuals at increased risk of having children with specific disorders. Approaches include ultrasound scanning for congenital malformations, offering chromosome studies to older mothers, screening for genetic causes of neonatal jaundice and for carriers of thalassaemias and sickle cell disorders, and neonatal screening using clinical and biochemical methods.

However, country differences in epidemiology, demographic factors, organisation of health systems, priorities, and available resources mean that no standard set of interventions can be recommended for universal application. A long-term programme including substantial research and development is required. The proposed WHO initiative therefore consists of a programme of work designed to support an organised approach to the control of congenital and genetic disorders in any country. It calls for formation of a national task force and development of a country plan, an epidemiological study to support planning and develop systems for education and audit, and a demonstration project followed by national implementation.

A corresponding programme of work is needed at the WHO level. This should be developed in a collaboration of selected experts, relevant WHO programmes, and country representatives, in a long-term working relationship.

The approach is recommended for consideration to all countries. Implementation of a collaborative international study with WHO technical support is foreseen for selected countries.

# Notes on terms used in this document

Many terms commonly used by specialists in congenital and genetic disorders are highly technical, or cumbersome, or lack an internationally agreed definition, and so are unsuitable for use in this document, which is intended for a non-specialist, multidisciplinary audience. In such instances the authors have selected terms that they consider will best convey their meaning, though they may not exactly coincide with current expert usage. The definitions of these terms are as follows (62-64):

*Congenital disorder:* any potentially pathological condition arising before birth. This includes all disorders caused by environmental, genetic and unknown factors, whether they are evident at birth or become manifest later in life.

*Disorder:* refers to a condition potentially leading to death or disease. The term excludes minor congenital abnormalities.

*Disability:* refers to a great number of different functional limitations occurring in any population. People may be disabled by physical, intellectual or sensory impairment, medical conditions or mental illness.

*Prevention:* reduction in the frequency and/or clinical manifestations of congenital and genetic disorders.

*A control programme for a congenital disorder:* a comprehensive strategy combining best possible patient care, with prevention through community information, population screening, and genetic counselling (including the offer of prenatal diagnosis when appropriate).

*A population:* a defined group e.g. all those residing in a defined area, all couples planning to marry, all pregnant women, all children with learning difficulties.

*Genetic screening:* a basic test that is systematically offered to a defined population, in order to identify a group at increased genetic risk, which may then be offered further tests leading to a definitive diagnosis.

*Genetic testing:* testing offered to people already known to be at increased genetic risk (e.g. the partner of a carrier of a haemoglobin disorder, an older pregnant woman, a woman with a fetus with increased nuchal translucency) in order to achieve a definitive diagnosis.

*Consanguinity:* blood relationship, e.g. of parents to children or siblings to each other.

*Consanguineous marriage:* a marriage between people who are blood relatives.

*Parental consanguinity:* situation when a person's parents are blood relatives.

*Primary health care:* first point of contact with the health service. It comprises community based health services, including public health components, reproductive health services, and services for front-line diagnosis and treatment.



# Table of contents

<b>1. INTRODUCTION .....</b>	<b>1</b>
<b>2. GLOBAL EPIDEMIOLOGY AND HEALTH BURDEN OF CONGENITAL DISORDERS .....</b>	<b>3</b>
2.1 Dilemmas for health services .....	5
2.2 The burden for families .....	8
2.3 Identifying priorities and key conditions for intervention.....	9
<b>3. BASIC REPRODUCTIVE HEALTH APPROACHES.....</b>	<b>10</b>
3.1 Family planning.....	10
3.2 Optimising women's diet .....	12
3.3 Managing maternal health problems .....	14
3.4 Avoiding maternal infections .....	15
3.5 Implementation of basic reproductive health approaches .....	17
<b>4. SCREENING FOR INCREASED RISK OF CONGENITAL DISORDERS .....</b>	<b>18</b>
4.1 General ethical principles of genetic population screening.....	18
4.2 Antenatal ultrasound screening for congenital malformations .....	19
4.3 Antenatal screening for chromosomal disorders .....	20
4.4 Identifying increased risk of inherited disorders .....	21
4.5 Genetic counselling and consanguineous marriage.....	23
4.6 Avoiding morbidity and mortality due to neonatal jaundice .....	23
4.7 Neonatal screening.....	26
4.8 The timing of population screening.....	27
4.9 Education for health workers, and information for the public .....	28
<b>5. THE WHO INITIATIVE .....</b>	<b>29</b>
5.1 Formation of a national task force .....	29
5.2 Development of a national plan.....	30
5.3 The baseline epidemiological study (the WHO mother and baby study) .....	30
5.4 The intervention study (demonstration project).....	31
<b>6. THE ROLE OF WHO.....</b>	<b>32</b>
<b>LIST OF PARTICIPANTS .....</b>	<b>35</b>
<b>REFERENCES.....</b>	<b>37</b>
<b>ANNEX 1 Prevalence of genetic and congenital disorders in populations of European origin, to age 12 .</b>	<b>41</b>
<b>ANNEX 2 Options for best possible care for common congenital disorders and birth defects .....</b>	<b>42-43</b>
<b>ATTACHMENT I: WHO initiative on the prevention and control of congenital and genetic disorders in developing countries: Baseline epidemiological study, draft protocol and data collection forms .....</b>	<b>1-21</b>
<b>ATTACHMENT II: WHO initiative on the prevention and control of congenital and genetic disorders in developing countries: Baseline epidemiological study, draft manual of operations .....</b>	<b>1-10</b>





# 1. Introduction

In December 1999 a group of WHO advisors met in Cairo to review the global epidemiology of congenital and genetic disorders, identify evidence-based interventions for their prevention and control, and recommend approaches for incorporating appropriate interventions into primary care services at the country level, making best possible use of existing infrastructures.

The meeting formed part of a WHO response to the changing pattern of health services required by populations, with a shift of focus from acute problems towards management of chronic disease, and from vertical programmes towards integrated primary health care systems. This change in emphasis that is needed is particularly marked in the area of child health because when infant mortality falls below 40-50 /1000, many infants with potentially disabling conditions, who would previously have died undiagnosed, survive, are diagnosed, and may require life-long medical and supportive interventions.

Infant mortality and birth rate are falling worldwide, even in the presence of serious economic problems. This is largely due to the implementation of simple packages of care recommended by the WHO to control infectious diseases and malnutrition, and improve reproductive health. Table 1 shows that by 1996 infant mortality was less than 50/1,000 in over 65% of countries, including more than 60% of the world population (1).

**Table 1. Change in the past 15 years in proportion of countries, and of the world population, in different infant mortality categories**

Infant mortality <sup>1</sup>	Number of countries <sup>2</sup>		% of countries		Population millions		% of world population	
	1981	1996	1981	1996	1981	1996	1981	1996
< 50	98	151	52	68	2,361	3,469	47	61
50 - 99	30	45	16	20	644	1,870	13	33
100 - 149	39	24	21	11	1,367	358	27	6
150 - 199	16	3	9	1	174	28	4	0.5
200 plus	5	0	3	0	19	0	0	0
Total	188	223	100	100	4,971	5,725	100	100

Available evidence indicates that the birth prevalence and potential burden of congenital disorders in developing countries is at least as great, and in many instances is greater than in more developed countries. There is therefore growing recognition of the need for an integrated global attack on congenital disorders, including services for diagnosis, best possible patient care and prevention. The initiative should be developed as soon as possible to maximize its long-term cost-effectiveness.

The causes of congenital disorders are numerous and varied, and multiple approaches are required. The initiative should therefore start by focusing on selected interventions that are

---

<sup>1</sup> Infant mortality rate (IMR) = deaths under 1 year of age per 1000 live births.

<sup>2</sup> The number of countries with data in the UN Demographic Yearbook series increased from 188 in 1981 to 223 in 1996.

effective in reducing health burden, are as simple as possible, can be implemented in primary health care, and provide a basis for further service development. Mechanisms for assessing implementation of the interventions, and the effect on health burden are integral to the programme.

Country differences in epidemiology, demographic factors, organization of health systems, priorities, and available resources mean that no standard set of interventions can be recommended for worldwide application. Some interventions can be confidently recommended in any circumstances, but for others the epidemiology of the target conditions is undefined, and/or it is uncertain that results will resemble those documented elsewhere.

The chosen approach is therefore to design a *programme of work* that will support an organized approach to the control of congenital disorders in any country. This falls into three distinct phases. The first, development of a country plan, requires assessment of the local epidemiology and health burden of congenital disorders, definition of priorities, selection of feasible interventions, and assessment of resources required. The second phase is a demonstration project implementing the chosen interventions in a defined setting, including audit of process and impact on the health burden of the selected disorders. The final phase is countrywide implementation of the chosen interventions. The programme of work will be conducted as a collaborative international study, supported by the latest evidence, and with access to guidelines and tools available through the WHO. The project is seen as initiating a major health care initiative, which will be built on progressively over the years.

The following steps are proposed for participating countries.

1. *Phase - development of the country plan:*

- Convene a national multidisciplinary task force, to design and supervise the programme of work. Their first task is to produce a *structured country report* on present knowledge of congenital and genetic disorders. This will include assessment of the current situation, local priorities and available resources; choice of appropriate interventions; outline of a country plan. The task force will liaise closely with the WHO.
- Design and conduct a pilot for the proposed WHO epidemiological study of the birth prevalence of congenital disorders.
- Conduct an epidemiological study. This will provide baseline data on the local epidemiology and health burden of selected congenital disorders, support selection of appropriate interventions, establish mechanisms for surveillance, and allow assessment of the feasibility of the interventions on a national scale, and manpower and training requirements.

2. *Phase 2 - the intervention study*

- Develop staff training packages, and establish systems for staff training.
- Initiate the selected interventions in a large-scale demonstration project, in a defined setting.
- Evaluate process and outcomes, including estimated impact on the health burden of the selected disorders.

3. *Phase 3 - national implementation:* will be developed according to the experience gained in the first two phases.

This report briefly reviews existing information on the scope of the problem and the range of appropriate interventions, outlines priorities identified at the meeting, identifies areas where further information is needed, and suggests how approaches deployed in more developed countries may be adjusted to meet the stringent cost-effectiveness requirements of less developed countries.

## **2. Global epidemiology and health burden of congenital disorders**

The frequency of congenital disorders is best described in terms of potential birth prevalence, i.e. as affected births/1,000 in the absence of a prevention programme. Prevalence varies considerably between populations due to differences in genetic make-up and demographic and environmental factors. Annex 1 summarizes data on the baseline birth prevalence of congenital disorders with a genetic component for populations of Northern European origin (2). Experience in many parts of the world shows that lower figures are usually due to under-diagnosis and under-reporting (3, 4): for example recent studies have overturned previous reports of a low birth prevalence of neural tube defects and Down syndrome in black South Africans (5). These figures exclude disability exclusively due to environmental causes or of undifferentiated or undetermined aetiology, and so tend to under-estimate the totality of physical and mental disability arising before birth. For example cerebral palsy, epilepsy, and conditions such as mental retardation due to maternal iodine deficiency, fetal alcohol syndrome, and deafness caused by maternal rubella infection, which are commonest in less developed countries, are not included. Nevertheless, in the absence of reliable data from these countries, the figures offer a provisional starting point for a minimum estimate of the global birth prevalence of serious congenital disorders.

Table 2 gives minimum estimates of the birth prevalence of congenital disorders by WHO region, based on the data for Northern European populations, with the addition of data for haemoglobin disorders (6) and glucose-6-phosphate dehydrogenase deficiency (7), and adjustment for the effect of customary consanguineous marriage (8). They clearly show the greater potential health burden of congenital disorders in most developing countries.

**Table 2. Minimum estimates for the birth prevalence of infants with serious congenital disorders, by WHO region (calculations using data in refs 1,2, 6, 7, 8)**

WHO Region	Population, millions, 1996	Births/yr millions, 1996	Congenital malformations /1000	Chromosomal disorders /1000	Single gene disorders /1000	Total congenital disorders /1000	Annual affected live-births
Eastern Mediterranean	506	18.1	35.7	4.3	27.3	69	1,237,225
African	540	23.0	30.8	4.4	25.0	61	1,412,427
S.E. Asian	1,401	38.2	31.0	3.9	14.7	51	1,946,606
European	867	10.8	31.3	3.7	12.4	49	522,832
American	782	16.2	30.9	3.8	11.9	48	774,235
Western Pacific	1,650	31.3	30.6	3.5	11.4	47	1,464,067
Total	5,746	137.6	31.5	3.9	16.8	53	7,357,392

Table 3 gives estimates for the morbidity and mortality associated with the main groups of disorder in developed countries, even with best possible management, and the types of service required (9-11). In less developed countries mortality is far higher.

**Table 3. Estimated outcome for different types of congenital disorders in developed countries (Refs. 9-11)**

Category of disorder	Births/1000 (est)	Main therapeutic needs	Outcome, % of cases		
			Early mortality	Chronic problems	Treatment successful
Major congenital malformations	31.3	Paediatric surgery, social support	22	24	54
Chromosomal disorders	3.7	Social support	34	64	2
Single gene disorders <sup>1</sup>	7.0	Medical management, social support	58	31	11
TOTAL	42.0		29	28	43

Table 4 shows the major contribution of lethal congenital disorders to global infant mortality. In many developed countries infant mortality is now lower than the birth prevalence of potentially lethal congenital disorders. This reflects the combined effects of widespread implementation of public health measures for primary prevention, cure when feasible (e.g.

<sup>1</sup> The figure for single gene disorders includes only those with onset in infancy or early childhood. It excludes dominantly inherited late-onset disorders such as familial hypercholesterolaemia.

paediatric surgery), long-term management that prolongs life when cure is not feasible, and prevention through prenatal diagnosis and selective abortion.

**Table 4. Comparison of infant mortality and birth prevalence of potentially lethal congenital disorders, by WHO Region (Data from 1996 UN demographic yearbook and refs 6-8 and 9-11.)**

WHO Region	Infant mortality	Congenital disorders /1000	Potentially lethal congenital disorders/1000	Potentially lethal, % of infant mortality
Eastern Mediterranean	85.1	69	32	38
African	91.6	61	23	25
South East Asian	72.8	51	15	21
European	17.0	49	15	87
American	31.7	48	13	42
Western Pacific	41.5	47	12	30
Total	61.2	53	18	29

## 2.1 Dilemmas for health services

Some congenital disorders can be partially prevented by public education (e.g. Down syndrome, neural tube defects, or complications of G6PD deficiency), and some can be relatively simply corrected (e.g. club foot, cryptorchidism, cleft lip and palate, patent ductus arteriosus, ventricular septal defect). However, many cause early death or require life-long, expensive and labour-intensive management.

The burden for individuals, families and society is determined by the birth prevalence of affected infants; their survival; availability, costs and effectiveness of treatment; availability of social support; and the extent to which affected individuals are accepted and integrated into society. Service requirements at any given point in time depend on the number of living patients in the population.

When affected infants do not survive, population prevalence (affected individuals /1,000) is a fraction of birth prevalence. However, once diagnosis and treatment become available population prevalence rises towards birth prevalence, and the rate of rise is a measure of the availability and effectiveness of treatment. That is:

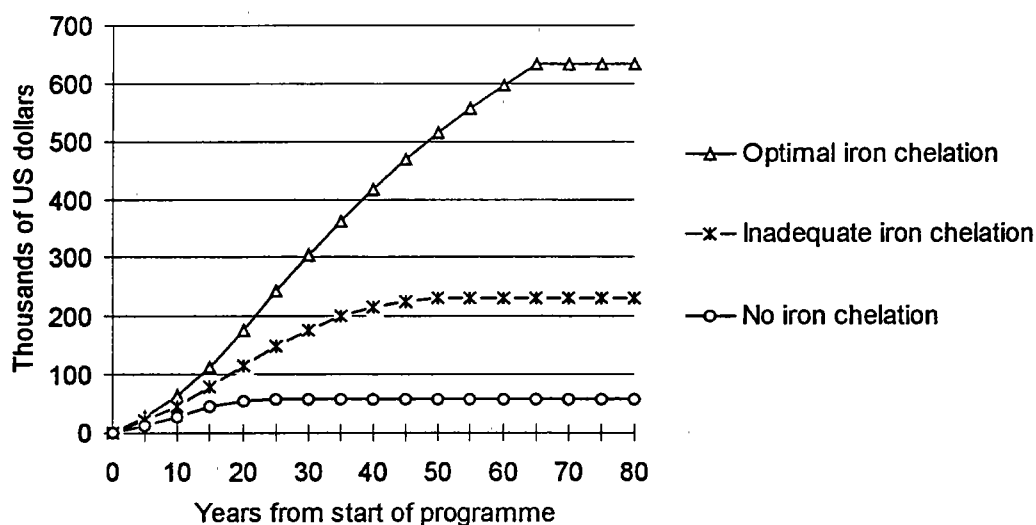
$$\text{Population prevalence} = \text{birth prevalence} \times \frac{\text{average survival of affected individuals (yr)}}{\text{average survival of the general population (yr)}}$$

The evolution of health services therefore inevitably leads to a cumulative increase in *numbers needing care*, because patients live longer. It also usually leads to an increase in *annual cost per patient* because cost of care usually rises as treatment possibilities improve. These combined effects can have very serious implications.

This process is just beginning in countries where infant mortality has recently fallen below 50/1,000. The resultant dilemmas can be illustrated using the example of thalassaemia, the presenting genetic problem in many countries. Children with thalassaemia major are easy to diagnose, and regular blood transfusion is available in most countries, is life saving and gives

excellent short-term quality of life. However, in the absence of iron chelation therapy it leads to death from iron overload at 12 to 24 years of age, so once transfusion treatment has been started patients, parents and health workers make great efforts to obtain iron chelation therapy to ensure long-term survival. Conventional treatment by subcutaneous infusion of desferrioxamine is so burdensome and expensive that bone marrow transplantation (when practicable) is a cost-effective alternative (6, 12). Thus major costs are bound to fall on the health service, the family, or both, and the majority of patients worldwide cannot obtain adequate long-term treatment. Figure 1 presents the cost implications in a format that can be applied for any country, when the expected annual number of affected births is known (calculations of Dr B Modell).

**Figure 1. Cumulative annual treatment costs when one patient with thalassaemia is born per year**



Figures can be adapted for any country by multiplying by annual affected births. Costs with three different treatment “policies” are projected from a notional date when the policy is initiated. The lowest curve shows the cost of adequate regular blood transfusion without iron chelation therapy: cost escalation is limited because patients live less than 20 years. The middle curve shows costs rise with adequate transfusion but half the recommended level of iron chelation therapy, giving patient survival of up to 30 years. The upper curve shows costs with optimal treatment including iron chelation therapy as recommended, giving long-term patient survival.

