

Global registry and database on craniofacial anomalies

Report of a WHO Registry Meeting on Craniofacial Anomalies

Bauru, Brazil, 4-6 December 2001

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Acronyms and abbreviations

AD	autosomal dominant
ASEAN	Association of South-East Asian Nations
BDMP	Birth Defects Monitoring Programme
BMDP	Biomedical [Dixon] Programme (statistical software package)
BPA	British Paediatric Association
CA	congenital anomalies or congenital abnormalities
CAPP	WHO Oral Health Country/Area Profile Programme
CDC	Centers for Disease Control and Prevention (United States of America)
CFA	craniofacial anomalies
CI	confidence interval
CL	cleft lip
CL/P	cleft lip with or without cleft palate
CLP	cleft lip and palate
CM	congenital malformations
CNS	central nervous system
CP	cleft palate without cleft lip
CVS	chorionic villus sampling
DNA	deoxyribonucleic acid
EBM	evidence-based medicine
EBS	evidence-based system
ECLAMC	Latin American Collaborative Study of Congenital Malformations
EEC	ectrodactyly-ectodermal dysplasia-cleft lip and palate
ENT	ear, nose and throat
ESF	European Science Foundation
EUROCAT	Surveillance of Congenital Anomalies in Europe
FAS	fetal alcohol syndrome

GEI	gene/environment interaction
HIV	human immunodeficiency virus
HLA	major histocompatibility complex
HRAC	Hospital of Craniofacial Anomalies of Baurú
ICBD	International Centre for Birth Defects
ICBDMS	International Clearinghouse for Birth Defects Monitoring Systems
ICD	International Classification of Diseases (WHO)
ICD-10	International Classification of Diseases (10th edition)
ICOCG	International Consortium for Oral Clefts Genetics
IDCFA	International Database of Cranio-Facial Anomalies
IFTS	International Federation of Teratology Societies
ISCN	International System for Human Cytogenetic Nomenclature (1995)
MACDP	Atlanta Congenital Defects Program
MBRN	Medical Birth Registry of Norway
MCA	multiple congenital abnormalities
MCM	multiple congenital malformations
MIM	Mendelian inheritance in man
MTHFR	methylenetetrahydrofolate reductase
NBDPN	National Birth Defects Prevention Network
NIH	National Institutes of Health (USA)
NGO	nongovernmental organization
NTT	Nusa Tenggara Timur (province)
OC	oral clefts; orofacial clefting
OFD	oral-facial-digital (Mohr)
PGH	Philippine General Hospital
SAS	Statistical Analysis System (software package)
SD	standard deviation
SPlus	StataPlus Statistical Programme (software package)
SPSS	Statistical Programme for Social Sciences (software package)
SR	sex ratio
TDT	transmission disequilibrium test
USP	University of São Paulo
WHO	World Health Organization
WHO-HGN	Human Genetics Programme of the World Health Organization

Executive summary

Background: With financial support from the United States National Institute of Dental and Craniofacial Research, the Human Genetics Programme of the World Health Organization (WHO) launched a five-year project in 2000 to advance international research on craniofacial anomalies (CFA). The first meeting, held in November 2000, focused on four selected areas of research (treatment of CFA, gene/environment interaction (GEI), genetics, and prevention); the second, held in May 2001, considered the prevention of CFA¹, and the third, held in December 2001, focused on the establishment of a global registry of CFA and is summarized in this report.

Aims and objectives: The idea of a global registry was among the original objectives of the scientists who sought to undertake international collaborative research in the field of CFA. The underlying concept was to create a disease-specific master database that would improve the current level of knowledge available on birth prevalence of CFA and the associated international, geographical, ethnic and cultural variations.

They agreed that, to begin with, the creation of such a database would only be possible for a specific disease entity; the first target being the commonest human craniofacial congenital condition, orofacial clefting (OC). The major challenge in this context was, and still remains, the task of eliciting appropriate information in parts of the world where not only is the information unavailable, but there is no infrastructure for ascertainment.

Consensus meeting: To appreciate the extent of this challenge and to seek solutions, a consensus meeting was held in Baurú, Brazil from 4-6 December 2001, with the participation of experts with relevant

¹ *Global strategies to reduce the health-care burden of craniofacial anomalies: Report of WHO meetings on International Collaborative Research on Craniofacial Anomalies, Geneva Switzerland, 5-8 November 2000; Park City, Utah, USA, 24-26 May 2001. Geneva, World Health Organization, 2002.*

Participants agreed on a common core set of data that should be available for all examined births

...

experience in a variety of disciplinary backgrounds. They provided a wide range of opinions that reflected their diverse cultural, geographical, political, social and economic backgrounds. Their discussions focused on the feasibility and potential problems and pitfalls relative to the registration of birth defects in general, and CFA in particular. They agreed on a common core set of information that should be available for all examined births. They also agreed that, while the core information would include a minimum set of essential data, other desirable information should be collected where possible. This could form another category of optional data which would be valuable for future research – for example, it would be highly desirable to have denominator information for births but, in some regions or countries, this would not be possible.

Birth prevalence rate: Current knowledge on the incidence and the birth prevalence of CFA around the world reveals not only the apparent variation but also significant differences in methods of data collection and birth defect registration. There are even differences in the basic ground rules for what data should be included in the registries and there is no international consensus on its classification. This is mainly because of interregistry or interregional differences in the application of the World Health Organization's *International Classification of Diseases* (ICD) Birth Defects Registration System that can be modified to meet different requirements in recording the appropriate details for specific or specialized anomalies.

Classification: Traditionally, “birth prevalence rate” has been the phrase that registries prefer for defects in liveborn and stillborn infants, but this is becoming increasingly inappropriate as terminated pregnancies are usually not included. Before material from different registries can be collected in a consistent manner, working definitions that transcend different types of categorization – such as clinical, developmental, etiologic or pathogenetic – are required; also, associated abnormalities and detailed definitions of inclusions and exclusions need to be recorded.