For example, in Iran the average birth prevalence of thalassaemia major is 0.74/1000, and the proportion of patients expected to survive at least into their late teens has risen from practically none thirty years ago to over 90% today. Over 15,000 patients are currently under care, representing a forward commitment of around \$200 million per year for at least the next thirty years (Dr A. Samavat, personal communication). In the absence of prevention, annual treatment costs could rise to over \$700 million per year.

Countries with limited resources are necessarily interested in more cost-efficient treatment. For example a new oral iron chelating agent (deferiprone) that is more acceptable to patients and potentially cheaper than desferrioxamine has long been used in India, and is gaining wider acceptance in industrialized countries (13). Though cheaper treatment can reduce the rate of cost escalation, it does not reduce the need for prevention.

**Table 5. Estimated costs of treatment and prevention for thalassaemia, in countries of the WHO Eastern Mediterranean Region. (Refs. 1,6,12)**

	Annual births beta	Annual cost of optimal treatment (no prevention) (\$1000s)		Annual cost of prevention (\$1000s)		Annual cost, treatment/prevention	
		Yr 1 = 1 birth cohort	Yr 10 = 10 birth cohorts	Year 1	Year 10	Year 1	Year 10
	Thalassaemia major						
Pakistan	3,087	30,564	305,635	16,549	16,549	1.8	18.5
Iran	1,251	12,387	123,874	7,730	7,730	1.6	16.0
Egypt	654	6,479	64,794	4,753	4,753	1.4	13.6
Iraq	571	5,648	56,482	3,408	3,408	1.7	16.6
Syria	521	5,162	51,620	2,868	2,868	1.8	18.0
Saudi Arabia	341	3,380	33,797	2,423	2,423	1.4	13.9
Jordan	90	671	6,712	449	449	1.5	15.0
Cyprus	68	894	8,943	394	394	2.3	22.7
Palestine	48	476	4,758	291	291	1.6	16.3
Lebanon	46	456	4,557	284	284	1.6	16.0
Oman	26	139	1,394	152	152	0.9	9.2
UAE	19	258	2,575	151	151	1.7	17.1
Bahrain	14	186	1,864	106		1.8	17.7
Qatar	6	55		34	553	1.6	16.3

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 (10, 14-17). In Iran a national prevention programme is now under development, and a national patient register already shows evidence of a reduction in affected births.

Table 5 compares estimated annual and 10 year projected costs for treating thalassaemia, with the estimated annual cost of prevention, for countries of the WHO Eastern Mediterranean Region. In most countries the estimated annual cost of prevention approximately equals the cost of treating one annual birth cohort of patients for one year. Annual prevention costs are effectively constant but annual treatment costs rise year-on-year, so the cost-effectiveness of prevention increases with every year that it is in place. The 10-year projection shows that it is impossible for most countries to provide optimal treatment for all patients who may be born, and that effective prevention is a necessary condition for those already living to be treated adequately.

The same general principle applies for many other congenital disorders including sickle cell disorders, haemophilia, cystic fibrosis, phenylketonuria, Down syndrome and neural tube defects.

The earlier effective interventions are implemented, the greater their value to families and society, while every year that passes without a national strategy contributes to long-term problems. For example in Cyprus a policy of community education and premarital screening has reduced affected births to less than 5% of expectation, and stabilized the annual cost of patient care at a small fraction of the projected cost (16). By contrast in the UK where there is no national policy, screening is part of pregnancy care, and only 50% of at risk couples are detected in time for the offer of prenatal diagnosis (17), the annual cost of treatment is 50% of the projected cost.

## 2.2 The burden for families

The main emphasis so far in discussing the service dilemmas associated with reduced infant mortality has been on financial costs, because of the obvious importance of this dimension to policymakers. High treatment costs make conditions such as thalassaemia and haemophilia highly "visible" to health services, but many equally serious disorders have smaller cost implications for medical services and so are less visible, though the burden for the family (and such social services as are available) is as heavy or even heavier. This group includes conditions like Down syndrome or sickle cell disorders, that are increasing in prevalence because they are particularly responsive to basic primary health care interventions. Thus the need for early planning for best possible care and effective prevention applies for the full spectrum of congenital disorders.

For policy purposes, the more visible disorders may be seen as *indicator conditions*, capable of reflecting both improvements in basic medical services, and the likely total burden of congenital disorders in the community.

Table 6 gives some examples showing that even in the absence of specialist services, appropriately trained primary health care workers can do a great deal to improve survival and quality of life for people with congenital disorders. More detailed possibilities for diagnosis, management counselling and support at the primary health care level are given in Annex 2.

Further work is needed on developing scientific principles and methods for describing the epidemiology of congenital disorders, measuring the financial and non-financial burden they



impose on patients, families and communities, and planning appropriate approaches at the primary health care level.

**Table 6. Some suggested interventions for improving prognosis and quality of life of people with common inherited disorders, and their families (Refs. 7, 10, 18, 63)**

Condition	Detection	Intervention	Benefit
Sickle cell disorders	Neonatal screening	Advice for parents on protection & avoidance of sickle cell crises: prophylactic penicillin and anti-malarials: genetic counselling	Increased survival and acceptance in the family, decreased hospitalization and over-protection, integration into society
G6PD deficiency	Neonatal screening	Avoiding precipitating factors such as moth-balls in baby clothes, and some traditional remedies	Reduced neonatal jaundice, heightened awareness and early diagnosis
G6PD deficiency	Public information	Educating parents not to give broad beans to children	Decreased paediatric admissions for favism
Oculo-cutaneous albinism	Clinical neonatal diagnosis	Protection from sun with clothing, sun block cream. Visual assessment & glasses.	Reduced incidence of skin disorders and skin cancer: improved survival

## 2.3 Identifying priorities and key conditions for intervention

Despite their variety and diverse causes, it is possible to identify priorities, and select appropriate target conditions, for a demonstration project on prevention and management of congenital disorders:

- *Congenital malformations:* neural tube defects provide an excellent “point of entry” for an initiative aiming to reduce the burden of congenital malformations because (a) they are so obvious that they are rarely missed in newborns, and reliable audit data can be collected - providing they are registered; (b) many may be prevented by periconceptional dietary folate supplementation for women; (c) the majority can be detected antenatally by ultrasound scanning, permitting the option of termination of pregnancy; (d) generic approaches developed for these disorders can be extended across the full spectrum of congenital malformations, with time.
- *Chromosomal disorders:* Down syndrome provides the appropriate point of entry for chromosomal disorders because (a) its birth prevalence can be greatly reduced by family planning; (b) survival and quality of life can be improved by information and relatively simple management strategies, and community support associations can be very helpful for families; (c) when karyotyping is available women at increased risk (e.g. on grounds of maternal age) can be offered prenatal diagnosis; (d) primary health care workers can be taught to make and report the clinical diagnosis, so birth prevalence can be monitored, and (e) laboratory-based registers can be used to audit prenatal diagnosis.

- *Inherited disorders*: haemoglobin disorders are a common point of entry for strategies aiming to reduce the burden of inherited disorders because (a) they are highly prevalent in many populations; (b) survival and quality of life can be greatly improved by simple protective measures for sickle cell disorders and transfusion programmes for thalassaemia; (c) carriers can be detected by cheap and simple haematological tests, and carrier couples can be advised prospectively of their risk; (d) prenatal diagnosis is highly acceptable to couples at risk; (e) diagnosis registers can be used for service audit; (f) screening strategies and DNA-based laboratory methods introduced for haemoglobin disorders can be extended for other inherited disorders, with time.
- *Customary consanguineous marriage*: a culturally appropriate approach for genetic counselling in relation to consanguineous marriage is required. A significant proportion of the estimated regional differences in birth prevalence of congenital disorders, shown in Table 2, is related to the genetic effect of customary consanguineous marriage.
- *HIV/AIDS* is an increasingly important cause of congenital disability and childhood death in most countries, and is the dominant cause in Africa. Approaches for reducing its birth prevalence must be integrated with any other programme for prevention of congenital disorders and disability. Liaison at WHO level on this topic between the human genetics, reproductive health and AIDS programmes is essential.

The planned initiative will help to fill important gaps in our knowledge of the public health importance of several common congenital disorders. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is an important cause of neonatal jaundice and life-threatening favism in South East Asia, the Mediterranean area and parts of the Middle East, but there is inadequate quantitative information on the actual burden in these areas, and the clinical effect of the milder mutations that are highly prevalent in Africa is almost completely undocumented (18). There is little information from developing countries on the potential burden of Rhesus incompatibility, and more is needed from Africa and other regions on the prevalence and burden of oculo-cutaneous albinism (19).

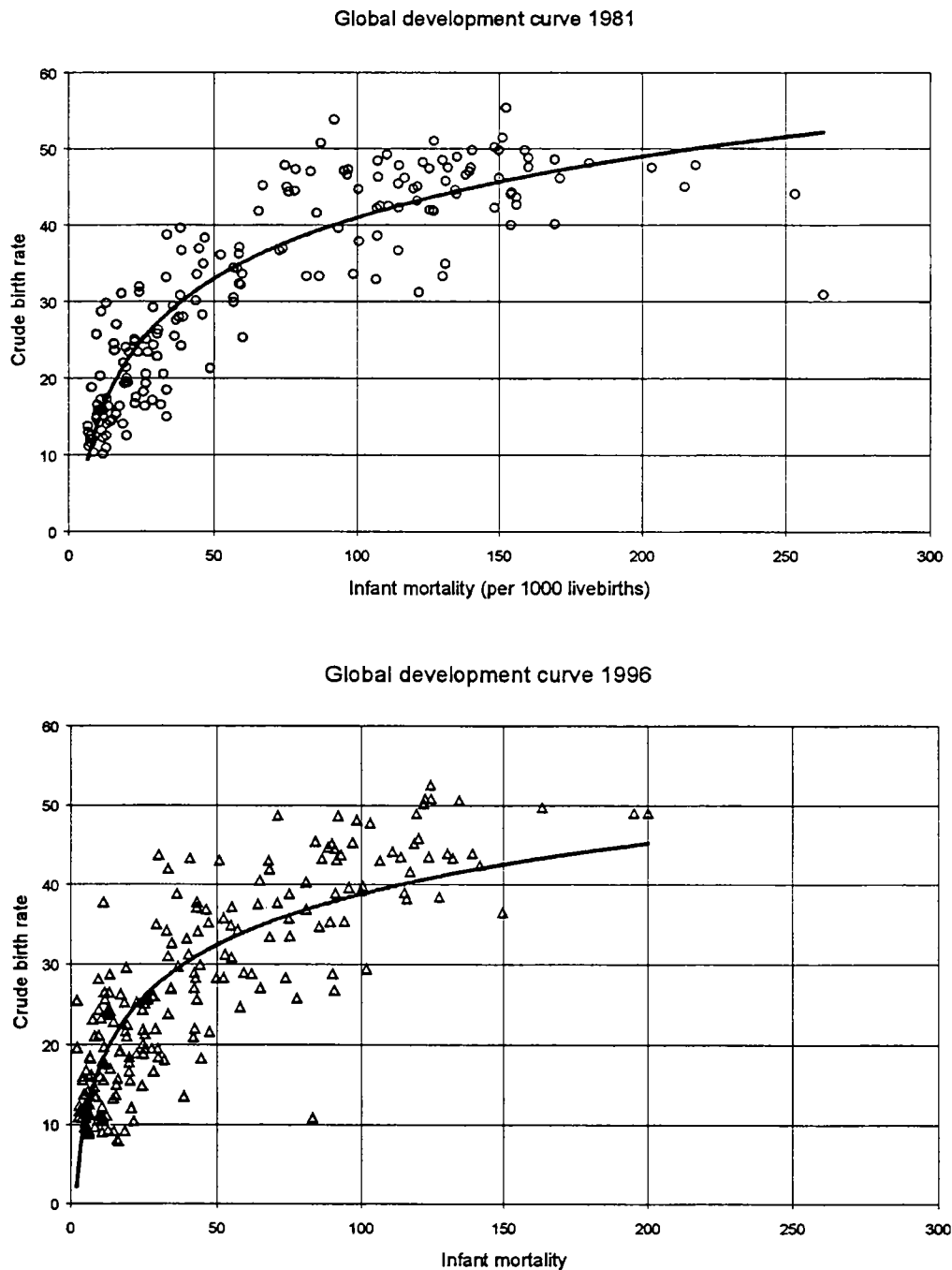
### 3. Basic reproductive health approaches

When the following relatively simple and effective measures are incorporated into primary health care and reproductive health services, many serious disorders will be prevented from arising in the first instance.

#### 3.1 Family planning

Availability of family planning has an important effect on the burden of congenital disorders. Once couples have a high expectation of their children's survival, and family planning is available, most stop reproducing when they have the desired number of children. Figure 2 shows the evolution of the relationship between infant mortality and birth rate. For example in Iran infant mortality has fallen by 75% (from 108 to 26/1,000) in the past 15 years. Family planning is provided through the primary health care system, and the crude birth rate has now fallen by 58%, from 43 to 18/1000 (1). Thus though the population has increased by 50% the annual number of children born with congenital disorders has fallen by 38%. For example (potential) births of children with thalassaemia major have fallen from over 1,200 to about 860 per year.

**Figure 2. Relationship between infant mortality and crude birth rate, 1981 compared with 1996**



The graphs contain a point for every country with data in the relevant UN Demographic Yearbook series (1). They show the general tendency for birth rate to fall when infant mortality falls below about 75/1000. The wide range of birth rate associated with a given infant mortality reflects availability of family planning, the extent to which it is promoted, and cultural conventions. (Four 1996 outliers with infant mortality 50/1000 or less but birth rate over 40/1000 are: Solomon Islands, Wallis and Futuna island (both WPR), Sao Tome and Principe (AFR), and Oman (EMR). American Samoa has an infant mortality of 11/1000 and a crude birth rate of 38/1000.)

Family planning usually leads to a particularly marked reduction in births to women over 35 years of age, and so to an even greater reduction in the number of children born with Down syndrome, because birth prevalence is strongly related to maternal age. In Europe the average calculated birth prevalence of Down syndrome fell by around 60% (from 2.5 to 1.0/1000) between 1950 and 1975, as use of family planning increased (9, 20). A similar effect can be safely predicted in any country, on the basis of current scientific knowledge.

Couples known to be at increased genetic risk on the basis of their family history, age, or results of screening tests, often limit further reproduction when family planning is available, and need guaranteed access to family planning services. In theory, when average family size is large restriction to two or three children could reduce the birth prevalence of major single gene disorders by 40-50%. When final family size is small there is proportionately less effect. However, there is no good observational data from developing countries.

Information obtained through the proposed WHO initiative on parental age distribution, and effects of genetic counselling after the diagnosis of an affected child, will permit calculation of such effects on a national and global scale.

## **3.2 Optimizing women's diet**

Women of reproductive age need an adequate diet. There is growing evidence that maternal health and nutrition can affect the children's predisposition to the common non-communicable diseases whose prevalence is increasing in the adult population of most developing countries. For example maternal malnutrition is related to low birth weight, which in turn is related to an increased risk of ischaemic heart disease and non-insulin-dependent diabetes mellitus in the offspring, while maternal anaemia appears to increase the risk of hypertension (21). As the mother's pre-pregnancy status appears to affect these outcomes, it is important to prevent maternal anaemia and malnutrition before, as well as during pregnancy. Because it is not easy to identify a pre-conception period with certainty, women should have an adequate diet throughout the reproductive span. In principle this means a diet that is adequate in terms of energy and of micronutrients such as iron, iodine and vitamins. However, the evidence from randomized trials for a beneficial effect on the fetus is rather unsatisfactory, the effects of multi-vitamin and folate supplementation being the best documented (22).

### **3.2.1 Protein/calorie nutrition**

A Cochrane review of randomized studies of providing malnourished women with nutritional supplements of energy (usually with protein) during pregnancy (23) reported that balanced protein/energy supplementation resulted in modest increases in maternal weight gain and fetal growth, with more effect when the energy content of the supplement was very high. It also seemed to reduce the risk of stillbirth and neonatal death. There was no evidence of larger benefits for undernourished women, or of long-term improvements in the child's growth or neurocognitive development, and there was inadequate evidence to evaluate effects on preterm birth or maternal health.

The apparent inconsistency between these results and the work mentioned above may be due to the relative insensitivity of the outcomes used, the likelihood that supplementation is more effective if started prior to pregnancy, and the inability of such studies to assess long-term outcomes. Studies of supplementation prior to pregnancy, or other approaches for assessing the long-term effects of maternal (mal)nutrition in developing countries are needed.

### ***3.2.2 Dietary folate***

Neural tube defects fall into the category of multifactorial disorders, with both genetic and environmental factors involved in their genesis. In Western populations, an increased risk of having an affected child is associated with altered maternal homocysteine metabolism and reduced folate levels, related to a 677 C to T polymorphism in the methyltetrahydrofolate reductase (MTHFR) gene. Randomized controlled trials in countries with a high birth prevalence of neural tube defects have shown that supplementing women's diet with folate prior to and in the first months after conception reduces the risk of fetal neural tube defect (22). No adverse effects of folate supplementation have been detected, apart from a possible small increase in multiple pregnancies. Multivitamins themselves did not have any observed effect, either alone or when given in addition to folate. The daily folate intake necessary for full protection is considered to be about 0.4 mg/daily, but the average (western) diet contains only half this amount (22). Folate supplementation starting at least two months before conception is therefore now recommended in most western countries. In China folate supplementation has been found to have more effect in the north than the south, possibly reflecting better nutrition in the south (24). Since women cannot always foresee a pregnancy, and it is difficult to ingest enough folate with usual Western diets, folate fortification of common foodstuffs may be indicated. This has recently been implemented in the United States. Data on the effect of the policy on prevalence of neural tube defects is now awaited.

Should dietary folate supplementation be universally recommended? Experience from South Africa shows that Western experience cannot be presumed to apply elsewhere (25). Firstly, the common predisposing MTHFR mutation is rare in black South Africans. Secondly, there is evidence of lower folate status in urban black South African women than in their rural counterparts, but paradoxically the urban birth prevalence of infants with neural tube defects is low, at 0.55 - 1.64 /1,000, while birth prevalences of 3.55 and 6.13/1000 have been recorded in rural populations. In this population therefore, an assumption that the problem would respond to folate supplementation could be misleading, and further research is needed before implementing recommendations for prevention in this setting.

In conclusion, quality baseline data is needed on birth prevalence of neural tube defects in every population where folate supplementation is considered. Ideally, evidence should also be sought on the prevalence of the MTHFR and other possible polymorphisms, folate content of the diet, blood folate status and homocysteine metabolism.

### ***3.2.3 Iodine deficiency***

Severe iodine deficiency in the mother can lead to impaired fetal brain development, and is probably the most important cause of mental retardation in arid or mountainous areas where iodine deficiency is prevalent (26). The current global campaign to prevent iodine deficiency by iodination of salt is likely to lead to a significant reduction in such mental handicap. Further information on this subject should be collected at the WHO level, and by the national task force in each country participating in the WHO initiative.

### ***3.2.4 Iron deficiency***

This is extremely common in pregnant women and in children in less developed countries (27). In principle, it should be corrected because haemoglobin level is directly related to physical energy i.e. there is evidence that infants of iron-deficient mothers have reduced iron stores, and iron deficiency causes a measurable, persistent reduction of IQ in children (28). Iron

supplementation of basic foodstuffs, or providing children with iron-supplemented biscuits is therefore recommended in some countries (29).

A Cochrane review of randomized studies in more developed countries (30) showed that iron supplementation for pregnant women with an initial haemoglobin level below 10 g/dl reduces anaemia in late pregnancy, but no detectable effect on maternal hypertension or infection, preterm or post term delivery, low birthweight or admission to a neonatal unit was observed. One trial showed a reduced likelihood of caesarean section and post-partum blood transfusion, but more stillbirths (possibly related to increased blood viscosity related to high haemoglobin) in the routinely supplemented group. Therefore, in developed countries the tendency is to suggest selective rather than routine iron supplementation.

The indication that routine iron supplementation may reduce the need for post-partum- blood transfusion could be important where there is a need to avoid blood transfusions. Otherwise these studies have little relevance for communities where iron deficiency is common and anaemia in pregnancy is a serious health problem, because the most important outcomes are long-term effects on the physical and mental development and health of the child, and the woman's physical ability to cope with her family. There is practically no information from less developed countries on the effect of iron supplementation in pregnancy on these outcomes. This important health issue could be adopted as special sub-study within the planned WHO initiative.

### ***3.2.5 Alcohol consumption and smoking***

It is not yet possible to definitely identify a safe limit of alcohol consumption during pregnancy. Moderate alcohol consumption during the first trimester of pregnancy (two or more drinks per week to two drinks per day) involves little if any additional risk of fetal malformation, but this might not apply for effects on intellectual development.

The effect of alcohol is likely to be continuous and dose related, starting with a healthy child and ending with the full blown fetal alcohol syndrome, including learning difficulties, poor growth, and sometimes congenital abnormalities involving the face, limbs, heart and nervous system (31). Unfortunately, there is a high recurrence rate of fetal alcohol syndrome in subsequent pregnancies. As with neural tube defects, polymorphisms influencing rate and route of alcohol metabolism occur with different prevalence in different populations, so population differences in susceptibility to fetal alcohol syndrome may be anticipated. Studies from wine-growing areas in South Africa showing an extremely high prevalence of fetal alcohol syndrome (32) suggest that this should be carefully studied in other areas with a significant alcohol producing industry.

There is no convincing evidence that smoking significantly increases the risk of congenital malformations, though there may be a small increase in prevalence of cleft lip with or without cleft palate. It does increase the chance of miscarriage, bleeding in pregnancy, premature birth, and sudden infant death syndrome (33). Stopping smoking in early pregnancy reduces these risks, and up to a quarter of women who smoke stop before their first antenatal visit.

## **3.3 Managing maternal health problems**

Women with insulin dependent diabetes have approximately a 6% risk of a seriously malformed child in each pregnancy (34). The risk can be greatly reduced by meticulous control of the blood sugar, but this must be started before pregnancy, because major malformations are already present by five weeks post-conception (35). Appropriate advice for women, and

assistance in achieving the necessary standard of blood sugar control should be a routine part of diabetes care.

### ***3.3.1 Epilepsy during pregnancy***

It is not possible to discontinue anti-epileptic drugs during pregnancy, as uncontrolled seizures can affect the fetus as well as the mother. However, care must be taken to ensure that doses are the lowest necessary for seizure control. The four commonly used anticonvulsants (phenytoin, carbamazepine, sodium valproate and phenobarbitone) convey a significant teratogenic risk, but more than 90% of women who receive these drugs during pregnancy deliver a baby free of birth defects (36).

### ***3.3.2 Treatment of malaria during pregnancy***

This is particularly relevant in many less developed countries. There is no evidence to suggest that any antimalarial drugs are teratogenic at standard dosages, and standard doses of quinine do not increase the risk of abortion or preterm delivery (37). Primaquine is not recommended because of the potential risk of intravascular haemolysis in a G6PD deficient fetus, but there is no evidence of an increased risk of kernicterus in the newborn following intrauterine exposure to antimalarial drugs containing sulphonamides or sulphones.

Information on the safety of doxycycline, halofantrine, and artemisinin derivatives in pregnancy is currently limited.

### ***3.3.3 Maternal inherited disorders***

People with serious inherited conditions are increasingly surviving to reproductive age because of improved medical care. It is important for them to be diagnosed and have access to appropriate pregnancy care. For example in sickle cell disorder an increased risk of sickle cell crisis can be fatal for the pregnant woman (38), while in thalassaemia there is an increased risk of stillbirth unless the mother is adequately transfused throughout pregnancy (39). A mother with phenylketonuria requires excellent dietary control throughout pregnancy because phenylalanine crosses the placenta, and a raised level in the mother causes mental retardation in the child even if their genotype is normal (40).

## **3.4 Avoiding maternal infections**

It is essential to diagnose maternal infections in order to reduce the risk of vertical transmission or teratogenesis:

### ***3.4.1 Human immunodeficiency virus (HIV) infection***

This is the major cause of congenital infection in the developing world. Over one million children had been infected from their mother by the end of 1998. The risk of mother-to-child transmission appears to be 15-20% in Europe, 15-30% in USA and 25-35% in Africa.

A number of strategies employed to reduce the risk of fetal infection have been assessed in randomized trials (41):

- Treatment with zidovudine appears to be safe in pregnancy. It significantly reduces risk of mother-to-child transmission at any dose, independently of whether the mother breast feeds, and decreases risk of stillbirth and infant death. Preliminary findings suggest a further decrease in risk when zidovudine is combined with lamivudine in the antenatal and

intrapartum period, or the intrapartum and postpartum period (42). However, these drugs are too costly for widespread use in the developing countries that need them most. Unfortunately there is no evidence of reduced transmission when combination therapy is given only at delivery.

- Elective caesarian section may decrease mother-to-child transmission by 50% - though its widespread use in less developed countries is also unrealistic. Disinfecting of the vagina prior to and/or during labour, and avoidance of artificial rupture of the membranes may reduce transmission, and could be adopted widely.
- Breast feeding may double the risk of mother-to-child transmission of HIV, but WHO recommends that HIV infected women should avoid breast feeding only if they have access to resources for safe artificial feeding.

Randomized trials are in progress in developing countries, to evaluate vaginal cleansing, vitamin and nutritional supplementation and breast versus artificial feeding. In addition nevirapine (a new long-acting anti-retroviral drug) requires urgent evaluation, to assess the benefit of a single dose in labour followed by a single dose to the neonate.

Once again, the first step in dealing with maternal transmission of HIV infection is to know the prevalence of the condition in the population, so that an appropriate strategy can be developed. The problem to be overcome here is the reluctance of some ministries and governments to acknowledge the true extent of the problem. Everything that has been said about early action to prevent congenital disorders applies even more strongly for HIV (e.g. with early recognition of the problem, it may be possible to afford treatment for pregnant women, but this may become impossible if infection becomes more common). Further information on this topic should be collected by liaison with the WHO AIDS programme.

### ***3.4.2 Rubella infection***

This infection is common world-wide, and is highly teratogenic. In many countries rubella is now included in childhood immunization programmes, and pregnant women are routinely screened to confirm their immune status. Intra-uterine death or congenital malformations due to rubella infection of the fetus, and congenital rubella have become extremely rare in these areas (43). The limited information available for less developed countries indicates that though the majority of girls may be immune by the time they reach reproductive age, congenital rubella syndrome still occurs (10). It is important to establish the proportion of non-immune adult women in relation to age in participating countries, in order to develop the most appropriate prevention strategy.

It is considered that rubella immunization should be included in the expanded immunization programme only if over 90% coverage can be achieved and sustained. This is because immunization interrupts natural transmission during childhood and coverage of less than 90% creates a pool of non-immune women with the risk of a future epidemic and an increase in congenital rubella syndrome. In the absence of universal immunization alternative strategies may be adopted. For example, immunization may be offered to schoolgirls. In countries where a premarital medical consultation is usual, women may be screened and those not already immune may be immunized. Failing that, women may be tested during pregnancy, and those not immune immunized after the baby is born.

Data is needed for each country on women's' age-related immunity to rubella, in order to select an appropriate approach.



### **3.4.3 Syphilis**

In females primary syphilis is often asymptomatic and as natural immunity does not eliminate the organism, an infected woman can transmit infection in every pregnancy. There is a considerable increase in the chance of a stillbirth or neonatal death, and about 20% of surviving infants later develop congenital infection. Congenital syphilis is entirely preventable if infected women are detected during pregnancy and treated with penicillin before fetal damage has occurred, and is now extremely rare where screening for anti-treponema antibodies is routine in antenatal care. However, this is not the case in many less developed countries. Statistics are needed on the prevalence of this avoidable cause of congenital disorders.

### **3.4.4 Toxoplasmosis and other maternal infections**

*Toxoplasma gondii* is a protozoan intracellular parasite that can be transmitted to the fetus and cause mental retardation, congenital blindness, or later onset blindness in humans. Though it is found in many animals, spore production occurs only in the intestine of the cat. Humans may become infected through contact with cat faeces or raw meat, or by eating under-cooked meat. Infection in pregnancy is usually asymptomatic, but leads to overt or latent infection of the fetus in about 10% of cases. Overt infection can cause miscarriage, neonatal disease, or severe ocular problems. Latent infection may become reactivated in childhood, leading to damage to the eye or brain. The effect of diagnosis during pregnancy and treatment with spiramycin in avoiding congenital abnormalities is still under review (44). However, risk of infection can be reduced by advising pregnant women to avoid contact with cat faeces, wash their hands carefully after handling raw meat, and cook meat carefully, and these simple steps may be promoted to all pregnant women. The risk of *listeriosis* may be reduced similarly by avoiding certain foodstuffs. Information is needed from less developed countries on the prevalence of *herpes simplex* infection and other maternal infections with implications for the fetus.

Diagnosis of infections in the newborn requires a skilled pathologist: the role of the perinatal pathologist is discussed below.

## **3.5 Implementation of basic reproductive health approaches**

The primary objective of the proposed WHO initiative is to help couples to achieve a healthy family by preventing avoidable congenital disorders, as well as improving the survival and quality of life of those affected by them. In order to reach the entire population of reproductive age the initiative must be based in primary care, and health workers in primary care and reproductive health need appropriate training and clearly written guidelines.

Ideally, health workers should ensure that women have the following information before their first pregnancy:

1. The risk of miscarriage and of fetal chromosomal abnormality rises with maternal age. Risks can be reduced by family planning.
2. Diet should be adequate in calories, iodine, vitamins (including folate) and iron, before as well as during pregnancy.
3. It is important for women to know their Rhesus blood group.
4. It is important for women to be immune to rubella.
5. Risk of infection with toxoplasma or *Listeria* can and should be avoided.

6. Smoking, alcohol, and medications for specific disorders can increase the risk of miscarriage, congenital abnormality and fetal growth retardation.
7. (When available) genetic counselling may be helpful for families with a history of repeated abortions, stillbirth, perinatal, infant and childhood death, congenital malformations, and inherited disorders.
8. (When available) carrier testing is advisable for specific common genetic risks (e.g. haemoglobin disorders).

Each national task force should design appropriate training packages for health workers: this is also an essential step towards an informed population. Educational requirements are addressed more fully below.

## **4. Screening for increased risk of congenital disorders**

Implementation of the above basic reproductive health approaches can reduce the birth prevalence of infants with serious congenital disorders to a baseline level. Further reduction requires population screening programmes, aiming to identify and inform individuals at increased risk of having children with specific disorders.

### **4.1 General ethical principles of genetic population screening**

Screening programmes target specific groups of conditions, and aim to reach the whole community. The support of the public health authorities is essential, and approaches must be adapted to the local health infrastructure.

Recognized requirements for population screening are as follows (46):

- The target condition should be common, or a serious though less common problem.
- Screening should be able to lead to a clear diagnosis in the majority of cases.
- The natural history of the condition should be well enough understood to permit prediction of outcomes.
- There should be an effective and acceptable management strategy (treatment and/or prevention).
- The programme should be cost-effective.

The predictive nature of population screening calls for the highest possible standard of diagnosis, quality control, information and counselling. On the other hand, the service must be delivered by large numbers of health workers with little pre-existing education in genetic diagnosis or counselling, to a population that is usually unaware of any increased risk. Genetic population screening should therefore be planned, executed and monitored systematically, and plans must include appropriate resources for education and training for health professionals and for the provision of information to the public.

The indications for and feasibility of different types of screening differ by country: each screening service should be introduced as a research project within the local medical and social context.

Screening for risk of inherited disorders in offspring can be done at any time of life. It should ideally be offered prior to pregnancy, so that individuals and couples at risk can choose from the fullest range of available options.

Screening for increased risk of sporadic conditions such as congenital malformations and chromosomal disorders is possible only during pregnancy, and can be provided within a national health service only when termination of pregnancy on medical grounds is accepted practice. (However, when ultrasound is used during pregnancy major malformations are inevitably diagnosed, and obstetricians cannot avoid decisions on what to offer the parents.)

When screening can lead to abortion, every effort should be made to offer screening as early as possible in order to reduce social difficulties, ethical conflicts, suffering and medical risks to the lowest level possible. In practice, in many developing countries genetic abortion is permitted only in the first trimester of pregnancy.

## **4.2 Antenatal ultrasound screening for congenital malformations**

Fetal anomaly scanning is the most powerful approach available for reducing the birth prevalence of infants with serious congenital abnormalities, and increasing the chance of survival for those who are born. The finding of a correctable abnormality can be an indication for delivery to take place at a centre with facilities for paediatric surgery: the finding of a severe uncorrectable abnormality may lead to the offer of termination of pregnancy:

- Fetal anomaly scanning is most sensitive at around 19 weeks' gestation, when 40-70% of major malformations can be detected by a trained operator (47).
- Possibilities for detecting severe malformations in the first trimester of pregnancy are increasing, with availability of more powerful machines and vaginal probes. For example with appropriate training most neural tube defects, and major cardiac anomalies can be detected from around 13 weeks gestation (48).
- Increasing experience has shown an association between chromosomal anomalies and ultrasound markers, including the shape of the ventricles at 19 weeks and increased nuchal translucency at 11 weeks (49). The indications for offering fetal karyotyping on the grounds of these findings are the subject of much current research.

Fetal anomaly scanning is a highly expert procedure and it is, therefore, generally recommended to be introduced in two distinct stages. Initially, it may be offered as a specialist service to women at recognized high risk (older women, those with diabetes or epilepsy, or a previous child with a congenital disorder, consanguineous couples). This arrangement permits the development of local expertise, training and audit, while the high frequency of abnormalities maintains operators' alertness and minimizes risk of error. The offer of fetal anomaly scanning to all pregnant women is a move to population screening, and should be seen as distinct second step. In particular, even with standardized training, routine scanning by less expert operators greatly increases the risk of false positives (leading potentially to abortion of healthy fetuses) and false negatives (because abnormalities are rare and alertness may be reduced). The high level of expertise required, and the serious implications of false positives and false negatives for both families and health services must be taken into account in planning programmes and in obtaining informed consent.

Falling prices are making ultrasound equipment increasingly available world-wide - e.g. in Egypt it is planned to provide machines at district health centres. When there is ready access to

ultrasound examination in the public or the private sector, routine fetal anomaly scanning is likely to be offered. The following were, therefore, strongly recommended by the expert group:

- Accreditation of ultrasound operators at different levels of expertise.
- Use of standardized protocols.
- Referral to a recognized expert centre when an abnormality is suspected.
- Mandatory registration of all abortions on the ground of fetal abnormality.
- Mandatory confirmation of the prenatal diagnosis by post-mortem examination of the aborted fetus. Full autopsy is desirable but not essential, as much information can be gained through a standardized non-invasive post mortem examination including external physical examination, clinical photographs, X-ray of the fetus, search for infections, chromosome analysis of the skin and or blood, and DNA banking when possible (50).

Each national task group needs to define the training and accreditation of ultrasound operators who will participate in the planned interventions. The national task group should include a member with expertise in perinatal pathology, who can train others and ensure that a standardized protocol appropriate for the country situation is followed.

### **4.3 Antenatal screening for chromosomal disorders**

For antenatal detection of chromosomal disorders, karyotyping is done on material obtained in the first trimester by chorionic villus sampling (CVS), or in the second by amniocentesis, fetal blood sampling or CVS. When a serious abnormality is found, termination of pregnancy is offered. In theory the proportion of Down syndrome births that can be prevented in this way depends on:

- the proportion of mothers over 35-37 years of age at conception.
- the efficiency with which younger women at increased risk can be detected.
- the acceptability of prenatal diagnosis and selective abortion to the population.

In practice, additional and crucial limiting factors are (a) the limited capacity of cytogenetic laboratories, (b) ignorance among primary care workers about whom to refer, when karyotyping is available, and (c) the fact that in many developing countries only first trimester diagnosis is considered acceptable. In each participating country the national task group should identify a policy for most cost-effective use of scarce laboratory resources, in the light of these considerations.

Usually the first step is to offer fetal karyotyping to known high-risk groups - older women, and those who have already had an affected child. This approach has the advantage of permitting first trimester diagnosis by chorionic villus sampling.

Risk of Down syndrome in younger women is presently assessed in Western countries by complex mid-trimester serum screening methods, an approach that is unsuitable for most developing countries, and will probably soon be superseded. Risk assessment using ultrasound indicators such as fetal nuchal translucency requires careful standardized training of ultrasound operators. However, it permits first trimester diagnosis by chorionic villus sampling and so could be an appropriate approach in many developing countries.