Comparability and compatibility of existing registries: One of the major challenges in relation to CFA registration is to identify all organizations that are already in the process of collecting information on CFA, many of which are using long-established, tried and tested procedures. Having identified these organizations, a process of comparison and assessment of compatibility will be required; then, on the basis of these findings, the conditions to facilitate the building of a worldwide collaborative network will have to be devised. Such a network should be capable of providing all the elements outlined in Chapter 7.

Common core research protocols: In those parts of the world that have already achieved reliable birth defect surveillance systems, some are developing protocols and projects to underpin research into the etiology

and pathogenesis of CFA. One such project presented at the meeting – the Common Core Protocols Project, established through the auspices of the European Science Foundation (ESF) – aims to achieve consensus on the minimum data sets required to enable research on GEI in OC. This includes recommendations for core information on case ascertainment, clinical assessment and classification, nutritional and lifestyle factors, maternal medical history and family history. Other presentations at the meeting covered protocols to obtain core information for genetic and biochemical analyses, and guidelines on bioethical issues (Mitchell et al., 2002).

WHO craniofacial anomalies web site (www.who.int/genomics): The feasibility of creating and sustaining a global database for CFA was discussed in terms of the potential and pitfalls surrounding systems based on information technology, bioinformatic technology, and the ability to obtain the appropriate information from communities throughout the world for input and dissemination via the Internet. Existing systems that aspire to similar aims and objectives were discussed and it was agreed that, in addition to a basic registry facility, it would be desirable to have a directory of resources that would include wide-ranging information on CFA, relevant to the general public, researchers, governmental and non-governmental organizations (NGOs), funding bodies and charities.

1

The development of registries to support birth defect research

Birth defects – congenital anomalies (CA) – are a major cause of infant mortality and childhood morbidity, affecting 2-3% of all babies. CA are also responsible for large numbers of embryonic and fetal deaths. The appropriate treatment of liveborn infants with significant birth defects makes heavy demands on health care resources. The epidemiological approach to birth defects has been the backbone of research into their causes. Hypotheses about possible causative agents may arise from many different sources – from the observations of astute physicians, from experimental animal teratology, from epidemiological studies themselves – but epidemiological techniques are usually necessary to test these hypotheses.

1.1 Type of registry

Whenever a system for the registration of birth defects is to be established (WHO, 1998, 2003), a number of decisions has to be made. These will be influenced by the purposes for which the registry is being established, the resources available and the practicability of the scheme in relation to geographical, administrative, cultural and other relevant factors. Among the most important decisions are the following:

- **Will the registry be population- or hospital-based?** A population-based registry records data relating to all births² to mothers resident within a defined area, irrespective of where the birth takes place. A hospital-based registry – based in one or many hospitals – records defects in babies born, irrespective of where the mother lives. Birth prevalence rates derived from hospital-based data are more liable to bias than are population-based rates.

² “Births” include live births and stillbirths and, where appropriate, pregnancies terminated because of prenatally diagnosed birth defects.

- **What sources of ascertainment will be used?** The more sources of information that can be used, the larger the proportion of cases that will be recorded. The basic source of information is usually the birth record, but this is often incomplete, particularly for congenital heart defects. Additional sources of information include hospital admissions, neonatal surgery records, attendance at special clinics (e.g., paediatric, cardiology) or child health clinics, postmortem reports and school health records.
- **Will all defects be recorded or only a selected list?** It is usual to exclude a number of minor anomalies, largely because of the difficulty of distinguishing between minor anomalies and normal variants, and because of the variability in the reporting of such “defects”. With these minor exceptions, it is desirable to record all defects. A monitoring programme that excludes any major defect runs the risk that a new teratogen may cause a defect which is not being recorded.
- **Will stillbirths be included?** If the objectives of the registry include the highest possible level of ascertainment, it is highly desirable that stillbirths be included, preferably with a postmortem report from a paediatric or perinatal pathologist.
- **Will termination of pregnancy following prenatal diagnosis be included?** As an increasing number and variety of congenital anomalies are being dealt with by terminating the pregnancy (where the law allows it and where the facilities exist), it becomes increasingly important that these defects should be included. For example, in many centres the pregnancies are being terminated for more than 90% of the cases of anencephaly and more than 50% of those with spina bifida and Down syndrome. By contrast, it is virtually impossible to collect information routinely on defects in spontaneously aborted fetuses; these are normally, by convention, excluded from registration.
- **For how long after birth will data be collected?** For obvious external defects ascertainment should be virtually complete at birth although, in practice, recognition is not always translated into notification. For some internal defects, notably congenital heart disease and anomalies of the genito-urinary tracts, diagnosis at birth is often seriously incomplete. A one-year follow-up is a common and useful compromise.
- **Will any control group of healthy babies be recorded to allow for comparison of demographic and other factors between the parents of healthy infants and those with birth defects?** The value of this is debatable. When the need arises for a case-control study of

a possible teratogenic risk factor, it is often the case that the variable to be studied has not been included in the predetermined list of factors to be recorded.

For the purposes of each individual scheme, decisions on these and other issues must be made to suit the circumstances and purposes. As long as the local rules and definitions are agreed upon, known and adhered to, useful comparisons can be made between one time period and another. However, if comparisons are to be made between one registry and another, or between one country and another, the greatest care must be taken to ensure that like is being compared with like.

Prevalence rates
vary from month to
month and from
year to year ...

Differences in birth defect prevalence between places and over time are inevitably affected by the time scale and extent of the geographical area examined. If a small area is studied, the number of cases of individual defects will be small. Significant time trends, whether increases or decreases, will be rare. If a large area is studied, case numbers will be higher and significant time trends will be easier to detect. However, it then becomes necessary to determine whether the trend is affecting the whole area or only parts of the area, whereupon the problem of small numbers arises again. However, the study of small areas increases the chance of identifying associations with specific environmental risk factors.