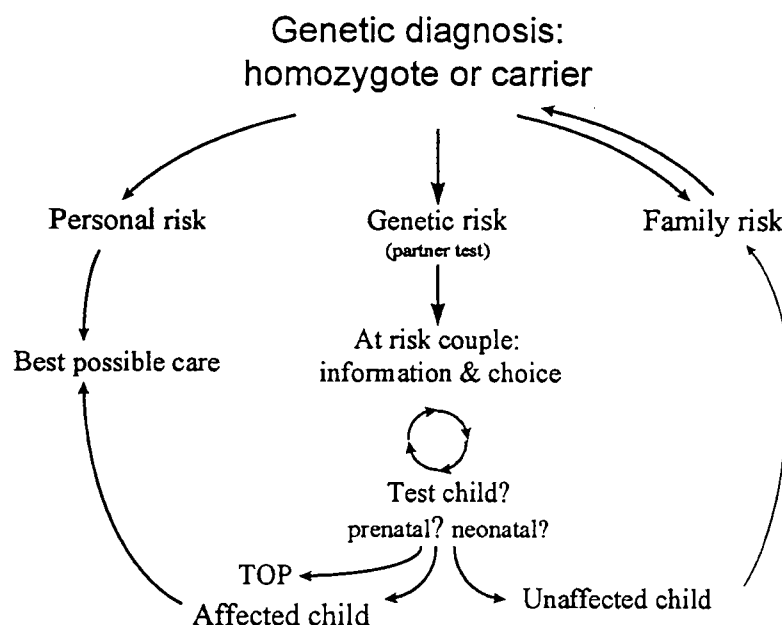
It is also necessary to consider the most cost-efficient laboratory techniques for developing countries: first trimester diagnosis by karyotyping of chorionic villus material is more complex than diagnosis using cells obtained by mid-trimester amniocentesis.

## 4.4 Identifying increased risk of inherited disorders

People who may develop an inherited disorder themselves or pass one on to their children may be identified either by family studies starting with an affected individual, or by population screening, or both. The diagnosis of an affected individual, or a carrier, has implications for the whole family. Everyone with a definitive genetic diagnosis or known to be at increased risk needs information and counselling.

Figure 3 shows the intimate relationship between the dual objectives of screening, best possible patient care and information and choice for those at risk. For every genetic diagnosis, information is needed on the implications for the person's own health, for their partner and children, and for other blood relatives. It is not possible to deal with a person with a genetic diagnosis as an isolated individual, or to focus on one objective or pathway of a genetic screening programme to the exclusion of the others.

**Figure 3. Diagram showing the types of information and care pathways needed by people with a genetic diagnosis**



The pathways apply for all genetic diagnoses, whether of carrier or affected, and whether predictive or diagnostic. A person with a genetic diagnosis is nested within a family group, itself nested within wider society. Hence individuals cannot be treated in isolation, and information and care pathways cannot be insulated from each other. (TOP = termination of pregnancy.)

### 4.4.1 Use of the family history

When a person is found to suffer from, or to carry an inherited disorder, they (or, in the case of children, their parents) should be informed of the implications for their own health, for the health of their possible children, and for other blood relatives. A health worker should collaborate with them (or their parents) in identifying and informing family members who could be at risk, so that they can be informed and offer testing when appropriate. The family history is a very powerful tool for early detection of people at risk for dominant and X-linked disorders (e.g. familial cancers), and is an important indicator of increased risk for

multifactorial conditions such as coronary heart disease or hypertension. When consanguineous marriage is common it is also a powerful tool for detecting carriers of recessively inherited disorders like cystic fibrosis, thalassaemia and sickle cell disorders (see below). However, the extent to which family studies are carried out in practice in developed countries is limited by availability of trained health workers, facilities for definitive diagnosis, and the context in which the diagnosis is made.

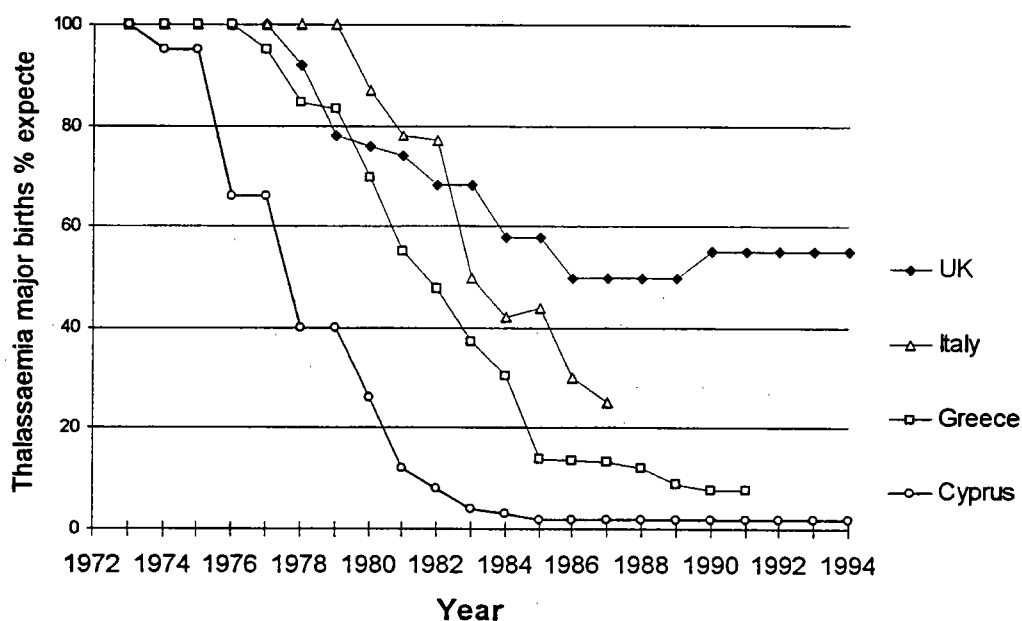
The family history can also be seen as a screening tool for scanning the general population for people at risk for a wide range of inherited disorders and genetic predispositions. To exploit this possibility a standardized method for taking a basic genetic family history in primary care and reproductive health services, and appropriate training packages are needed.

#### 4.4.2 Population screening for carriers of inherited disorders

When an inherited condition is common and serious and carriers can be reliably detected, it may be appropriate to offer genetic screening to the whole population. The by now extensive experience of population screening for carriers of Tay-Sachs disease or haemoglobin disorders provides a general model for genetic population screening programmes, and should be reviewed by each national task group. There is as yet limited practical experience of screening for cystic fibrosis (51, 52).

Figure 4 shows the fall in the birth rate of children with a major thalassaemia in four countries where screening is standard practice, and national audit data is available (14-17).

**Figure 4. Fall in the birth rate of children with thalassaemia major in three countries where audit data is available (Based on ref 12, updated.)**



The most marked fall has been in Cyprus, Italy and Greece where national programmes promote premarital screening, most at risk couples are identified in time for the offer of prenatal diagnosis in the first pregnancy, and the majority use this service to obtain a healthy

family. The lower (50%) fall in the UK reflects problems in service delivery, rather than lack of interest on the part of potential parents (17). The absence of a national policy leads to geographically uneven service delivery, while carrier screening only in the context of pregnancy care leads to late identification of risk, lack of continuity of care from one pregnancy to the next, and failure to provide family information and counselling. The UK data clearly demonstrate the need for policies aiming to identify all at risk couples in time for counselling before or early in their first pregnancy, and to involve primary health care as well as reproductive health services.

Sickle cell disorders are more unpredictable than thalassaemias, and counselling is correspondingly more complex (53). Many affected individuals have a good quality of life, and in some parts of the world (Eastern Saudi Arabia, Bahrain, India) additional genetic factors reduce the severity of the disorder. Neonatal diagnosis is recommended because simple protective measures including information for the parents, prophylactic penicillin and antimalarial treatment, provide a high degree of protection for affected children (54). Though most at risk couples would like to know the diagnosis in the fetus, many decline prenatal diagnosis because of the risk to the pregnancy. Uptake is higher in the first than the second trimester, and more couples decide to continue an affected pregnancy than is the case with thalassaemia (53).

#### **4.5 Genetic counselling and consanguineous marriage**

The focus of genetic counselling for consanguineous marriage is on risk of recessively inherited disorders, as marriage pattern has no known effect on the prevalence of other congenital disorders (10). In populations where consanguineous marriage is common, studies of the extended family of affected children (or healthy carriers) might be the appropriate approach, because family members are not only at particularly high risk, but are also likely to have personal experience of the target condition (10, 55).

This approach has been tested for thalassaemia in Pakistan, where carrier prevalence is approximately 5% and prenatal diagnosis is available (56). In this situation, with random mating 1 in 400 couples would be at risk and approximately one at risk couple would be identified per 420 people screened. In the extended family study 30% of family members tested were carriers, and one at risk couple was found for every 32 individuals tested. Unmarried carriers were also informed of their carrier status and its implications. Follow-up studies are planned on the effect of partner choice and reproductive behaviour (Dr Suhaib Ahmed, in preparation).

Further work is obviously needed, but the findings suggest that extended family studies, though labour-intensive, offer a highly cost-effective approach for risk detection in such populations. The approach also has the great advantage of being equally valid for rare and for common conditions - providing carriers can be detected. Recent advances in genetic science are increasing the feasibility of carrier detection and simplifying the laboratory techniques required.

#### **4.6 Avoiding morbidity and mortality due to neonatal jaundice**

Neonatal jaundice is a multifactorial condition which can cause death or severe life-long disability if untreated. Preventable genetic causes include Rhesus incompatibility between mother and fetus, and glucose-6-phosphate dehydrogenase (G6PD) deficiency in the newborn.

**Table 7. Average prevalence of Rhesus negativity, and genetic and clinical implications, in different parts of the world**

Region	d gene frequency	% of population Rh -ve	% of Rh -ve women with Rh +ve partner	% of women alloimmunised <sup>1</sup>	Potential severe problems due to Rh negativity / 1000 <sup>2</sup>	Rh -ve women, % of partners Dd or DD	Rh -ve women, % of fetuses dD	Rh -ve women, % chance of becoming isoimmunised
N Europe	0.45	20.3	16.1	1.13	5.4	80	55.0	6
N Europe, S Europe	0.35	12.3	10.7	0.75	3.6	88	65.0	7
N Africa, Middle East	0.3	9.0	8.2	0.57	2.8	91	70.0	7.5
W Africa, Middle East	0.25	6.3	5.9	0.41	2.0	94	75.0	8.1
N India & Pakistan	0.2	4.0	3.8	0.27	1.3	96	80.0	8.6
Sub-Saharan Africa	0.1	1.0	1.0	0.07	0.3	99	90.0	9.7
China and SE Asia max	0.05	0.3	0.2	0.017	0.08	99.8	95.0	10.2
China and SE Asia min	0.01	0.0	0.01	0.0007	0.003	99.99	99.0	10.7

<sup>1</sup> Estimated 7% of Rh negative with incompatible partner become alloimmunized.

<sup>2</sup> Severe problems - stillbirth, neonatal death or kernicterus due to Rh alloimmunization.



#### ***4.6.1 Rhesus incompatibility***

In a Rhesus negative woman, alloimmunisation by red cells from a Rhesus positive fetus (or Rhesus positive blood transfusion) can cause hydrops fetalis in subsequent pregnancies, or kernicterus in the newborn. The prevalence of Rhesus negativity differs widely in different parts of the world (Table 7), and the risk to a Rhesus negative woman of having a Rhesus incompatible fetus, and becoming alloimmunised, increases with falling prevalence.

Administration of anti-D immunoglobulin to Rhesus negative women after childbirth, miscarriage or abortion reduces the risk of alloimmunisation by more than 95%. Policies for prevention (according to prevalence and available resources) range from giving anti D postpartum only to Rhesus negative women with a Rhesus positive partner and an ABO-compatible newborn, to giving all Rhesus negative women two prophylactic doses during pregnancy, plus one dose within 72 hours of birth (57).

Data is needed for each country on the proportion of Rhesus negative women who become alloimmunised, on the present practice in screening for Rhesus blood group and antibodies during pregnancy, and on the availability and cost of anti-D immunoglobulin.

#### ***4.6.2 Glucose-6-phosphate dehydrogenase (G6PD) deficiency***

G6PD deficiency is a common predisposing factor for severe neonatal jaundice. It can also lead to life-threatening acute haemolytic anaemia following consumption of a limited range of common medications or fava (broad) beans (58). In areas where fava beans are a common basic food, as in the Mediterranean area, parts of the Middle East Iran and southern China, G6PD deficiency is responsible for seasonal waves of favism among young children. Neonatal screening for G6PD deficient infants, and informing their parents and primary care workers of the increased risk, can greatly reduce the incidence of these complications. In some countries screening for risk of neonatal jaundice is considered unnecessary because all jaundiced infants are routinely diagnosed and appropriately managed, but the risk of favism remains. This can be greatly reduced by public education - for example in Cyprus, hospital admissions for favism declined abruptly following a campaign advising parents to avoid giving fresh broad beans to children, especially boys (Dr M Angastiniotis, personal communication).

Programmes of neonatal screening for G6PD deficiency and advice for parents are now established in parts of South East Asia, such as Singapore and Malaysia, where G6PD deficiency is common, the usual mutation is severe, and haemolysis is exacerbated by environmental factors including contact with baby clothes stored with moth-balls, or presence in breast milk of components of herbal remedies taken by the mother (18). Parents are advised to ensure that G6PD-deficient newborn children are exposed to light and to avoid storing baby clothes with naphthalene-containing preparations. Later in life they should avoid fresh fava beans, and medications that can precipitate a haemolytic crisis.

There is a serious lack of reliable information on the health burden of G6PD deficiency for use in health service planning, especially from Africa. Information is needed from each participating country on prevalence of G6PD deficiency and neonatal jaundice, and the proportion of children with neurological and learning disorders (possible sequelae of severe neonatal jaundice) who have G6PD deficiency. Data on the effectiveness of existing screening programmes should also be reported.

## 4.7 Neonatal screening

Neonatal screening involves organized examination of new-borns in order to diagnose specific disorders and provide appropriate treatment, as far as possible. It includes both clinical and laboratory approaches.

### 4.7.1 *Clinical neonatal screening*

All live-born babies should be examined systematically for congenital malformations by a doctor or a trained nurse using a checklist. The neonatal examination is a key element in the proposed WHO study, where all abnormalities detected will be confirmed by a paediatrician, and registered for epidemiological purposes. An agreed standardized protocol for neonatal examination is needed. Attachment 2 includes some conditions that can be diagnosed by careful neonatal examination, with relatively simple interventions possible at the primary health care level. Randomized studies have cast serious doubt on the safety and efficacy of neonatal screening for congenital dislocation of the hip using the Ortolani-Barlow manoeuvre, which has long been standard practice in developed countries. This will not form part of the WHO initiative.

Early identification of *congenital deafness* followed by appropriate intervention avoids difficulties in speech acquisition and promotes integration of deaf children into society. A careful UK review of the benefits and efficacy of deafness screening in infancy identified neonatal testing using automated evocation of auditory brainstem response as the most cost-effective approach (59). It can be used selectively for infants in high-risk groups (who have been in intensive care, suffered a neonatal infection or have a family history of deafness), but universal screening was recommended as the most cost-effective approach. Since recessive inheritance is particularly important in profound deafness, neonatal screening for congenital deafness could be particularly valuable in countries where consanguineous marriage is common. The report, which includes a detailed assessment of costs, should be reviewed by the national task group of participating countries.

All stillborn infants or infants dying in the perinatal period should have a post mortem examination, performed by a trained person. This is an important element in the WHO study. Since full autopsy is unacceptable in many societies and is not available in many countries, a standardized agreed protocol for non-invasive perinatal post-mortem examination will be required for the WHO study (50).

### 4.7.2 *Biochemical neonatal screening*

Neonatal screening for phenylketonuria, congenital hypothyroidism, sickle cell disorders and G6PD deficiency meet the criteria for a screening service in many countries. In most developed countries, a midwife or nurse routinely takes heel-prick blood samples onto a filter paper (Guthrie) card at 5-10 days after birth, and posts it to a central newborn screening laboratory. The system was introduced in the 1960s for phenylketonuria, because a low phenylalanine diet prevents severe mental retardation if started in the first weeks of life. The feasibility of implementing routine neonatal screening depends on the health care and communications infrastructure, but once it has been set up for one condition, it is relatively simple to add screening for other conditions, and to carry out epidemiological research.

The cost benefit equation of neonatal screening needs careful evaluation in each country, in the light of the prevalence of each disorder and local priorities. For example, testing for phenylketonuria is cheap but the diet is expensive, can be difficult to obtain, and is not

completely effective. By contrast, screening for congenital hypothyroidism is relatively expensive, but thyroxine treatment is easy, cheap and completely effective. In addition, samples may be needed at different times for different diagnoses: cord blood samples taken at birth can be used for screening for sickle cell disorders or G6PD deficiency, while screening for metabolic disorders should be done at the very earliest at 48 hours after birth, to allow the baby's metabolism to stabilize sufficiently for reliable results.

There is growing recognition that inherited metabolic disorders can be a significant cause of neonatal and infant death, and that they are particularly important in populations with a high prevalence of consanguineous marriage (60). A wide range of these disorders can now be diagnosed on dried Guthrie blood spots using tandem mass spectrometry, and the case for introducing this form of screening in developed countries has been reviewed (61).

## 4.8 The timing of population screening

A basic requirement in population screening is a "turnstile" - an appropriate point at which the relevant population routinely comes into contact with the health system and can be offered screening. Three common turnstiles are marriage, onset of pregnancy, and birth.

Table 8 shows the optimal timing for the interventions and screening procedures discussed above (10).

**Table 8. Optimal timing in reproductive life of the recommended preventive interventions**

Desirable prior to pregnancy	Feasible only during pregnancy	Feasible only neonatally
Family planning	Ultrasound screening for congenital malformations	Clinical examination for congenital abnormalities
Advice on women's diet	Screening for risk of chromosomal disorders	Biochemical screening
Appropriate management of maternal disorders e.g. diabetes	Diagnosis and treatment of maternal infections	
Avoiding infections by immunization and precautions		
Screening for Rh blood group		
Screening for risk of inherited disorders		

In countries where most couples marry before starting a family, a premarital medical consultation can provide an ideal opportunity for pre-pregnancy advice. However this does not apply in many countries (e.g in Western Europe), and screening is often offered only when

women attend for antenatal care. This greatly reduces the impact of interventions aiming to reduce fetal abnormality. For example:

- Information on the importance of folate and other nutrients reaches mothers too late in pregnancy to be useful.
- Pre-pregnancy testing for maternal infection, pre-pregnancy treatment and immunization are not possible. This applies for rubella, hepatitis, syphilis, tetanus, and also for HIV.
- Risk of inherited disorders may be detected only in the second trimester. Since late abortion is unacceptable to many couples, uptake of prenatal diagnosis is lower than with earlier risk identification (17, 53).
- There is no chance to ensure optimal control of maternal insulin-dependent diabetes prior to conception.

Admittedly, information obtained during the first pregnancy may be used in subsequent pregnancies, but when fertility is low this is a very ineffective approach.

In countries where premarital screening and counselling is not an option another pre-pregnancy turnstile must be found. The feasibility of integrating genetic screening and counselling into family planning services should be investigated in a range of settings.

Each participating country needs to review the optimal timing for providing information and testing, and identify an approach that will permit pre-pregnancy information and counselling, as far as possible. The chosen policy will determine the pattern of health workers involved, and their educational and training needs.

## **4.9 Education for health workers, and information for the public**

The educational task required when a new programme is introduced into a health service may be analyzed as follows:

- Description of the aims of, and evidence base for the intervention.
- Analysis of tasks and activities involved, allocation of each to the appropriate level of the health system, and identification of the appropriate health workers.
- Definition of the knowledge, attitude and skills required for each task, the means for imparting them, and the training time required.
- Decision on whether and how training fits into existing courses, and where training time will come from.
- Development of curricula and full supporting training materials for each category of health worker.
- Decision on method and frequency of data collection, and preparation of relevant supporting systems (forms, software, etc).

No comprehensive model is available for this substantial programme of work. The services that exist in more developed countries have grown up in an ad hoc and unrelated manner, so though they offer examples of good practice they are not seen as components of a single discipline. For the purposes of the WHO initiative it is necessary to identify examples, bring them into a systematic relationship, develop an outline curriculum and training materials and make these widely available.

Similarly, the important issue of information for the public has been relatively neglected, even though information is a key component in medical genetic interventions. Available examples of methods for imparting appropriate knowledge about genetics to the public should also be collected and reviewed.

## 5. The WHO initiative

Despite significant gaps in knowledge, existing evidence shows an urgent and growing need for systematic national and international initiatives aiming to reduce the health burden of congenital and genetic disorders. This proposal for a WHO programme on the control of congenital and genetic disorders in primary health care is a major new initiative, designed in response to increasing global demand. It was originally initiated at a meeting of a Working Group convened at the Eastern Mediterranean Regional Office of WHO in November 1995 and elaborated further at the Cairo meeting of December 1999. There is as yet no existing model that can be implemented at the country level, and a long-term programme including substantial research and development is required.

Because of wide differences between countries, the appropriate approach is to implement a *programme of work* intended to support an organized approach to the control of congenital disorders in any setting. The proposed programme of work has three distinct phases: development of a country plan, execution of a demonstration project implementing selected interventions, and countrywide implementation.

The approach is recommended for consideration to all countries. Implementation within a collaborative international study with WHO technical support is foreseen for selected countries. The following steps are proposed for participating countries.

### 5.1 Formation of a national task force

A national (or local) multi-disciplinary task force should be convened to review the local epidemiology and health burden of congenital and genetic disorders and identify priority areas for intervention. The long-term aim of the task force is to define and monitor national policy on control of congenital and genetic disorders.

The task force should include representatives of the Ministry of Health (and relevant professional associations), specialists in e.g. epidemiology, statistics, informatics, paediatrics, genetics, pathology, haematology, obstetrics, maternal and child health and primary care, laboratory experts in biochemistry, cytogenetics and molecular medicine.

The task force needs a *coordinator*. This person must have certain characteristics, e.g. must be highly motivated, understand the principles of genetics and public health, be familiar with local health services, and have a collaborative outlook, facilitating working with professional colleagues. Their chief responsibilities should be coordinating evidence-based decision-making, organizing the programme, carrying out evaluation, and providing information at all levels. They should have the position, training and technical and clerical support required to perform these duties.

The task group coordinator will require skills in paediatric and/or reproductive medicine, medical genetics, public health, epidemiology, education and information technology. No recognized training course exists to fit individuals for this role. Many necessary skills may be obtained through collaboration with the WHO task group, and training country representatives

should be seen as one of its principal tasks. The WHO should also encourage governments to arrange individually tailored training for the country coordinator in areas where it is needed.

## **5.2 Development of a national plan**

The first task for the task force is to produce a country report, in standardize format (to be developed). The report should contain:

- Description of the organization of primary health care and reproductive health services (which differ greatly by country).
- Basic demographic data, by administrative and ethnic subdivisions of the population.
- A summary of available data on the local frequency and causes of congenital disorders.
- An assessment of the resources available for the initiative.
- A plan for a pilot of the proposed epidemiological study.
- Referral pathways for patients, and families thought to be at risk.
- Recommended approaches for surveillance of congenital disorders.
- Issues surrounding acceptability of prenatal diagnosis and genetic abortion at different stages of pregnancy.

The task force will then develop a draft national plan taking account of:

- local priorities.
- realistic approaches, in the light of local resources and cultural conventions.
- possible “entry points” for a programme.
- whether programmes should be vertical or integrated.
- whether it is best to start with a single issue, or whether a more general approach should be adopted from the outset.

Every national plan should promote both best possible patient care and appropriate approaches for prevention.

## **5.3 The baseline epidemiological study (the WHO mother and baby study)**

The epidemiological study is intended to generate reliable data to support planning, and to set up some systems (e.g. for education and audit) that are required for the proposed demonstration project, and for national implementation (Attachments I and II).

The epidemiological study will be conducted using standardized methods in facilities where babies are born, in the area where the demonstration project will be conducted. The draft protocol is given in Attachment I. It includes a core study with optional components:

- A target population of at least 15,000 recently delivered women will be interviewed to obtain information on their demographic background and obstetric history. Previous stillbirths and deaths will be included. Attachment I includes data collection sheets for mother and the baby. These are intended only to show the data that should be collected. They need not be used in the study, as duplication must be avoided. When the required data is already collected in standard antenatal records, these may be photocopied. If

existing antenatal records do not include all the necessary data, they may be modified for the study and photocopied. Alternatively, the forms in Attachment I may be used.

- Whether the outcome of the current pregnancy is a live- or stillbirth or a neonatal death, the baby will be examined and the findings recorded using a standard checklist for examination of the newborn (see baby data collection sheet 1 - screening examination). If a congenital anomaly is suspected in a liveborn baby this will be noted, and the baby will be examined by a specialist member of the study team, where available. The findings and provisional diagnosis will be recorded (see baby data collection sheet 2 - live baby with congenital anomaly), using a checklist. Special attention should be directed to ensuring that babies in intensive care are included.
- It is a priority to examine all stillborn babies and those that die in the neonatal period, in the target population. Wherever possible, an expert will examine each baby and the observations recorded (see baby data collection sheet 2 - stillbirth or neonatal death). Standard photographs and whole body X-rays may be taken, and added to the record. Reports (or copies) of intra-uterine, pre-mortem or post-mortem ultrasound examinations may be included. An autopsy may not be feasible, but blood or tissue samples may be taken for tests relevant to diagnosis, to provide information on which to base counselling for the parents. If no diagnosis is made, a parent may be asked if samples can be stored for future testing, in the event of relevant diagnostic tests becoming available.
- As an *optional study*, blood samples will be collected from the mother, agreed haematological tests will be conducted, and serum separated, labeled and stored. Blood tests will be carried out using methods locally available and chosen by the research team. A discussion of selected methods is to be included in the manual of operations. It is a priority to ensure quality control.
- As an *optional study*, blood samples from all babies will be collected onto Guthrie cards and forwarded to the study centre, or a designated laboratory, for selected investigations. Guthrie cards for study later will be sealed in plastic envelopes and stored in a metal box in a cool environment. A special effort will be made to include a sample from each dead baby: in this case blood may be taken by cardiac puncture.

All records will be forwarded to the national study team. They will be checked, coded and entered on the database by staff of the study team. Any uncertainties or incompleteness in data collection will be corrected as soon as possible by liaison with the staff at the place of birth.

Initial coding of disorders detected in mothers and infants will use ICD10. Where possible, abnormalities will be coded by the specialist doctor undertaking the diagnostic examination. In addition to basic ICD10 coding they will use McKusick (OMIM) codes, as these are more detailed than ICD10 in recording congenital anomalies.

Parents of all stillborn babies, of liveborn babies with a congenital disorder diagnosed at birth or later, and all carriers of inherited disorders diagnosed in the course of the study will be referred for expert counselling on steps they can take to reduce (recurrence) risks.

The status of all data will be reviewed at regular meetings of the study team.

## **5.4 The intervention study (demonstration project)**

It is too early to make detailed plans for the demonstration intervention project that is the final objective of this WHO initiative. The epidemiological study will provide the data needed for

planning, and offers an opportunity for developing and testing instruments, creating primary care training packages, and establishing methods for monitoring process and outcomes.

## 6. The role of WHO

It is appropriate for WHO to take the lead in this important global initiative, including seeking support from relevant international organizations and donors.

The WHO human genetics and reproductive health programmes should collaborate in:

- defining and assessing the health burden related to congenital disorders.
- identifying evidence-based interventions, and examples of good practice.
- identifying realistic priorities for countries at different stages of development, and with different health systems.
- guiding the process of national policy development and service planning.
- providing training packages and electronic tools.
- establishing and applying methods for surveillance.
- providing long-term support for task forces in interested countries.

The first step is to commission a collaboration between selected experts and relevant WHO programmes, including human genetics, reproductive health, primary health care, iodine supplementation, AIDS etc. The aim should be to draw on existing experience to update knowledge of the global epidemiology and health burden of congenital and genetic disorders. A standard format for describing epidemiology and health burden should be developed for supporting health service planning in any country.

This collaboration will form the basis for a WHO multi-disciplinary task force, bringing representatives of WHO programmes and appropriate experts into a long-term working relationship. Corresponding multidisciplinary groups should be created at the WHO regional level. The WHO task force should collaborate with representatives of participating countries in the following programme of work:

1. Improving information on epidemiology and health burden. Existing data should be reviewed in the light of its relevance to congenital and genetic disorders, gaps should be identified, and plans made to fill them. For example, information is needed on:
  - iodine deficiency: prevalence in pregnancy, and likely effects of the current prevention programme on maternal and child health.
  - iron deficiency: prevalence in pregnancy, and likely effects of supplementation on maternal and child health.
  - infectious diseases: prevalence of HIV, syphilis and rubella in pregnancy, including age-related data on immunity to rubella in order to select the appropriate approach for immunization.
  - Rhesus blood group: the proportion of Rhesus negative women who become alloimmunised, and present practice in screening and prevention of alloimmunisation.
  - G6PD deficiency: role in neonatal jaundice and its sequelae, prevalence of acute haemolysis, and data on existing neonatal screening programmes.



2. Review recommended interventions and new evidence-based developments (e.g. in neonatal deafness screening).
3. Agree standard methods and finalize protocols for:
  - clinical examination of the newborn.
  - non-invasive perinatal post-mortem examination.
  - taking a basic genetic family history.
4. Identify cost-effective approaches for:
  - cost-effective use of scarce laboratory resources.
  - tracking prevalence of iron deficiency at the population level.
  - identifying genetic risk, e.g. extended family studies versus screening.
5. Agree training, education and accreditation requirements:
  - for country coordinators. This is crucially important for the success of the initiative: see page 29.
  - identify feasible approaches for deploying the recommended interventions using existing health care infrastructures.
  - identify the health workers involved, and their educational and training needs.
  - review existing training courses.
  - develop an outline curriculum, and appropriate training packages for health workers, and disseminate them appropriately.
  - agree required training and accreditation of ultrasound operators.
6. Collaborate on developing appropriate information materials for patients and the public:
  - set up an information/education task group.
  - review existing information resources, and agree on basic information and standards.
  - examine the value of a global approach to standardizing, translating, and disseminating quality information: consider IT-based approaches.
7. Research: organize international research studies on:
  - birth prevalence of infants with metabolic disorders using tandem mass spectrometry examination of Guthrie blood spots.
  - short and long-term effects of iron supplementation in pregnancy on the health of mother and child.

Interested countries should recruit a national task group and start collecting background data for a country report and country plan, without delay. The WHO task group will recommend a format for and comment on country reports, check the design of pilot studies and be responsible for the design of the baseline epidemiological study, and methods for recording and analyzing results. They will ensure standardization of all recommended tests and procedures, and co-operate with participating countries in producing training packages, first for the epidemiological study, and later for the intervention study. The WHO task force group will be

ultimately responsible for programme surveillance, and assessment of the impact of the interventions on national and global health burden.

## List of Participants

**Dr O.O. Akinyanju**, Professor of Medicine, College of Medicine, University of Lagos, P.M.B. 12003, Lagos, **Nigeria** [fax: +234 1 618 778; e-mail: oluphysic@cyberspace.net.ng]

**Dr. Shaikha Al-Arrayed**, Chief, Genetics Unit, P.O.Box 12, Manama, **Bahrain** [fax: 00973 275612/689959]

**Dr W. Anwar**, Director General, Technical Department, Ministry of Health, Cairo, **Egypt**

**Dr P. Baird**, Professor of Medical Genetics, University of British Columbia, 222-6174 University Blvd., Vancouver, British Columbia, V6T 1Z3, Canada [fax: 604 822 3565; e-mail: pbaird@interchange.ubc.ca]

**Dr J.M. Cantú Garza**, Chief, Genetics Division, Centro de Investigación Biomédica de Occidente, Instituto Mexicana del Seguro Social, Siena No. 1068 Lomas de Providencia, Guadalajara, Jalisco, **Mexico** [fax: +523 6188 069; e-mail: jmcantu@koch.mb.udg.mx]

**Dr J. Chapple**, Consultant, Kensington & Chelsea and Westminster Health Authority, 50 Eastbourne Terrace, London W2 6LX, **UK** [Fax: 0044 171 281 8004; e-mail: jean.chapple@HA.kcw-ha.nthames.nhs.uk]

**Professor A.L. Christianson**, Head, Department of Human Genetics and Developmental Biology, Faculty of Medicine, University of Pretoria, P.O. Box 667, Pretoria 0001, **South Africa** [fax: +27 12 323 2788; e-mail: christal@medic.up.ac.za]

**Mr M. Darlison**, WHO Collaborating Centre on the Control of Hereditary Disease, RF & UC Medical School, Department of Primary Care & Population Sciences, Holborn Union Building, Archway Campus, Highgate Hill, London N19 3UA, **UK** [Fax: 0044 171 281 8004; e-mail: m.darlison@ucl.ac.uk]

**Dr N. Firdous**, Consultant, Ministry of Health, Maldives, c/o WR, **Maldives** [fax: 00960 32 2221; e-mail: she8804@dhivehinet.net.mv] (unable to attend)

**Dr L. Heredero**, Director, Centro Nacional de Genética Médica, Calle 31 esquina a 146, Cubanacan, Playa, Havana, **Cuba** [e-mail: lhere@infomed.sld.cu]

**Dr Huang Shangzhi**, Director, Department of Medical Genetics, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences 5, Dong Dan San Tiao, Beijing 100005, **China** [fax: 0086 10 65229323; e-mail: huangsz@263.net]

**Dr Lim Nyok Ling**, Consultant, Dept. of Paediatrics, Hospital Selayang, Lebuhraya Selayang-Kepong, 68100 Batu Caves, Selangor, **Malaysia** [fax 03 613 77097 – tel. 03 613 7788, ext. 5050; e-mail: drchin@tm.net.my]

**Dr M. Modell**, Consultant, Department of Primary Care & Population Sciences, Holborn Union Building, Archway Campus, Highgate Hill, London N19 3UA, **UK** [Fax: 0044 171 281 8004; e-mail: m.modell@ucl.ac.uk]

**Dr E. Abdel Saalam**, Professor of Paediatrics & Genetics, Cairo University, Cairo, **Egypt**

**Dr Ashraf Samavat**, Ministry of Health and Medical Education Under Secretary of Health, Disease Control & Prevention Department, South Iranshahr Avenue, Tehran, Islamic Republic of **Iran** [Fax: 009821 830444]

**Dr Kamel Shadpour**, Senior Expert, Primary Health Care Department, Ministry of Health and Medical Education, Tehran Islamic Republic of Iran

**Dr Ishwar Verma**, Head, Department of Medical Genetics, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi 110060, India [fax: +91 11 685 4434; e-mail: icverma@giasdL01.vsnL.net.in]

**Dr Pornswan Wasant**, Chief of Genetics, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, 10700, Thailand [fax: +662 419-8414; e-mail: sipws@mahidol.ac.th]

## **WHO/HQ**

**Dr A. Alwan**, Director, Division of Noncommunicable Disease Prevention, CH-1211 Geneva 27, Switzerland [fax: +41 22 791 4259; e-mail: alwana@who.ch]

**Mrs G. Bellevaux**, Human Genetics, Division of Noncommunicable Disease Prevention, CH-1211 Geneva 27, Switzerland [fax: +41 22 791 47 69; e-mail: bellevauxg@who.ch]

**Dr V. Boulyjenkov**, Human Genetics, Division of Noncommunicable Disease Prevention, CH-1211 Geneva 27, Switzerland [fax: +41 22 791 47 69; e-mail: boulyjenkovv@who.ch] (Secretary)

**Dr B. Modell**, WHO Consultant, Head of the WHO Collaborating Centre on the Control of Hereditary Disease, RF & UC Medical School Department of Primary Care & Population Sciences, Holborn Union Building, Archway Campus, Highgate Hill, London N19 3UA, UK [Fax: 0044 171 281 8004; e-mail: b.modell@ucl.ac.uk]

**Dr Q.M. Islam**, Reproductive Health and Research, WHO, CH-1211 Geneva 27 [Fax: +41 22 791 4189; e-mail: islamm@who.ch]

## **WHO/EMRO**

**Dr Hussein A. Gezairy**, Regional Director, WHO Office for the Eastern Mediterranean, P.O. Box 1517, Alexandria 21511, Egypt [Tel. 203 48 202 23; fax 203 48 38 916]