Just as studies of small areas have limitations, it is unlikely that significant time trends will be detectable from observations limited to a short period of time. In both cases, the denominator (the total number of births) is small. The longer the period over which baseline observations are made, the more confidence can be placed in the significance of changes in prevalence. However, comparing later rates with previous rates is not without risk. A careful analysis of previous rates is necessary to be sure that no clusters or trends were already present. It is important to note that ascertainment techniques change over time.

As most birth defects appear to be random events, prevalence rates vary from month to month and from year to year. To establish reasonably stable baseline rates, registries covering relatively small numbers of births (e.g., fewer than 20 000 per year) may need a 10-year baseline; large registries (e.g., more than 100 000 annual births) may need 5 years. In the first year of operation of any new registry, when lines of communication are being established, ascertainment is usually less complete than in subsequent years.

1.2 Birth-defect surveillance and support of research using registries

Prevalence information is a basis for comparison and collaboration ...

As the main purpose of most registries is to provide information on the prevalence of birth defects, collection of good prevalence data is likely to be expensive and difficult. Depending on logistic opportunities, registries range from those with (assumed) complete coverage of all births of a defined population to hospital-based registries that cover populations that are more vaguely defined. When comparing prevalence from such different registries it is important to acknowledge differences – both in the ways birth defects are diagnosed and reported, as well as in the reliability of numerators of prevalence estimates.

The traditional paradigm of prevalence data surveillance has been that detection of a particularly high prevalence in one particular population, or a sudden increase in prevalence over time, could help identify possible environmental causes (Lie et al., 1991). Prevalence information therefore serves as a basis for comparison and collaboration. Examples of such collaborations are the International Clearinghouse for Birth Defect Monitoring Systems (ICBDMS) and the Surveillance of Congenital Anomalies in Europe (EUROCAT). This approach to environmental surveillance, however, has significant statistical problems and may only detect effects of common environmental factors that are either very unevenly distributed geographically or are introduced suddenly.

BOX 1

Traditional paradigm of birth defect registration and surveillance

- Careful collection of cases in a defined population makes it possible to detect changes in prevalence.
- Once a change in prevalence is detected, its source may be identified through supplementary studies.
- Synchronized surveillance across nations increases the capacity to detect new teratogens.

BOX 2

The historic record of surveillance

- General surveillance gives limited results.
- It is extremely difficult and expensive to operate a reliable registration system.
- Surveillance has a relatively low capacity to detect effects of risk factors (drugs).
- Most birth defect registries must justify their existence by also using data for other (research) purposes.
- Environmental teratogens and clusters are still issues of concern.

There are limited results from general surveillance through registries, although registries played a role in the detection of the two teratogens, thalidomide and valproic acid. A shift in public concern from teratogenic effect of drugs to teratogenic effects of other environmental and occupational exposures still motivates the awareness represented by birth defect registries.

BOX 3

Types of registries used for prevalence estimation

- Population-based birth registries with identification of cases.
- Case registries with good estimates of numerators (number of births in population).
- Case registries with vague estimates of population size.

The Medical Birth Registry of Norway (MBRN) is a population-based registry that covers all births in Norway and has moderately good estimates of birth-prevalence of several birth defects (Lie et al., 1994).

BOX 4

To enrich a registry with exposure information on cases and controls

- Target specific types of exposure (medication, smoking, vitamins, alcohol).
- Collect random controls from a defined population in population-based registries, if possible.
- Consider collecting matched controls (hospital-based) from case-based registries.
- Be aware that it costs more to collect good controls than to collect cases.

An alternative to making environmental surveillance conditional on good prevalence data could be to collect information directly on a set of candidate exposures. Hypothetically, the collection of arbitrary cases with

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matched controls that have information on key exposures would shortcut the expensive first step of collection of prevalence data. It would also make it possible to run studies of the effects of several exposures once sufficient amounts of data are collected. To the degree that candidate exposures are identified and may be studied in matched case-control studies, this appears to be an attractive alternative to collection of prevalence data, particularly in populations where prevalence data are hard to collect. However, there are inherent problems with such matched case-control studies. Problems with the quality of the controls, as well as recall bias, may be serious enough to make it difficult to defend a pure case-control approach to surveillance of environmental exposures. Regardless of whether prevalence data are available or not, pooling of case-control data with cohort data on exposures in meta-analyses may serve as another basis for collaboration and comparison (Wacholder et al, 1992a-c).

During a period in the 1990s, the MBRN collected drug exposure information on birth defect cases and matched controls. This was done as part of a collaborative project called “MADRE”, coordinated by ICBDMs. The collection targeted information on medications noted on antenatal records. Such prospective information should be free of recall bias. However, the data appeared to be incomplete and had limited value for most medications. The importance of having information available on key exposures (medication, smoking, intake of alcohol and vitamins) motivated MBRN to redesign the registry and, since 1999, they have collected this information on all births.

BOX 5

Limitations of matching versus random controls in case-control studies

- Exposures that are correlated with matching criteria cannot be studied (geographical environmental exposures, time etc. are difficult to estimate).
- Matched controls do not represent the population (cannot estimate exposure prevalence, attributable risks, gene frequencies, Hardy-Weinberg equilibrium, etc).
- Each case-group need separate controls.
- Matching requires special statistical techniques.

The MBRN has also served as a base for a case-control study of CLP, the cases not being recruited from the registry, but from treatment centres in Norway. For the collection of controls, however, the registry was instrumental. Choosing candidate controls by random selection from the whole population ensured that the controls represented the same population as the cases. There was, however, no matching involved so it was strictly a case-cohort design.

BOX 6**Studies of genes, exposures and GEI**

- Case-parent triads may be more informative and even easier to collect than (matched) case-control data.
- (Matched) case-control data will enable estimates of the main effects of the exposures.

There are many variations in the data codes of different registries...

To date, discussions have addressed the possible detection of environmental exposures. Despite their limitations, case-control studies may yet be a supplement to prevalence registries. In some situations where prevalence data are extremely hard to get, case-control data may still serve some surveillance purposes. If the aim is to study genes or GEI, however, traditional case-control data may be less attractive than data and biological samples collected only from the cases and their biological parents (Weinberg et al., 1998; Wilcox et al., 1998). Comparison of such data from different sources should be relatively unproblematic.

1.3 Definitions, classifications and coding of birth defects and craniofacial anomalies

For the purpose of handling and exchanging data, it is customary to translate words into codes. Here again, although most birth defect registries use codes based on the WHO *International Classification of Diseases* (ICD), there are many variations, and some registries use their own codes in preference to those in the ICD. The ICD has to deal with the entire scope of human diseases so it is not sufficiently detailed for many specialized purposes; extensions of its codes have therefore been developed by some organizations. Among the best known are:

- the British Paediatric Association (BPA) extension, which covers all medical conditions of childhood,
- the US Centers for Disease Control and Prevention (CDC) extension of the birth defects section, and
- the extension, for birth defects only, devised by EUROCAT.

At the time of writing this report, the most recent versions of the ICD are the 10th and 11th editions (ICD-10 and ICD-11). In addition to problems with the terminology of birth defects, there are also some difficulties with the epidemiological terminology. After long years of debate, the preferred term to describe the frequency of occurrence of birth defects is “prevalence” rather than “incidence”. Traditionally, defects in liveborn and stillborn infants have been reported in terms of birth prevalence rates,

There are
to date
no internationally
accepted terms
for defining
birth defects ...

usually per 10 000 related births. This remains appropriate for defects unaffected by prenatal diagnosis and terminated pregnancies. However, as these techniques are applied to an ever-increasing range of defects in many countries, the term “birth prevalence rate” becomes increasingly inappropriate because terminated pregnancies are not births in the usual sense. By the same token, the term “fetal defect” may be preferable to “birth defect” in these cases. For defects subject to prenatal diagnosis and termination of pregnancy, the term “prevalence” may be sufficient. “Total prevalence” has been suggested, but logically this should include defects in spontaneously aborted fetuses and embryos.

The increasing practice of terminating pregnancies makes it necessary to consider the appropriate denominator to use in the calculation of rates. The traditional denominator is the total number of live births and stillbirths. If significant numbers of fetuses – most of which would have become either live births or stillbirths – are being treated by terminating the pregnancy, an addition to the denominator seems appropriate. Logically, this should be the total number of pregnancies terminated – for whatever reason – but, because this figure is not always easy to obtain, many registries add the number of pregnancies terminated because of fetal defects to the total live births and stillbirths. As technical advances now allow prenatal diagnosis and termination of pregnancy earlier than in the past, the possibility arises that some of these fetuses would have aborted spontaneously. This could result in an apparent (but not real) increase in prevalence rates. Very early termination of pregnancy also adds to the difficulties of “postnatal” confirmation of prenatally diagnosed defects.

These problems are not likely to make a profound difference to reported rates of congenital anomalies. They are simply matters to be borne in mind when making comparisons between reported rates from different registries.

1.3.1 Terminology

It is unfortunate that there are to date no internationally accepted terms for defining birth defects. Attempts have been made to give specific and restricted meanings to such words as *association*, *deformation*, *malformation*, *sequence*, *syndrome*, etc., but the recommendations published from time to time have not been universally adopted. Even more important than these global terms are the definitions of individual defects. There is scarcely a single defect or group of defects that does not present some extremely difficult problem. For example, several common birth defects are abnormalities of size. Most often, the affected part is abnormally small (microcephaly, microphthalmos, microtia) but it may also be abnormally large (macrocephaly, megalocornea). The measurements upon which these diagnoses are based are continuous variables, but the extent

An array of
terms has
evolved over
several centuries
to describe
craniofacial
and other
malformations ...

of the variation from the mean which underlies such diagnoses, in terms of centiles or standard deviations, is rarely defined. Furthermore, the actual measurements are not necessarily very precise or reproducible.

Infants with more than one defect (multiples) present a different problem in classification. If the combination of defects constitutes a recognized syndrome, sequence or association, the appropriate collective term will commonly be used. When the defects do not add up to any recognized condition, a decision must be made as to how to record them. If each defect is recorded separately, the number of defects on record will, of course, exceed the number of affected infants.

There are a few widely adopted, pragmatic conventions. For example, extensive non-closure of the neural tube may result in anencephaly and spina bifida. In these cases, the spinal lesion is regarded as an extension of the cranial lesion and spina bifida is not usually recorded as a separate defect. Defects that are consequential upon other defects (e.g., hydrocephalus, talipes and dislocated hips associated with spina bifida) are often not counted as separate defects.

The same problem may arise in relation to individual organs. Congenital heart disease is frequently complex. If the four components of Fallot's tetralogy are present, the case will be given the single diagnosis, Fallot's tetralogy. However, if there are multiple defects that do not constitute a recognized *syndrome*, a decision must be made on whether to record one defect (in which case, which one?) or all. Also within the field of congenital heart disease are the problems of the ventricular septal defect (which frequently closes spontaneously) and patent ductus arteriosus (which is very common in small, pre-term babies and may require active measures to close it).

In the tenth revision of the *International Classification of Diseases* (ICD-10), the term "congenital anomalies" was replaced by "congenital malformations, deformations and chromosomal abnormalities" to denote structural malformations and exclude conditions such as inborn errors of metabolism. "Craniofacial malformations" is therefore an appropriate term.

An array of terms that is sometimes confusing has evolved over several centuries to describe craniofacial and other malformations. After consultation with professional colleagues and teratology researchers, the Human Malformation Terminology Committee of the International Federation of Teratology Societies (IFTS) has developed a comprehensive list of the various terms used for congenital malformations, deformations and so-called disruptions. The IFTS Committee's list provides "preferred" terms, "acceptable" terms, "non-preferred" terms and definitions.