**Dr Z. Hallaj**, WHO Representative, Magles el Shab Street, Cairo, Egypt [Tel. +202 355 3708; e-mail: wregypt@intouch.com]

**Dr K. Al Roomi**, Consultant, WHO Regional Office for the Eastern Mediterranean, Alexandria, Egypt

## References

1. United Nations Demographic Yearbook series. United Nations, New York.
2. Baird PA, Anderson TW, Newcombe HB, Lowry RB. 1988. Genetic disorders in children and young adults: a population study. *American Journal of Human Genetics* 42: 677-693.
3. Baird PA. 1999. Prenatal screening and the reduction of birth defects in populations. *Community Genetics* 2: 9-17.
4. De Wals P, Weatherall JAC, Lechat MF. Registration of Congenital anomalies in Eurocat centres 1979 - 1983. An EEC Concerted Action Project. Cabay 1985.
5. Christianson AL. Down syndrome in sub Saharan Africa. 1996. *Journal of Medical Genetics* 33: 89-92.
6. WHO 1994. Guidelines for control of haemoglobin disorders. Unpublished document of the WHO. WHO/HDP/HB/GL/94.1. Updated global epidemiological data available at [www.chime.ucl.ac.uk/APoGI/](http://www.chime.ucl.ac.uk/APoGI/)
7. WHO 1985. Glucose-6-Phosphate Dehydrogenase Deficiency. Report of a WHO Working Group. Unpublished WHO Document HDP/WP/G6PD/85.9.
8. Bittles AH. 1990. Consanguineous marriage: current global incidence and its relevance to demographic research. Population studies center, University of Michigan. Research report no 90-186.
9. Modell B, Kuliev AM, Wagner M. Community Genetics Services in Europe. WHO Regional Publications, European Series No 38. WHO Regional Office for Europe, 8 Scherfigsvej, DK-2100, Copenhagen, Denmark. 1992.
10. Alwan AA, Modell B. Community Control of Genetic and Congenital Disorders. EMRO Technical Publications Series 24. World Health Organization Regional Office for the Eastern Mediterranean. 1997.
11. Costa T, Scriver C, Childs B. 1985. The effect of Mendelian disease on human health: A measurement. *American Journal of Medical Genetics* 21: 231-242.
12. Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. NHS R&D HTA Programme. 1999. ISSN 1366-5278. (Full text available at [www.hta.nhsweb.nhs.uk](http://www.hta.nhsweb.nhs.uk))
13. Hoffbrand AV, Wonke B. 1997. Iron chelation therapy. *Journal of Internal Medicine* 242 (Supplement 740): 17-41.
14. Loukopoulos D. 1996. Current status of thalassaemia and the sickle cell syndromes in Greece. *Seminars in Hematology* 33: 76-86.
15. Cao A. Results of programmes for antenatal detection of thalassaemia in reducing the incidence of the disorder. 1987. *Blood Reviews* 1: 169-76
16. Angastiniotis MA, Kyriakidou S, Hadjiminis M. 1986. How thalassaemia was controlled in Cyprus. *World Health Forum* 7: 291-297.
17. Modell B, Harris R, Lane B, Khan M, Darlison M, Petrou M, Old J, Layton M, Varnavides L. 2000. Informed choice in genetic screening for thalassaemia during

pregnancy: audit from a national confidential enquiry. *British Medical Journal* 320: 325-390.

18. WHO 1989. Glucose-6-Phosphate Dehydrogenase Deficiency. Report of a WHO Working Group. *Bulletin of the World Health Organization* 67: 601-611.
19. Kromberg JGR, Castle D, Zwane EM, Jenkins T. Albinism and skin cancer in southern Africa. *Clinical Genetics*, 1989. 36 : 43 - 52.
20. Modell B, Kuliev AM. 1989. The impact of public health on human genetics. *Clinical Genetics* 36: 286-298
21. Barker DJP (ed). Fetal and infant origins of adult disease. *British Medical Journal*, Tavistock Square, London WC1H 9JR.
22. Lumley J, Watson L, Watson M, Bower C. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects (Cochrane Review). In: *The Cochrane Library*, Issue 4, 1999. Oxford: Update Software.
23. Kramer MS. Balanced protein/energy supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 4, 1999. Oxford: Update Software.
24. Shangzhi Huang. Genetic Epidemiology Studies in China. Working paper prepared for this meeting.
25. Ubbink JB, Christianson AL, Bester ML, Van Allen MI, Venter PA, Delport R, Blom HJ, van der Merwe A, Potgieter H, Vermaak WJH. Folate status, homocysteine metabolism, and methylene tetrahydrofolate reductase genotype in rural South African Blacks with a history of pregnancy complicated by neural tube defects. 1999. *Metabolism* 48 (2): 269-274.
26. Pharoah PO. 1993. Iodine-supplementation trials. *American Journal of Clinical Nutrition* 57 (supplement) 276S-279S.
27. Herberg S, Galan P. 1992. Nutritional anaemias. *Baillieres Clinical Haematology* 5: 143-68
28. Walter T. 1994. Effect of iron-deficiency anaemia on cognitive skills in infancy and childhood. *Baillieres Clinical Haematology* 7(4): 815-27.
29. Cook JD, Skikne BS, Baynes RD. 1994. Iron deficiency: the global perspective. *Advances in Experimental Medicine and Biology* 356: 219-28.
30. Mahomed K. Iron supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 4, 1999. Oxford: Update Software.
31. Vitez M, Koranyi G, Goncy E, Rudas T, Czeizel A. 1984. A semiquantitative score system for epidemiologic studies of fetal alcohol syndrome. *American Journal of Epidemiology* 119: 301-308.
32. Viljoen DL. Fetal alcohol syndrome (editorial) *South African Medical Journal* 1999. 89: 958 - 959.
33. DiFranza JR, Lew RA. 1995. Effect of maternal cigarette smoking on pregnancy complications and sudden infant death syndrome. *Journal of Family Practice* 40: 385-94
34. Olofsson P, Liedholm H, Sartor G, Sjoberg N-O, Svehnigsen NW, Ursing D. Diabetes in pregnancy. A 21 year Swedish material. *Acta Obstetrica Gynaecologica Scandinavica* 122 (supplement): 1-62. 1984

35. Ylinen K, Aula P, Stenman U-H. 1984. Risk of minor and major malformations in diabetes with high haemoglobin A1c values in early pregnancy. *British Medical Journal* 289: 345-6.
36. Samren EB, van Duijn CM; Christiaens GC; Hofman A; Lindhout D. 1999. Antiepileptic drug regimens and major congenital abnormalities in the offspring. *Annals of Neurology* 46: 739-46.
37. Phillips-Howard P A, Wood D. 1996. The safety of antimalarial drugs in pregnancy. *Drug Safety* 14(3): pp.131-145.
38. Adams S. 1996. Caring for the pregnant woman with sickle cell crisis. *Professional Care of Mother and Child* 6: 34-6.
39. Afifi AM. 1974. High transfusion regime in the management of reproductive wastage and maternal complications of pregnancy in thalassaemia major. *Acta Haematologica* 52: 331-335.
40. Drogari E, Smith I, Beasley M, Lloyd JK. Timing of strict diet in relation to fetal damage in maternal phenylketonuria. *The Lancet* ii, 927-930. 1987.
41. Newell ML, Peckham C. Risk factors for vertical transmission of HIV-1 and early markers of HIV-1 infection in children. *AIDS* 1993;7(Suppl 1):S91-7.
42. Brocklehurst P. Interventions aimed at decreasing the risk of mother-to-child transmission of HIV infection (Cochrane Review). In: *The Cochrane Library*, Issue 4, 1999. Oxford: Update Software.
43. Clarke C, Whitfield AGW. 1984. Deaths from rhesus haemolytic disease in England and Wales during 1980 and 1981 and a comparison with earlier years. *Journal of Obstetrics and Gynaecology* 4: 218-222.
44. Peyron F, Wallon M, Liou C, Garner P. Treatments for toxoplasmosis in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 4, 1999. Oxford: Update Software.
45. Wilson JMC, Jungner G. 1968. Principles and practice of screening for disease. *Public Health Papers WHO* No 34.
46. Cuckle HS, Wald NJ. Principles of screening. In: *Antenatal and neonatal screening*, NJ Wald (ed). Oxford University Press, Oxford, New York and Toronto. 1984
47. Chitty L. Ultrasound screening for fetal abnormalities. In CH Rodeck and MJ Whittle (eds): *Fetal Medicine. Basic science and clinical practice*. Churchill Livingstone, London. 1999.
48. Blaas HG, Eik-Nes. First trimester diagnosis of fetal malformations. In CH Rodeck and MJ Whittle (eds): *Fetal Medicine. Basic science and clinical practice*. Churchill Livingstone, London. 1999.
49. Nicolaides KH, Souka AP, Noble PL. Fetal nuchal translucency at 10-14 weeks of gestation. In CH Rodeck and MJ Whittle (eds): *Fetal Medicine. Basic science and clinical practice*. Churchill Livingstone, London. 1999.
50. Baayou Z. 1998. Non-invasive perinatal post mortem examination. M Phil thesis. University College London.
51. Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J. 1999. Screening for cystic fibrosis. *Health Technology Assessment* 3: No 8. (Full text available at [www.hta.nhsweb.nhs.uk](http://www.hta.nhsweb.nhs.uk))

52. Kronn D, Jansen V, Ostrer H. 1998. Carrier screening for cystic fibrosis, Gaucher disease, and Tay-Sachs disease in the Ashkenazi Jewish population: the first 1000 cases at New York University Medical Center, New York, NY. *Archives of Internal Medicine* 158: 777-81.
53. Petrou M, Brugiattelli M, Ward RHT, Modell B. 1992. Factors affecting the uptake of prenatal diagnosis for sickle cell disease. *Journal of Medical Genetics* 29: 820-3.
54. Serjeant GR. Sickle cell disease. Oxford University Press. Oxford, New York, Tokyo. 2nd edition 1992.
55. Rajab A, Patton MA 1999. Analysis of the population structure Oman. *Community Genetics* 2: 23-26.
56. Ahmed S, Saleem M, Sultana N, Raashid A, Waqar A, Anwar M, Modell B, Karamat KA, Petrou M. 2000. Prenatal diagnosis of beta thalassaemia in Pakistan: experience in a Muslim country. *Prenatal Diagnosis* 20: 378-383.
57. Crowther CA, Keirse MJNC. Anti-D administration in pregnancy for preventing Rhesus alloimmunisation (Cochrane Review). In: *The Cochrane Library*, Issue 4, 1999. Oxford: Update Software.
58. Luzzato L, Mehta A. Glucose-6-phosphate dehydrogenase deficiency. In Scriver CR, Beaudet AL, Sly WS, Valle D. (Eds). *The metabolic basis of inherited disease*. 6th edition. McGraw Hill Inc, New York. 1989.
59. Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S. A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment. *Health Technology Assessment* 1997. 1: 10. (Full text available at [www.hta.nhsweb.nhs.uk](http://www.hta.nhsweb.nhs.uk))
60. Ozand T, Devol EB, Generoso GG. 1992. Neurometabolic diseases at a national referral centre: five years experience in the King Faisal Specialist Hospital and Research Centre. *Journal of Child Neurology* 7: Supplement. S4 - S9.
61. Seymour CA, Thomason MI, Chalmers RA, Addison GM, Bain MD, Cockburn E et al. Newborn screening for inborn errors of metabolism: a systematic review. *Health Technology Assessment* 1997: 1 (11).
62. WHO 1996. Report of a WHO Scientific Group. Control of hereditary diseases. WHO Technical Report Series 865, Geneva: 1-86.
63. WHO 1999. Services for the prevention and management of genetic diseases and birth defects in developing countries. Report of a WHO meeting (WHO/HGN/GL/WAOPBD/99.1): 1-100.
64. UN 1994. The standard rules on the equalization of opportunities for persons with disabilities: 1-41.



# Annex 1

## Prevalence of genetic and congenital disorders in populations of European origin, to age 12 (Ref. 2)

Category	Sub-group	Examples of common diagnoses	Estimated births/1000	
			sub-group	category
	dominant	Familial hypercholesterolaemia, adult polycystic kidney disease, neurofibromatosis, Huntington disease, achondroplasia	7	
Inherited (single gene) disorders	X-linked	Fragile X mental retardation, Duchenne muscular dystrophy, haemophilia A & B, colour vision disorders	1.33	10.0
	Recessive	Glutathione deficiency, cystic fibrosis, alpha-1 antitrypsin deficiency, phenylketonuria, Werdnig-Hoffman disease, haemoglobin disorders	1.66	
Chromosomal disorders	Autosomes	Down syndrome	1.7	3.5
	Sex chromosomes	Klinefelter & Turner syndrome	1.8	
Congen. malformations	Inherited	Multiple malformation syndromes, polydactyly etc	0.6	0.6
		Neural tube defect	1 - 6	
		Congenital heart disease	7 - 10	
Congen. malformations	Multifactorial	Talipes equinovarus	1.5	30.0
		Congenital dislocation of hip	0.1 - 14	
		Pyloric stenosis	1.5	
		Cleft lip +/- palate	1.0	
Multifactorial disorders		Epilepsy, diabetes mellitus, obesity		10.6
Genetic, type unknown				1.2
<b>TOTAL GENETIC</b>				<b>55.9</b>
No genetic component		Terminal transverse limb deficiency		0.1
		Fetal rubella syndrome, fetal alcohol syndrome		0.6
<b>TOTAL</b>				<b>56.6</b>

## Annex 2

### Options for best possible care for common congenital disorders and birth defects (Ref. 63)

Condition	Diagnosis	Specific complications	Investigations	Therapeutic intervention
Spina bifida	Clinical, newborn examination	Spinal lesion, hydrocephalus, developmental delay, paraplegia, incontinence	Brain scan, developmental* / psychometric assesment, urological evaluation	Surgery, palliative care, NDT*prevention of urinary tract infections*, self catheterisation*
Cleft lip/ Palate	Clinical, newborn examination	Feeding problems, speech problems	Audiological/ speech evaluation	Surgery, buccal plate, NDT*
Talipes Equinovarus	Clinical, newborn examination	Abnormal foot position	X-rays*	Manipulation*, plaster of Paris*, surgery
Undescended testes	Clinical, newborn examination	Sub-fertility, testicular cancer		Surgery
Congenital hypothyroidism	Neonatal screening*, clinical, thyroid function tests	Growth deficiency, mental retardation, umbilical hernia	Growth monitoring* developmental* / psychometric assesment	Thyroxine*, NDT*, surgery
Achondroplasia	Clinical, newborn examination, confirm by DNA	Short stature, spinal gibbus, spinal cord compression, hydrocephalus, obstructed labour	DNA, X-rays*, brain scan	Counselling on spinal posture*, surgery, Caesarian section*
Neurofibromatosis	Clinical, confirm by DNA	Tumors, plexiform neurofibroma, optic glioma, seizures, learning disability, long bone bowing	X-rays*, ophthalmological assesment, EEG, developmental* / psychometric assesment	Surgery, anticonvulsant therapy*, NDT*
Haemochromatosis	Clinical, serum iron or ferritin, confirm by DNA	Iron overload, cirrhosis, diabetes, cardiac failure, arthritis, liver cancer	Liver function tests, glucose tolerance test, ECG* / X-rays* / ultrasound / angiogram	Venesection*, diet* / Insulin* / diabetic medications*, cardiac failure therapy*, anti-inflammatories*
Fragile X-syndrome	Clinical, confirm by DNA	Mental retardation, behavioural problems	Developmental* / psychometric assesment	NDT*, behavioural management*
Haemophilia A	Clinical, confirm by clotting studies and DNA	Bleeding diathesis, joint arthroses	PI / PTT, Factor VIII assay, X-rays*	Factor VIII replacement*, physiotherapy* / surgery

\* Can be undertaken at primary health care level.

## Annex 2

Options for best possible care in common congenital disorders and birth defects (Continued)

Condition	Diagnosis	Specific complications	Investigations	Therapeutic intervention
<b>Thalassemia</b>	Clinical, blood film, Hb F estimation	Chronic anaemia, hypersplenism, iron overload	Hb level, annual blood consumption, ferritin	Blood transfusion*, folic acid*, splenectomy, desferrioxamine*, deferiprone*
<b>Sickle cell disorders</b>	Clinical, blood film, Hb electrophoresis, sickle test	Chronic anaemia, susceptibility to overwhelming infection, painful crises	Regular review,	Information for parents*, protective precautions*, prophylactic antibiotics and antimalarials*, treatment of acute complications
<b>Oculo-cutaneous albinism</b>	Clinical, newborn examination	Skin lesions, nystagmus, visual problems, skin cancer		Advice, sunscreen, glasses
<b>Trisomy 18 syndrome</b>	Clinical, newborn examination, confirm by chromosome studies	Growth deficiency, congenital heart defect, early death	Growth monitoring*	Palliative care*
<b>Fetal alcohol syndrome</b>	Clinical	Growth deficiency, mental retardation, behavioural abnormalities, congenital cardiac defects	Growth monitoring*, developmental* / psychometric assessment, psychological assessment, ECG* / x-rays* / ultrasound / angiogram	NDT*, neuro-behavioural therapy, cardiac failure therapy* / surgery
<b>Fetal rubella syndrome</b>	Clinical, confirm by Rubella virus IgM / IgG	Growth deficiency, microcephaly, mental retardation, visual defects, deafness, congenital heart defects	Growth monitoring*, developmental* / psychometric assessment, ophthalmological assessment, auditory / speech assessment, ECG* / X-rays* / ultrasound / angiogram	NDT*, surgery, cataract removal / glasses, hearing aid, cardiac failure therapy*

*For all conditions in the table, clinical diagnosis, genetic counselling and psycho-social support are possible at primary health care level.*



# Attachment I

## WHO Initiative on the Prevention and Control of Congenital and Genetic Disorders in Developing Countries\*

### Base-line epidemiological study *Draft protocol and data collection forms*

#### Table of contents

1. Objectives and general structure of the study .....	1
2. Study design .....	1
3. Study size .....	4
4. Data collection .....	4
5. Coding and entry of data .....	7
6. Initiating the study .....	7
7. Pilot studies .....	8
8. Draft data collection sheets for mother and baby .....	9
Mother's data collection sheet 1: Demographic data .....	10
Mother's data collection sheet 2: Obstetric history .....	12
Mother's data collection sheet 3: Parental consanguinity .....	13
Mother's data collection sheet 4: This pregnancy .....	15
Baby data collection sheet 1: Screening examination .....	17
Baby data collection sheet 2: Specialist examination .....	20

---

\* The first draft of this protocol was developed by a Working Group convened at the Eastern Mediterranean Regional Office of WHO in November 1995 and elaborated further at the Cairo meeting of December 1999.



# 1. Objectives and general structure of the study

This is a multicentre prospective epidemiological study of the birth prevalence of congenital and genetic disorders. The study will provide an evidence base for interventions aiming to reduce the burden of these disorders.

The study will involve training health workers to collect data and examine new-borns in a standardised way, and will establish a basis for national surveillance of congenital and genetic disorders.

There are six basic objectives. Objectives 1 and 2 are *core objectives* to be carried out by all participants. The other, optional objectives can be met at varying levels, according to the resources available to each study team.

**Objective 1:** To gather basic demographic data on parents, including data on parental consanguinity.

**Objective 2:** To establish the birth prevalence (on a community, geographical base wherever possible) of structural congenital anomalies detectable by clinical examination of new-borns, including stillbirths.

**Objective 3:** To establish the prevalence of risk factors for congenital disorders in mothers through blood testing (for example, haemoglobin disorders, rubella, syphilis, HIV and other maternal infections, folate and iodine levels, and G6PD deficiency).

**Objective 4:** To establish the birth prevalence (on a community, geographical base wherever possible) of haemoglobin disorders, G6PD deficiency and a range of metabolic disorders, by analysis of Guthrie blood spot samples in new-borns, including stillbirths.

**Objective 5:** To establish the frequency of antenatally diagnosed congenital disorders in the study population.

**Objective 6:** To link the later outcome in the babies with observations at birth, and to establish the prevalence of congenital disorders presenting after the neonatal period.

Standardised methods will allow international pooling of "core" and optional data.

## 2. Study design

The core study of the target population can be set up either (a) using anonymous data only, for purely epidemiological purposes, or (b) using named data, in order to allow the possibility of follow-up of target babies. Research teams need to look carefully at the advantages and disadvantages of each approach.

An anonymous study is the simplest to execute. Clearly, mothers and babies with abnormalities detected at the time of data collection must be referred for appropriate clinical management, when possible. However, in an anonymous study it is not possible to arrange for follow-up of babies when abnormal findings emerge later, e.g. through tests carried out on the mother's

blood, or on Guthrie cards. The working group did not favour an anonymous study, for these reasons.

When the investment has been made to carry out the initial epidemiological study, it may prove desirable and feasible in some areas to develop it into a prospective follow-up study of the cohort of registered babies, in order to identify congenital and genetic disorders that cannot be readily diagnosed at birth (such as many congenital malformations, thalassaemia, haemophilia, mental retardation,<sup>1</sup>). This requires recording of confidential details of the mother and baby, including name and address.

With appropriate support, birth cohorts can be followed at regular intervals for a long period (e.g. the 3 UK birth cohorts (1947, 1958, 1970), still being followed, include a random sample of all babies born in one week of that year). Such studies give an increasingly valuable yield of health information with the passage of time.

It is essential for each study team to decide at an early stage whether they will conduct an anonymous core study or a follow-up study, since the decision will affect all aspects of data collection. For example, if follow-up is contemplated, a parent's consent to all parts of the study, including later follow up, should be obtained at the outset. If a team is undecided, a named study may be selected, since it allows room for a later decision to follow up the cohort.

## **2.1 Concerns about ethics and confidentiality**

There are ethical issues and concerns about confidentiality for any study with named data, or studies where subjects can be identified through case numbers. In a named study, a parent will need an explanation of the study objectives before they can give informed consent. They also need to know if samples of either maternal or infant blood will be stored for future use. The consent of a parent may be refused for all or parts of the study and this will remove data on that mother and baby from results.

Measures to ensure confidentiality of study data are extremely important if named data are collected in order to facilitate follow up. These may include using stand-alone computer systems and passwords, and avoiding accidental access to study data by setting up appropriate security systems.

## **2.2 Optional objectives**

Each optional objective can be implemented at different levels, according to the resources available in each study centre. There are also choices within each level about the risk factors and diseases to be studied. Protocols for screening and testing for each disorder will be available in the manual of operations.

**Objective 2:** To establish the birth prevalence (on a community, geographical base wherever possible) of structural congenital anomalies detectable by clinical examination of new-borns, including stillbirths.

Level 0            Omit this objective.

---

<sup>1</sup> Separate epidemiological studies of such conditions may also be arranged with appropriate country specialists.



Level 1 Describe the birth population in terms of structurally normal and structurally abnormal stillborns and neonates. Record what abnormalities are found. (This may be the appropriate level in some studies based in primary health care in rural communities.)

Level 2 As level 1 plus immediate referral to a specialist in genetic diagnosis (usually a paediatrician) for investigation, diagnosis, counselling and any possible treatment of the abnormality. The specialist will keep a record of all children from the community identified through this initial screen, but will use an exclusion list (see appendix) when reporting cases for the study.

**Objective 3:** To establish the prevalence of risk factors for congenital disorders in mothers through blood testing (for example for haemoglobin disorders, G6PD deficiency, rubella and other maternal infections, folate and iodine levels).

Level 0 Omit this objective.

Level 1 Store maternal sera for future testing.

Level 2 Test the maternal samples for carrier status for some genetic disorders and potentially teratogenic disorders, such as haemoglobin disorders, rubella, cytomegalovirus (CMV), toxoplasmosis and other maternal infections, folate and iodine levels, G6PD deficiency and the hereditary anaemias.

**Objective 4:** To establish the birth prevalence (on a community, geographical base wherever possible) of haemoglobin disorders, G6PD deficiency and some metabolic disorders by analysis of Guthrie blood spot samples in new-borns, including stillbirths.

Level 0 Omit this objective.

Level 1 Establish a bank of Guthrie spots for later analysis.

Level 2 Collect Guthrie spots for analysis for disorders which may include haemoglobinopathies, G6PD deficiency and metabolic disorders.

Level 3 As for level 2, plus referral of possibly affected babies to a specialist for investigation, diagnosis, counselling and any possible treatment of the abnormality.

**Objective 5:** To establish the frequency of antenatally diagnosed congenital disorders in the study population.

Level 0 Omit this objective.

Level 1 Report all structural abnormalities, including chromosomal markers, detected by ultrasound after the first trimester.

Level 2 As level 1, plus reporting all chromosomal abnormalities, haemoglobin disorders and metabolic disorders detected by chorionic villus sampling (CVS) or amniocentesis. the indication for the fetal sampling procedure (e.g.

suspicious ultrasound findings, maternal serum screening results, both parents demonstrated carriers etc).

Level 3 As for level 2 plus follow up of all pregnancies to confirm the sensitivity and specificity of ultrasound screening.

**Objective 6:** To link the later outcome in the babies with parental demographic data, to establish the prevalence of genetic disorders which can only be diagnosed after the neonatal period.

Level 0 Omit this objective.

Level 1 Arrange for each child in the birth population cohort to be examined at a later interval (for example, when immunisations are done or on admission to nursery school) and to record any structural, genetic or developmental abnormalities found.

### 3. Study size

The target population of mothers and babies studied must be large enough to link social and health data on the parents with the outcome of the present pregnancy. Ideally, the study should focus on all women living within a defined geographical area, whether they have their baby at home or in an institution.

The minimum target population size is 15,000, but a population of up to 50,000 would provide more valuable figures. The size of the study population selected, and the duration of the study, will inevitably differ from one place to another, depending on local circumstances. Some small countries may aim for complete national data collection. Others may select a geographical area, such as a health region or district for study. As the study is population-rather than institution-based, the study team must try to cover as many pregnant women resident in the area as possible, including births at home and those in private and military hospitals which serve the population under study. Failure to include births outside large institutions will cause bias. In countries where almost all births occur in hospitals, a population-based study will also be institution-based. Countries where home births are common may have to use birth registration systems, local health offices, centres or clinics and traditional birth attendants to ascertain which babies are born at home.

### 4. Data collection

Core data will be captured by existing health workers involved in maternal and child health as soon after delivery as possible, as mothers pass through health care and birth registration systems. Data will be collected through a standardized interview with the mother and by standardized examination of each baby.

The health workers involved in the study will require careful training, and in view of staff turnover, regular training and education sessions will be needed. The content of the training should be defined. It is hoped that by using health professionals to record data, awareness of

the effect of congenital disorders on morbidity and mortality will be strengthened. Health professionals will also gain clinical skills by learning how to examine new-borns systematically.

When one of the primary workers suspects a congenital abnormality, the baby should also be examined and the findings recorded by an expert member of the research team.

Local study teams should decide whether the staff who collect the basic data should code information, or whether the data they collect will later be coded by the expert group.

A standardized user-friendly and flexible computer programme will be devised for protocol generation and data-entry in each country. Data-collection may be computer generated, and “personalised” for the institutions and countries participating.

Data collection is not necessarily limited to that on the standardized forms. Research teams may choose to modify the forms to include additional items of interest to themselves. They will be responsible for recording and analysing any additional data: only the standardized items will be included in the EMRO Mother and Baby Study.

#### **4.1 Collecting data on mothers**

The consent of a parent for all objectives of the study which are to be included should be obtained at the time of completing the first data collection form. Each participating mother will be given a unique identifying number.

A target population of at least 15,000 recently delivered women will be interviewed (where possible while in hospital or at a community health office, centre or clinic) to obtain the information on their demographic background and obstetric history shown on the appended **Mother’s data collection sheets**.

It is a priority to include previous stillbirths and deaths to each woman, in the collected data.

#### **4.2 Collecting blood from the mother**

If included in the study, blood samples will be collected from the mother, agreed haematological tests will be conducted, and serum separated, labelled and stored. Blood tests will be carried out according to the methods locally available and chosen by the research team. A discussion of selected methods is included in the manual of operations. It is a priority to ensure quality control.

#### **4.3 Collecting data on babies**

Each baby will be given a unique identifying number. This will be the mother’s number plus /A, or in the case of multiple births, /B, /C etc.

Whether the outcome of the current pregnancy is a live- or still-birth, or a neonatal death, the baby will be examined and the findings recorded using a standard check-list for examination of the new-born, on the appended **Baby data collection sheet 1 (screening examination)**.

If a congenital anomaly is suspected in a live-born baby the suspicion will be noted, and the baby will be examined by a specialist member of the study team, where available. The findings

and provisional diagnosis will be recorded on the appended **Baby data collection sheet 2 (live baby with congenital anomaly)**, using the check-list attached.

Special attention should be directed to ensuring that all babies in intensive care are included in the study.

#### **4.4 Collecting data on stillbirths and neonatal deaths**

It is a priority to examine *all* stillbirths and neonatal deaths in the target population.

Wherever possible, each baby that is born dead or dies will be examined by an expert and the observations recorded using **Baby data collection sheet 3 (stillbirth or neonatal death)**. Standard photographs and whole body X-rays may be taken, and added to the record. Reports (or copies) of intra-uterine, pre-mortem or post-mortem ultrasound examinations may be included.

An autopsy will not be feasible in most countries of the EMR but samples may be taken for relevant tests to help diagnosis and provide information on which to base future genetic counselling. These samples may only be taken after a parent has given consent. Samples taken may include:

- Skin biopsy taken within two hours of death for chromosomal analysis.
- Needle biopsy samples.
- Blood samples obtained by cardiac puncture.
- Blood samples from the umbilical cord.
- Placental samples.

If no diagnosis is made, a parent may be asked if such samples can be stored for testing in the future, in the event of further relevant diagnostic tests being discovered.

#### **4.5 Collecting a blood sample from the baby**

If included in the study, blood samples from live-born babies will be collected onto clearly marked Guthrie cards, and forwarded to the study centre or designated laboratory for selected investigations. Each Guthrie card will then be sealed into a plastic envelope, and all will be stored in metal boxes in a cool environment, for study later.

When this objective is included in the study, a special effort should be made to include a sample from each dead baby whenever possible: blood may be taken by cardiac puncture.

## 5. Coding and entry of data

All records will be forwarded to the study team. They will be checked, coded and entered on the database by staff of the study team. Any uncertainties or incompleteness in data collection will be corrected as soon as possible by liaison with the staff at the place of birth.

Initial coding of mother and infants will use ICD10 . Where possible, abnormalities found by the study will be coded by specialist doctors undertaking the diagnostic examination. In addition to basic ICD10 coding, they will use McKusick codes, as these are more detailed in recording congenital disorders than ICD10.

The status of the data will be reviewed at regular meetings of the study team.

## 6. Initiating the study

Within each country a **national or local steering group** will be convened to consider available country/local information on the health burden of congenital and genetic disorders, and to identify priority research areas. Topics considered should include those listed in the introductory document (Regional Consultation on Standardisation of Research Methods Related to Control of Hereditary Disorders), and others that are considered locally relevant.

The steering group will be multi-disciplinary. It may include a representative of the Ministry of Health, and specialists in e.g. epidemiology, statistics, paediatrics, genetics, haematology, obstetrics, maternal and child health and primary care, and laboratory specialists in e.g. biochemistry and cytogenetics. Consideration should also be given to including local health service professionals (such as midwives ) who will be involved in the day to day execution of proposed studies.

The initial task of the steering group is to write a **country report**. The country report should include existing country information, whether published or not, on all the topics listed in the introductory document (Regional Consultation on Standardisation of Research Methods Related to Control of Hereditary Disorders). It should review the local feasibility and indications for carrying out the Mother and Baby study in whole or in part. Topics to be considered include the following:

- Feasibility and desirability of including each study objective.
- Necessary target population, and the method and length of study necessary to achieve the desired numbers.
- Resources available within the country to assist the study.
- Feasibility of assistance to or from other countries within the Region with specific aspects (such as neonatal screening).
- The feasibility and desirability of developing the core study into a prospective longer-term cohort study.

More specific information required will include:

- Any methods of locating place of residence geographically - for example, post codes, province codes.
- Ethnic origins and religions that should be recorded in each country, their distribution in the population and any methods of coding used.
- Languages that should be recorded in each country and any methods of coding used.
- Existing data on place of birth (hospital, home etc), for both urban and rural populations.
- How long women stay in hospital after delivery (precise information in the form of a frequency-distribution).
- Existing methods of recording deaths (time limits for stillbirth, perinatal death, infant death etc).
- Existing status of prenatal diagnosis, and legal and religious conventions regarding prenatal diagnosis and termination of pregnancy.
- Feasibility of longer term follow-up of study mothers and babies. This must take account of the fact that babies "lost to follow-up" are likely to include babies who died from congenital or genetic disorders, or have other problems.

If a decision is made to undertake the EMRO Mother and Baby study, a **study team** will be selected to plan, implement and carry out the study. The study team will be small, and able to take executive action to set the study up and run it on a day to day basis. Each country study should be supported by a **small group with computer facilities** to collect, enter, verify and analyse the data.

In smaller countries or local studies, the steering group and study team may be the same, but in larger countries and multicentre studies a management team will be required at each participating centre. Data entry and analysis will usually be centralised at the country level.

## 7. Pilot studies

Standardised instruments such as the *data collection sheets*, the *manual of operations* and the *teaching package* should be piloted in one or a few countries of the Region, before being recommended for the study.

In each participating country the main Mother and Baby study should be preceded by a pilot study over a set period of time or of a set number of mothers interviewed - e.g. 500. The aim of the country pilot study is to identify and sort out problems in data collection, entry and interpretation.

Co-ordination and collaboration within the Region through regular study workshops will greatly assist the implementation of studies in different countries.

## **8. Draft data collection sheets for mother and baby**

The following data collection sheets are designed to show the type of data collection proposed. They are not necessarily intended for use in the study. When the required data is already collected in standard antenatal records, these may be photocopied. When existing antenatal records do not include all the required data, they may be modified for the study and photocopied. Alternatively, the appended forms may be used.

The draft protocol permits considerable flexibility. For example, items in italics in the following sheets apply only when a named follow-up study has been chosen, rather than an anonymous epidemiological study. Other optional items are indicated where they arise.

# MOTHER'S DATA COLLECTION SHEET 1: DEMOGRAPHIC DATA

## Identification

Country code (Computer generated)

Code/Name of Institution (Computer generated)

Medical record number

Serial number (Computer generated)

Mother's ID No: ..... (unique identifier, e.g social security number etc)

Mother's consent for epidemiological study (if needed) YES/NO

Mother's consent for named follow-up study (if needed) YES/NO

Mother Name: ...../...../.....

Mother's date of birth: dd/ mm/yy or age in years now ..... estimate / certain

Mother's address: Area

City/village

Province number or other geographic code

Street and house number

Telephone number

Address if different a year ago (area, city/village, street and house number)

Primary Health Care Unit attended in this pregnancy.....

Date and time of delivery of this baby dd/mm/yy at 00.00 (24 hour clock)



## Details obtained by interview

Date and time of interview: . dd/mm/yy at 00.00 (24 hour clock)

Father Name...../...../.....

Father's date of birth: dd/mm/yy: or age in years now..... estimate / certain: or age unknown

Mother's age at marriage to this husband (years) .....

Mother

Father

Mother-tongue (include unknown)

Years of formal education (include unknown)

Able to read - YES / ? / NO / UNKNOWN

(if any doubt ask mother to read a standard letter)

Occupation (include unknown)

Industry worked in (include unknown)

## MOTHER'S DATA COLLECTION SHEET 2: OBSTETRIC HISTORY

[illegible]

### *Additional comments*

# MOTHER'S DATA COLLECTION SHEET 3: PARENTAL CONSANGUINITY

*The health worker will address the following questions to the mother. Both questions I & II will be asked.*

**I. Is the father of your child related to you on your father's side?** Yes    No

If no, go to next section

If yes, is he:    your father's brother's son? Yes    No

your father's sister's son? Yes    No

If no, ask specifically about the relationship

**II. Is the father of your child related to you on your mother's side?** Yes    No

If no, go to the next section

If yes, is he:    your mother's brother's son? Yes    No

your mother's sister's son? Yes    No

If no, ask about specific relationship

The health worker will then ask whether the woman's parents are related, in the same way:

**I. Is your father related to your mother on her father's side?** Yes    No

If no, go to next section

If yes, is he:    her father's brother's son? Yes    No

her father's sister's son? Yes    No

If no, ask specifically about the relationship

**II. Is your father related to your mother on her mother's side?** Yes    No

If no, go to the next section

If yes, is he:    your mother's brother's son? Yes    No

your mother's sister's son? Yes    No

If no, ask about specific relationship

---

The health worker will then ask whether the woman was married before.	Yes	No
If yes, she will ask how the woman was related to her previous husband		
<b>I. Was your previous husband related to you on your father's side?</b>	Yes	No
If no, go to next section		
If yes, was he: your father's brother's son?	Yes	No
your father's sister's son?	Yes	No
If no, ask specifically about the relationship		
<b>II. Was your previous husband related to you on your mother's side?</b>	Yes	No
If no, go to the next section		
If yes, was he: your mother's brother's son?	Yes	No
your mother's sister's son?	Yes	No
If no, ask about specific relationship		

# MOTHER'S DATA COLLECTION SHEET 4: THIS PREGNANCY

Month of gestation when pregnancy was confirmed

Month of gestation when antenatal care started

1 2 3 4 5 6 7 8 9    gestation unknown    No care

If antenatal care given, who gave it ?