BOX 7**Examples from the IFTS Committee's terminology list**

Preferred term	Acceptable term	Non-preferred term/s
Scaphocephaly	Dolichocephaly	Leptocephaly; Boat head; Dolichocrania Cymbocephaly; Mecistocephaly
Microcephaly	Microcrania	Nanocephaly
Cleft lip		Harelip; Cheiloschisis; Stomoschisis; Stomatoschisis

1.3.2 Working definitions

Craniofacial anomalies (CFA): this term covers a poorly defined group of congenital anomalies named after the anatomical location of a given defect present at birth. According to working definitions, it could include any etiologic category (chromosomal, environmental, Mendelian, multifactorial, etc.), as well as any pathogenetic mechanism (malformation, deformation, disruption, dysplasia), or any clinical category (developmental field complex, isolated defect, sequence, syndrome, etc). Therefore, in this work we will only refer to oral clefts, including typical cleft of the lip and/or palate as an example of CFA. In the future, other congenital anomalies of this group could be considered (*see Table 1 below*). Whenever not specified otherwise, we will refer in this work to the isolated forms of oral clefts, without other congenital defects detected in the same child.

Oral clefts (OC), including cleft lip, with or without cleft palate (CL/P), and isolated cleft palate (CP), occur in approximately 1 in every 700 live births; that is, with about the same frequency as Down syndrome, neural tube defects, polydactyly, and other so-called “common” congenital anomalies.

Registries and registers, monitoring and surveillance: If the primary objective of the planned system is not to monitor but to *register* oral clefts in the specific sense of the word – to *register*, namely, to recruit and follow up cases in a central repository (Last, 1995) – the quality of recorded data should be of more concern than completeness of ascertainment. (*See Box 9 below.*)

BOX 8**ICBDMS definitions**

The definitions and characteristics summarized here were published by the International Clearinghouse for Birth Defect Monitoring Systems as norms for the 28 participating programmes (ICBDMS, 1991, 2001).

Even though minor deviations can be adopted for other studies, a detailed definition including a list of inclusions and exclusions must be compiled and agreed upon before material from different registries can be collected.

- **“Cleft lip with or without cleft palate (CL/P):** a congenital malformation characterized by partial or complete clefting of the upper lip, with or without clefting of the alveolar ridge or the hard palate. Excludes midline cleft of upper or lower lip and oblique facial fissure (going towards the eye) (ICBDMS, 2001).

“Cleft of the lip arises by non-fusion of various processes that build up the face. Clefting of the lip (“harelip”) may also include the alveolar processes and the palate. Clefts may be unilateral, predominantly on the left side, or bilateral. Most infants with clefts of the lip have no associated malformations. Clefts may be surgically repaired with some functional and cosmetic restoration, but often a series of treatments is necessary until the child is of school age or more. There is a genetic background to cleft lip and a recurrence risk exists for siblings. Exogenous factors probably play a role, e.g. certain drugs and maternal smoking. Facial clefts may be detected prenatally by ultrasound, but usually not until late pregnancy (ICBDMS, 1991).

- **“Cleft palate without cleft lip (CP):** a congenital malformation characterized by a closure defect of the hard and/or soft palate behind the foramen incisivum without cleft lip. Includes sub-mucous cleft palate. Excludes CLP, cleft uvula, functional short palate, and high narrow palate (ICBDMS, 1991).

“This condition is characterized by a cleft throughout the soft and hard palate, usually positioned in the midline, but without clefting of lips or alveolar process. The cleft originates in the non-fusion of the maxillary palatal processes during the tenth week of embryonic development, but details of the pathogenesis are debated. The cleft may be sub-mucous. Some clefts are associated with a small lower jaw (micrognathia) where the tongue may have mechanically prevented fusion of palatal processes (Pierre Robin sequence). CP is often associated with other malformations in various syndromes. Genetic factors play a role in non-syndromic isolated cleft palate, and a recurrence risk exists in siblings. Environmental factors may increase the risk for an isolated cleft palate, e.g., certain drugs and, possibly, maternal smoking. The palatal cleft impairs swallowing and, later, speech. Treatment usually starts with a prosthesis to cover the cleft, followed by surgical repair. If no chromosomal abnormalities or serious malformations are associated, prognosis is excellent (ICBDMS, 1991).”

Table 1: The spectrum of CFA*

Cleft lip (CL)	Cleft lip with or without cleft palate	Cleft lip and/or palate; oral clefts	Craniofacial anomalies
Cleft lip & palate (CLP)			
Cleft palate (CP)	Cleft palate		
Oblique facial cleft		Atypical facial clefts	
Macrostomia			
Midline cleft lip	Holoprosencephaly		
DeMyer facies		CNS defects	
Other CNS defects			
An/microphthalmus		Eye defects	
Other eye defects			
An/microtia		First and second branchial arch defects	
Preauricular tags			
Preauricular sinus			
Agnathia		Mandibular defects	
Micrognathia			
Other jaw defects			
Anodontia		Dentition defects	
Other dental defects			

* This list of CFA is not exhaustive.

BOX 9**Aims of a coordinating registry**

In terms of the above concept (*para. 1.3.2*), a coordinating registry should aim to:

- build up a collaborating network, with the participation of all member registries, as a permanent activity, suitable for descriptive epidemiology, surveillance (including monitoring), activities in preventive public health, interactions with support organizations, education and training;
- conduct research programmes, with the participation of some member registries, as temporary, short or long-term activities aimed at specific objectives.

1.4 Clinical support of craniofacial anomaly registration

Three interrelated research issues, within the clinical theme, were addressed at the meeting.