Traditional birth attendant,    health worker    doctor                      other                      ( please specify)

Mode of delivery (normal, vaginal breech, forceps or suction, caesarean)

Best estimate of gestational age of baby in weeks

## Maternal illness:

Diabetes    yes / no / unknown                      If yes: Insulin    dependent / Non-Insulin    dependent /  
Gestational

Epilepsy    yes / no / unknown                      If yes: was there drug treatment in pregnancy?    Yes / /  
no / unknown

If yes, specify.....

Other illnesses (see check list)    yes/no/unknown

If yes - specify.....

Maternal infections    yes/no/unknown

Maternal therapy    yes/no/unknown

Family history of genetic or handicapping disorder? (Check-list as for obstetric history)

yes/no unknown                      (if yes, draw family tree according to separate protocol)

Mother's blood group: ..... / unknown                      Isoimmunised    yes / no / unknown

Father's blood group: ..... / unknown

**Haemoglobin disorders    Known carrier?: diagnosis    Major disorder?: diagnosis**

Mother

Father

**Maternal cigarette smoking in this pregnancy**

Any cigarettes smoked in this pregnancy?    yes / no / unknown

If yes, estimate number of cigarettes smoked per day..... / day

Optional: **Maternal alcohol intake in pregnancy:** Occasional (1 drink/week) / regular drinker / unknown

**Social data:** Ethnic origin (check list, including unknown: country generated)

Religion    (check list, including unknown : country generated)

**Maternal blood sample sent to lab** yes / no / unknown / **permission refused**

**Signature of health worker who interviewed the mother**

.....

# BABY DATA COLLECTION SHEET 1: SCREENING EXAMINATION

Mother's Name: ...../...../..... Unknown

Baby serial No: = mother's serial no, with /1 (computer generated)

In case of multiple births, spare sheets are filled in with mother's number /2, /3 etc

Live birth / stillbirth / neonatal death (age at death in hours) .....

## PHYSICAL EXAMINATION\*

Date of examination dd/mm/yy

Date of birth of baby dd/mm/yy unknown

Gestational age... term/preterm Best estimate, weeks

Are there any obvious abnormalities on looking at the baby ?

If yes, please specify.....

Sex : Male / Female / Undetermined

Birth weight (kg): ..... / not weighed

Apgar score

Length: Crown-heel\* in cms ..... / not measured Optional - see protocol

Head circumference in cms: ..... / not measured

*(Appropriate cut off points for referral to specialist are needed)*

General condition of baby	good ??	sick
---------------------------	---------	------

Colour (pallor, cyanosis etc) and respiration	good ??	sick
---	---------	------

Activity (sucking, moving limbs, tonus, crying)	good ??	sick
---	---------	------

Jaundice      yes / no	Meconium passed	yes / no
------------------------	-----------------	----------

**Baby front: abnormality?    Yes    No      Specialist's comments and diagnosis**

Scalp defects

Ears    deformity

pre-auricular tags or pits

Eye abnormalities

Nose abnormalities

Cleft lip/ cleft palate/ both                      Right/ left/ both/ midline

Neck: sinuses, abnormal swellings

Chest: deformity

Abdomen: marked abnormality

Anus patent/ not patent

Genitalia:      Male penis -                      normal size                      hypospadias

                    Testes descended                      left / right

Genitalia:      Female                      normal / abnormal

Genitalia:      Ambiguous

**Baby back: Abnormality?**                      Yes    No                      **Specialist's comments and diagnosis**

Skull shape    size    defects

Spine defects

Sacral abnormality    sinus

                                    hair tuft

### **Extremities**

Abnormality of arm    R

                                    L

Abnormality of hand    R

                                    L

Abnormality of leg    R

                                    L



L

**Joints: restriction of elbow(s)**

## Skin

hyper or hypo pigmentation

abnormality of skin texture

**oedema :-**

## Tone

hypotonia     /hypertonia

Moro reflex	normal / abnormal
-------------	-------------------

**Paralysis of any limbs**

Additional comments (free field)

Guthrie spot taken    yes / no / permission refused

Baby referred for specialist examination yes / no

If referred, name of person to whom baby referred

**Signature of health worker who examined baby.....**

## **BABY DATA COLLECTION SHEET 2: SPECIALIST EXAMINATION**

Mother's Name:..... Baby ID No:.....

Date of Birth: yy/mm/dd

### **LIVE BABY WITH CONGENITAL ABNORMALITY**

Name of examining doctor: .....

Ultrasound scan conducted during pregnancy?      YES / NO      seen YES / NO

Photograph      YES / NO / permission refused

X rays of relevant parts      YES / NO

Ultrasound scan      YES / NO

Screen for CMV, rubella and toxoplasmosis taken      YES / NO

Attach report of ultrasound examinations (prenatal and post-natal) and X rays, and pictures where possible

**Provisional diagnosis**

**Signature of specialist who examined baby** .....

---

### **STILLBIRTH OR NEONATAL DEATH**

Consent given for examination      YES / NO / permission refused

Name of examining doctor: .....

Ultrasound scan conducted during pregnancy:      YES / NO.      seen YES / NO

Photograph of dead baby. YES / NO / permission refused

X rays : whole body YES / NO / permission refused

Autopsy YES / NO/ permission refused

Full YES / NO/ permission refused

Limited YES / NO/ permission refused

Screen for CMV, rubella and toxoplasmosis taken YES / NO / permission refused

Attach report of autopsy examination, ultrasound , pictures and X rays, where possible

**Provisional diagnosis**

**Signature of specialist who examined baby .....**



## **Attachment II**

### **WHO Initiative on the Prevention and Control of Congenital and Genetic Disorders in Developing Countries\***

#### **Base-line epidemiological study *Draft manual of operations***

#### **Table of contents**

<b>Instructions for completing the forms.....</b>	<b>1</b>
<b>Mother's data collection sheet 1.....</b>	<b>2</b>
<b>Mother's data collection sheet 2: Obstetric history.....</b>	<b>4</b>
<b>Mother's data collection sheet 3: Parental consanguinity.....</b>	<b>4</b>
<b>Mother's data collection sheet 4: This pregnancy.....</b>	<b>4</b>
<b>Baby data collection sheet 1: Screening examination.....</b>	<b>6</b>
<b>Baby data collection sheet 2: Specialist examination.....</b>	<b>7</b>
<b>Appendix.....</b>	<b>8</b>

---

\* The first draft of this manual was developed by a Working Group convened at the Eastern Mediterranean Regional Office of WHO in November 1995 and elaborated further at the Cairo meeting of December 1999.



# INSTRUCTIONS FOR COMPLETING THE FORMS

Standard WHO data forms will be provided on diskette to country teams, and forms will be customised and printed locally. (May need to be in local language, in view of personnel collecting the data?)

The questionnaire should be administered to the mother in privacy by a trained attendant, at a time when she is rested and at leisure.

## Selection of participants

All women delivering in the selected institution or geographical area will be invited to join the study. If this is not possible, participants must be selected in a way that ensures they form a random sample, e.g. those delivering on certain days of the week.

## Consent

All participants must give consent to join the study. If consent is refused the mother's wish must be respected. (But what if a mother who refuses consent has a malformed baby or stillbirth? Probably pregnancy outcome should be recorded in any case?)

## Identifiers

- *Epidemiological study:* Country code, institution code (when the study is hospital based) and mother's serial number are the necessary identifiers.  
When the study is community-based, identifiers should include postcode or equivalent.
- *Follow-up study:* If a follow-up study is selected, identifiers must include exact name and address of the mother, and any other details necessary to ensure follow-up of the baby. A key element in ensuring effective follow-up in other long-term studies (e.g. the UK birth cohort studies) has been to send the parents / child a birthday card every year, with a request to reply, and reminder to report any change of address. (This incidentally provides an opportunity to test mothers' reading ability when there is any doubt, by asking the mother to read an example of a follow-up letter.)
- *Use of existing hospital notes:* Study workers may take data from existing notes (this may speed parts of the questionnaire up), but should check the data with the mother in the course of the interview. Use of the notes will allow entry of data such as mother's Rh and other blood groups, isoimmunisation etc.

# MOTHER'S DATA COLLECTION SHEET 1

## Country code

- The official WHO country code will be printed on forms produced locally.

## Institution code (or name)

- This should appear on customised country forms printed locally.

## Serial numbers

- Each mother's computer-generated serial number will be unique in each country.
- Each mother's form will have 1 correspondingly-numbered baby's form attached.
- In case of multiple births a new un-numbered baby form must be produced, and numbered by the interviewer (see below for coding of baby forms).

## Mother's ID number

In many countries adults have a unique social security number that allows them to be identified reliably. For follow-up studies such an identifier should be recorded.

## Consent

- This could be quite difficult, as many mothers may feel unable to give consent unless they have first discussed it with their husband.
- For an epidemiological study, some participants favoured simply informing the mother that the study is taking place. If consent is refused, should mother's form finish here, or should outcome of this pregnancy be reported (to ensure extent of bias if any)?
- Parents' consent and information for the parents will definitely be needed for a follow-up study. Experience will be needed.

## Parents' names

Mother's and father's names are always recorded on the data collection sheets. They are entered in the computer only for a named study.

## Mother's date of birth

Day/month/year e.g. 01 01 66. This will not always be known. In this case an approximation should be obtained (may be based on year of marriage in some cases).

## Address

- Will be entered on form, but not on computer (except for a named study).
- Discuss availability of post-codes or similar, in tracing families for follow-up studies.



- Telephone number will not be recorded, except for a follow-up study.

### **Primary health care unit attended in this pregnancy**

Necessary for a follow-up study.

### **Date and time of this baby's birth. Day, month, year (e.g. 01 08 96)**

- Time of birth. 24 hour clock. Hour, minutes. e.g. 08 50. or 23 10.
- It is essential to enter time, for interpretation of Guthrie results.

### **Date and time of interview (record as above)**

### **Age at marriage to this husband: years**

- May be the most reliable indicator of maternal age in some cases. Though divorce is uncommon, widowhood is not.
- A check-list is needed for each country. It must include "none" and "unknown".
- Harmonisation may be achieved at first WHO workshop.

### **Years of formal education.**

- Record separately for mother and father.
- Code 0 - however many years of education.

### **Able to read?**

It may be advisable to check the mother's literacy, especially if a long-term follow-up study is contemplated. This may be done by asking her to check a standard letter of the kind that may be sent to her to maintain contact.

### **Occupation**

- Record separately for mother and father.
- Actual occupation be entered, and coded by the team. Note: if occupation entered, e.g. "army" is not enough: an indication of rank is required. (Or is it, in view of information on education?) If the mother does not work outside the home, "housewife" should be entered.

### **Industry worked in (for risk of exposure to toxic chemicals)**

## **MOTHER'S DATA COLLECTION SHEET 2: OBSTETRIC HISTORY**

We considered asking about miscarriage, whether induced or not, but excluded it because we did not expect to obtain reliable data. However, in some circumstances the replies might be reliable. In this situation the question might be included as a local sub-study.

If there has been more than one partner, draw a line across the chart at the appropriate point and indicate (Partner 1, partner 2 etc).

Any abnormality (in previous pregnancy) - specify - CHECK-LIST: use the following categories:

- physical abnormality
- mental handicap
- blindness
- deafness
- inherited disease (thalassaemia, sickle cell haemophilia, etc) developmental delay
- other

Enter precise diagnosis when the mother knows one.

## **MOTHER'S DATA COLLECTION SHEET 3: PARENTAL CONSANGUINITY**

This still needs some work, to help researchers record relationships other than 1st cousins correctly. A list of local terms in the local language is needed.

## **MOTHER'S DATA COLLECTION SHEET 4: THIS PREGNANCY**

### **Antenatal care, and mode of delivery**

Self-explanatory

### **Maternal illness**

Maternal illness. Other illness? - CHECK LIST:

- Pre-eclampsia / eclampsia
- Bleeding needing transfusion
- Obstructed labour
- Prolonged labour (> how many hours?)

## **Maternal infections**

We considered this at length and decided no useful or reliable list could be made. Any information from mother or notes should be recorded.

## **Maternal therapy**

Though we also doubted the value of recording this, it was concluded that any unusual drug treatment should be recorded.

## **Parents' blood groups**

This, and details of iso-immunisation and father's Rh group must be taken from (or at least checked in) the obstetric notes. If minor groups are tested for, they may be included.

## **Family history of genetic or handicapping disorder?**

## **Maternal and paternal haemoglobinopathy status**

Complete from notes, and also ask woman

*There follow questions that may be delicate. These are asked last and, in some countries, it may be inappropriate to ask them.*

## **Maternal cigarette smoking in pregnancy**

In estimated number of cigarettes smoked per day. May be calculated from number of packets per week etc.

## **Alcohol consumption during pregnancy**

Optional

## **Ethnic group**

Ethnic group must be entered separately for mother and father.

A check-list is needed, generated by each country team. It must include "unknown". Harmonisation of coding may be achieved at first WHO workshop.

## **Religion**

- This is an optional question, as it may be delicate in some countries.
- Religion must be entered separately for mother and father.

## **Maternal blood sample sent to laboratory**

Workers must be trained to fill this in honestly!

# BABY DATA COLLECTION SHEET 1:

## SCREENING EXAMINATION

All live and still born babies in the study population should have a standard physical examination. The protocol leaves room to expand the physical examination, depending on the expertise of the examiner. **Note: For babies in intensive care, the examination must be done by the doctor.**

The examiner must have:

- a good torch,
- a proper tape-measure,
- a good tongue depressor.

### Length

(Optional, as not all participants were convinced of its reliability). Measured either using a stadiometer, or as follows:

- 2 people are needed. One lies the baby on a surface with its head held against an upright headrest, and extends the legs. The second uses a tape-measure to measure the baby's length along the surface (not on the baby).
- This requires a teaching package or video teaching method.

### Physical examination

All rows in this part of the questionnaire should be completed. (**Note:** congenital dislocation of the hip is not included in the physical examination.). **General impressions** are recorded first.

### Detailed examination

- The (non-specialist) conducting the first examination should tick in "yes" or "no" for each item. When an abnormality is suspected the baby should be examined by a specialist, who makes fuller comments in the final column.
- Minor peculiarities should not be recorded. The following is an indication of the order of abnormalities to be reported.
- Ear deformity (not rotation or simplification of pattern).
- Eye abnormalities (absence of eyeball, microphthalmia, irregularity of pupil (all eyes must be examined with a torch)).
- Nose abnormality (e.g. bifid nose, absent nares).
- Cleft palate (look with tongue-depressor and torch).
- Abdomen (Umbilical hernia, omphalocele, gastroschisis, bladder extrophy).
- Abnormality of hand polydactyly:
  - Syndactyly.

- absence of digits.
- absence of nails.
- Skin: hyper or hypo pigmentation - 1 cm diameter or more.
  - abnormality of skin texture: e.g. epidermolysis bullosa, or collodion baby.

Exclusions are listed in the Annex. **Note.** In a community-based study, deceased babies will not reach an expert for examination. Therefore, participating health workers should carry a camera if possible.

## **BABY DATA COLLECTION SHEET 2: SPECIALIST EXAMINATION**

Should be completed in all cases with an abnormality (part 1 of the form), and for all dead babies (part 2 of the form).

**Live baby:** a note is made of examinations, including ultrasound during pregnancy. Reports are attached when possible.

**Stillbirth or neonatal death.**

**Photographs of (dead) baby:**

- whole body (front and back),
- AP and lateral views of head and neck
- close-up of specific abnormalities

Report of post-mortem examination, photograph, ultrasound and x-ray pictures should be attached to the reporting form.

# APPENDIX

## Exclusions of minor anomalies and conditions not considered to be malformations

These anomalies will be reported to specialists for exclusion of syndromes, but will not be reported by the specialist to the main study:

### **Minor anomalies<sup>1</sup>**

Spina bifida occulta - uncomplicated

Stenosis or stricture of lachrymal duct

Anomalies of ear - minor or unspecified

Anomalies of nose - minor or unspecified

Deformity of face - minor or unspecified

Anomalies of nipple - minor, for example accessory nipple

Congenital umbilical hernia, inguinal hernia, paraumbilical hernia

Undescended testicle

Ectopic testicle

Congenital hydrocoele or hydrocoele of testis

Glandular hypospadias - if meatus lies before coronary sulcus

abnormal palmar crease

Skin anomaly - surface less than 4cm<sup>2</sup> : skin tag, naevus, angioma, haemangioma; glomus tumour, lymphangioma, birthmark

Clicking hip - unless confirmed as dislocatable

Clubfoot of positional origin

Anomalies of toes - minor or unspecified such as hallux valgus, hallux varus or 'orteuil en marteau'

Cardiac murmur - functional or unspecified

Anomaly of umbilical artery - absence or hypoplasia, single umbilical artery

---

<sup>1</sup> (Source: EUROCAT)

## **Conditions not considered to be malformations<sup>2</sup>**

Abdominal distension

Abnormality - blood group

Acidaemia - organic

Atelectasis

Australia antigen

Bruising splenic region

Cephalohaematoma

Cerebral palsy

Cyst on cord

Deafness, congenital

Dystocia, shoulder

Haematoma

Haematoma, umbilical cord

Hyaline membrane disease

Hyperventilation

Intra-uterine growth retardation

Meconium liquor

Meconium peritonitis

Necrotising enterocolitis

Palsy of facial nerve - traumatic

Perforated gut

Phimosis

Pleural effusions

Polycythaemia

Respiratory distress syndrome

Ruptured bowel

Sclerema

---

<sup>2</sup> (Adapted from EUROCAT)

Two teeth or congenital teeth

Umbilical granuloma

Weak femoral pulses