1.4.1 Evidence-based care

Evidence-based care focuses on the replacement of current widespread uncertainty and confusion in clinical care with a sound evidence base derived from rigorous clinical research. There is a pressing need to mobilize a critical mass of clinical research expertise and to access sufficiently large samples of patients for adequately-powered clinical trials. Initial efforts should include:

There is an urgent need for work on psychological and quality-of-life measures ...

- 1) Trials of surgical methods for the repair of different orofacial cleft subtypes, not just unilateral clefts.
- 2) Trials of surgical methods for the correction of velopharyngeal insufficiency.
- 3) Trials of the use of prophylactic ventilation tubes (grommets) for middle-ear disease in patients with cleft palate.
- 4) Trials of adjunctive procedures in cleft care, especially those that place an increased burden on the patient, family or medical services, such as presurgical orthopaedics, primary dentition orthodontics and maxillary protraction.
- 5) Trials of methods for perioperative pain, swelling and infection management, and nursing.
- 6) Trials of methods to optimize feeding before and after surgery.
- 7) Trials addressing the special circumstances of care in low- to middle-income countries in respect of surgical, anaesthetic and nursing care.
- 8) Trials of different modalities of speech therapy, orthodontic treatment and counselling.

Equally urgent is the need to either create collaborative groups or improve the networking of existing groups in order to develop and standardize outcome measures. There is an especially urgent need for work on psychological and quality-of-life measures, and economic outcomes.

For rare interventions, prospective registries should be established to hasten collaborative monitoring and critical appraisal, equivalent to Phase I trials. Relevant topics would be craniosynostosis surgery, ear reconstruction, distraction osteogenesis for hemifacial macrosomia and other skeletal variations, midface surgery in craniofacial dysostosis and correction of hypertelorism.

1.4.2 Quality improvement

Quality improvement requires the development and dissemination of methodologies for monitoring and improving the delivery of clinical services.

The international adoption of a set of guidelines for the provision of clinical services and the maintenance and analysis of minimum clinical records of cleft care is proposed. Various registries of clinical outcomes have recently emerged and are working independently. Efforts should be made to harmonize them.

1.4.3 Access and availability

Access and availability requires the identification of strategies to maximize access to adequate levels of care for all affected individuals, irrespective of nationality. In large parts of the world, routine public health care services are unable to afford treatment for CFA. Three general approaches can be identified:

- high volume indigenous centres of excellence,
- contractual agreements initiated by NGOs with local hospitals, and
- voluntary short-term surgical missions.

The long-term benefit of these efforts could be developed by:

- 1) A survey of the charitable organizations involved and the scale of their work.
- 2) An appraisal of the cost-effectiveness and clinical effectiveness of the different models of aid.
- 3) The promotion of dialogue between different NGOs to develop commonly-agreed codes of practice and the adoption of the most appropriate forms of aid for local circumstances, with an emphasis on support that favours indigenous long-term solutions.
- 4) The initiation of clinical trials concerning the specifics of surgery in low- to middle-income country settings, one-stage operations, optimal late-primary surgery, anaesthesia protocols (e.g., local anaesthetic, inhalation sedation), antisepsis.
- 5) The development of common core protocols for genetic, epidemiological and nutritional studies alongside surgery.

2

Craniofacial anomalies and associated birth defects

2.1 Global distribution of craniofacial anomalies

Congenital anomalies (CA) are a major cause of infant mortality and childhood morbidity, affecting 2-3% of all babies. Approximately 1% of these newborns have syndromes or multiple anomalies; CFA are often a component part. Syndromes are composed of multiple malformations thought to be etiologically and/or pathogenetically related. Syndromes that have cleft lip and/or cleft palate as one of the features are of interest in the quest for etiologic and pathogenetic factors, and it is estimated that 30% of cleft cases are syndromic. Conversely, therefore, approximately 70% are non-syndromic.

Studies suggest that associated anomalies occur with a frequency of 44 % to 64 % in patients with clefts (Cohen, 1978). Isolated cleft palate (CP) is more frequently associated with congenital malformations (up to 50%), than CL/P (approximately 5 to 10%). There is however considerable variation in these figures in different populations.

Oral clefts (OC) therefore are among the most widely known and common CFA, occurring in approximately 1 in every 700 live births. CFA, other than cleft lip and palate, occur in 1 in every 1600 newborns in the United States of America (USA) and include jaw deformities, malformed or missing teeth, defects in the ossification of facial or cranial bones, and facial asymmetries. Clefts occur proportionately more often among the Asian populations than among African populations. Many factors contribute to cleft conditions, among them being heredity, pre-natal nutrition, drug exposure, and other environmental factors (WHO, 2002).

2.1.1 Global data for oral clefts

Coincidental findings reported from partially independent data bases – ICBDMs (Rosano & Mastroiacovo, 2001), EUROCAT (Bianchi, 2001), and NBDPN (2000) – as well as from the recent literature review by Mossey & Little (2002) are here summarized as representing non-spurious observations:

- **Cleft lip, with or without cleft palate (CL/P):** The highest reported prevalence rate (2.28 per 10 000) in the world is that of Bolivia (Rosano & Mastroiacovo, 2001; Mossey and Little, 2002). Known data comes mainly from the city of La Paz, at 4000 meters above sea level, with a large proportion of its population being of Amerindian ethnic background. The role of both environmental (chronic hypobaric hypoxia from altitude) and genetic (Mongolic Amerindian ethnicity) etiologic factors and their interactions are still unknown (Castilla, Lopez-Camelo & Campana, 1999). Interestingly, a similarly high-prevalence rate for CL/P seems to exist in the ethnic Mongolian population of Tibet at an almost equally high altitude (Zhang, 2001).
- **Cleft palate (CP):** The highest reported prevalence rate (10.0 to 14.0 per 10 000) in the world is that of Finland, where CP frequency is higher than that expected for northern Europe, followed by Scotland (8.0 per 10 000).

The prevalence for both OC main types, CL/P and CP, seems to depend largely on the same macro ethnicity, with maximum values among Mongols, lowest among Africans, and intermediate in Caucasians. The populations of two Asian countries, Japan (Neel, 1958) and the Philippines (Murray et al., 1997), as well as the mixed-race populations such as the American Indians of British Columbia (Lowry, Thunem & Uh, 1989) and California (Croen et al., 1998), and the mestizo populations in countries such as Argentina, Bolivia and Chile (Mossey and Little, 2002), fit into the Mongolian category. Likewise, low frequency of OC among Africans is reflected among African countries, Nigeria (Iregbulem, 1982), as well as North America's African Americans (Conway & Wagner, 1966) and Latin American countries with a substantial African ancestral background, namely, Venezuela (Mossey and Little, 2002) and Santo Domingo (Garcia-Godoy, 1980).

For CL/P in Europe, higher prevalence rates are reported from northern than from southern countries (Mossey and Little, 2002). Nevertheless, as expected, some inconsistencies to this general set of rules can be found, such as the low prevalence of CL/P in Japan reported by Kondo (1987) and of CP in China reported by Xiao (1989), as well as the high frequency for CL/P in Nairobi reported by Khan (1965). Such exceptional situations

may be reflecting operational differences in ascertainment or case definition, or “micro” ethnic situations such as geographical clusters.

2.1.2 Study on prevalence of non-syndromic oral clefts (OC)

A study on CL/P and CP occurrence was based on information collected from 1993-1998 by 57 registries worldwide (14 from the Americas, 5 from Asia, 2 from Oceania, 36 from Europe), all of which were members of either the ICBDMs or the EUROCAT. This data comprised the frequency of infants registered with a diagnosis of CL or CP, isolated or associated with other defects, from a total of 16 923 870 live births and stillbirths.

Rates were calculated by dividing the relevant cases by the number of live birth and stillbirths; a 95% confidence interval (CI) was calculated for each rate, using the Poisson distribution or the normal approximation when the number of cases exceeded 30. Heterogeneity within and among registries was tested using the chi square test.

Cleft palate without cleft lip (CP) prevalence at birth ranged from 1.3-25.3 per 10 000 births. The overall rate was 5.0 per 10 000 births, but the rate of distribution varied significantly among registries ($p<0.001$). Considering the 5th and 95th centile of the rate distribution, the rates varied from a low of 2.2 to a high of 8.1, with the registries of Canada and Finland showing the highest rate and those of Cuba, Colombia and South Africa showing the lowest.

Cleft lip with or without cleft palate (CL/P) prevalence at birth varied from 3.4-22.9 per 10 000 births. The overall rate was 7.9 per 10 000. The rate distribution was not homogeneous among registries ($p<0.001$). Higher values were found in Asian (China, Japan) and South American (Bolivia, Paraguay) countries, while Israel, South Africa and Southern European countries showed the lower values.

The proportion between infants with CL/P and CP was higher among Asian registries (from 4 to 6 times) and lower among Canadian and Finnish registries (from half to two thirds).

Findings in the study confirmed the low prevalence of CP observed among Africans. Caucasians and particular peoples from Canada and Northern European countries showed the highest prevalence rate for CP, i.e., twice as high as that in other countries. The prevalence of CL/P is also lower among Africans, and higher among Amerindians, Chinese and Japanese compared with Caucasians. By comparison with other countries CL/P prevalence, i.e. 7.4 (CI 95%: 7.3-7.6), the rate among Chinese and Japanese is double, 14.8 (CI 95%: 14.2-15.5). These differences might be explained by different methods of ascertainment. However, a high level of ascertainment has been broadly reported for facial clefts so different

Differences in rates in this study could be due to different methods of ascertainment ...

levels of ascertainment are unlikely to explain the differences reported. The level of the rate of CL/P was not correlated with that of CP, however Asian registries, which showed the highest rates for CL/P, showed low rates for CP.

2.1.3 Study on the sex ratio

A study on the sex ratio (SR) was based on information provided by 17 registries of congenital anomalies, also members of the ICBDMs, collected from 1974-1997. For the purpose of the study, 23 954 cases with CL/P (19 191 isolated and 4763 associated) and 14 000 cases with CP (9978 isolated and 4022 associated) were selected (EUROCAT, 1997; ICBDMs, 2001).

The SR was 0.93 (CI 95%: 0.89-0.96) among isolated cases with CP, and 1.81 (CI 95%: 1.75-1.86) among isolated cases with CL/P. An excess of prenatal mortality risk was found among females with cleft lip (CL). Among orofacial clefts associated with other defects, the sex ratios shrank towards the normal value, i.e. 1.01 (CI 95%: 0.96-1.07) for CP and 1.33 (CI 95%: 1.27-1.34) for CL/P.

Findings of this study confirm the known predominance of females among infants with CP and the known predominance of males among infants with CL/P. The sex ratio of CP was not significantly different from normal values when associated non-facial malformations existed, and was much lower than that for CL/P. The findings of previous studies that a male excess was less marked in races where CL/P is more common was not confirmed in this study in which Latin-American countries, with a higher prevalence of CL/P, had a lower sex ratio for males than the estimated common sex ratio.

CL/P, which is predominant among males, showed a greater intra-uterine mortality for females. The fact that liveborn infants with isolated CL usually have a good survival rate suggests that stillborn infants with an apparently isolated CL may, in fact, have other – unnoticed – anomalies, such as holoprosencephaly which, because of its female predominance, could explain the excess of females among stillborn cases.

2.2 Congenital anomalies associated with craniofacial anomalies

Cleft lip, with or without cleft palate, (CL/P) and isolated cleft palate (CP) are frequently associated with other major congenital malformations. It has been reported that about 20% of liveborn infants with facial clefts have associated malformations, and the figure is much higher among

Stillborn infants
with an
apparently
isolated CL
may have other
– unnoticed –
anomalies ...

stillbirths. The study of associated anomalies is useful in identifying pathogenetically homogeneous patterns of malformations and hence contributes to more powerful etiologic studies and better public health monitoring.

2.2.1 Study on multi-malformed infants

This study was based on data collected from 15 registries that are members of the ICBDMs and participate in the collaborative project on monitoring multi-malformed infants. Data were collected from 1992-1999 in the 15 registries as case records of infants registered with a diagnosis of CL or CP, associated with other defects, from 7 180 511 live births, stillbirths and terminated pregnancies (ICBDMS, 2001).

Out of 6454 cases of multi-malformed infants, the study found 739 cases (11.4%) of CL/P and 544 cases (8.4%) of CP. The most frequently associated anomalies with CL were congenital heart defects (28.6%), polydactyly (16.2 %), deformation/s (14.6%), hydrocephaly (11.4%), and a-microphtalmia (8.3%). The proportional analysis showed anencephaly, encephalocele, a-microphtalmia and polydactyly to be the preferential patterns associated with CL/P.

CP was more frequently associated with congenital heart defects (31.1 %), deformation/s (22.4%), hydrocephaly (11.2%), urinary tract defects (9.7%) and polydactyly (9.2%). CP was preferentially associated with neck anomalies.

To distinguish between isolated and associated cases in birth-defect epidemiology it is useful to provide clues for the etiology of the defect. The definitions of associated anomalies may vary among researchers, and the completeness of the identification and registration of such anomalies will depend on the data-collection method and the length of follow-up time. The ICBDMs collaborative project on monitoring multi-malformed infants allows comparable and reliable data – in terms of data collection, coding and analysis – to be gathered.

Findings in literature show that the most frequent defects associated with facial clefts are malformation of the limbs, followed by cardiovascular and other facial anomalies. The collaborative effort of the 15 registries participating in the ICBDMs project for monitoring multi-malformed infants has made it possible to obtain these findings. This is a significant research project, unique for the extent of its coverage of collected cases and the variety of races and ethnic groups represented.

The definitions
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researchers ...

2.3 Hungarian population-based data set of multi-malformed cases including orofacial clefts

MCA represent
about 10%
of the recorded
CA in the
Hungarian ...
Registry

Multiple congenital abnormalities (MCA) – the occurrence of two or more different congenital abnormalities (CA) in the same person (Czeizel et al., 1988a) – represent about 10% of the recorded CA in the Hungarian Congenital Abnormality Registry (Czeizel, 1997). The birth prevalence of recorded cases affected by MCA was 4.0 per 1000 total births (range: 3.7-4.5) in Hungary for 1973-1982. The stillbirth and infant death rates for the MCA category were 8.67% and 23.8%, respectively, that is, about 10 times higher than the corresponding national figures for the study period (Czeizel et al., 1988b).

Cases with MCA, including CL/P and posterior CP were evaluated in the population-based, almost-complete data set of the Hungarian Congenital Abnormality Registry. For the evaluation, the clinically recognized and notified syndromes and associations were included; the proportion of unspecified, multi-malformed cases being reduced when new or supplemental information was requested from clinicians. Furthermore, an attempt was made to classify unidentified, multi-malformed cases as syndromes or associations. This was done by referring them either to the regional multiple congenital abnormality examination centres or the so-called registry diagnoses in well-defined multiple-congenital abnormality entities. Finally, the remaining unidentified multi-malformed cases were evaluated on the basis of their component abnormalities. Of 651 cases with multiple congenital abnormalities, including OC, 58 (8.9%) had identified syndromes:

- Mendelian 23 (3.5%),
- chromosomal 31 (4.8%),
- teratogenic factors (hydantoin) 4 (0.6%).

The majority of the previously delineated syndromes were not identified. 78 (12.0 %) cases were affected with the so-called schisis association. The rest of the multi-malformed cases (351 [53.9 %] and 169 [26.0 %], including those with CL/P or posterior cleft palate, had unidentified multiple congenital abnormalities with mention of component abnormalities, respectively. These cases, all with two to eight component abnormalities, were evaluated together on the basis of different pairs of component abnormalities in the hope that this approach might help to identify and/or delineate syndromes or associations, thus reducing the proportion of random combinations of congenital abnormalities. Of 31 cases with ADAM sequence, 8 had CL; of 31 cases with holoprosencephaly, 7 had CL and 2 had CP. (See Box 10 below.)

BOX 10**Definitions of some isolated CA entities that include CL and/or CP**

- **Robin sequence (or Pierre Robin syndrome)** includes a U-shaped cleft palate, micrognathia and/or glossoptosis without other major CA.
- **ADAM sequence** comprises asymmetric limb deficiencies caused by an amniotic band with atypical anencephaly/encephalocele and/or orofacial cleft and/or ectopic cordis-thoracoschisis and/or abdominal wall defect.
- **Holoprosencephaly** is the consequence of a prechordal mesoderm defect with varying degrees of deficit of midline facial development (from cyclopia to hypotelorism), especially the median nasal process and incomplete morphogenesis of the forebrain. This CA-entity frequently includes CL and CP.

In the past, the classification of CA was based on anatomic localization. In the future, an etiologic classification will be established. At present, the cause in several CA and MCA groups is still unknown so a pathogenetically oriented classification, as outlined below, would be a reasonable compromise:

- 1) Differentiate isolated and multiple CA (Czeizel et al., 1988a).
- 2) Separate subclasses within the above two categories (Spranger et al, 1982; Opitz et al, 1987), e.g., delineate MCA association as a schisis association (Czeizel, 1981).
- 3) Separately evaluate the known etiologic MCA entities, i.e., syndromes and associations.

BOX 11**Definitions of MCA patterns**

- **MCA syndromes** are recognized patterns of component CA presumably having the same etiology, e.g. mutant autosomal or X-linked dominant or recessive genes, chromosomal aberrations or teratogenic factors.
- **MCA associations** are recognized patterns of non-random associations of two or more different component CA that do not have the same etiology; they are currently not considered to constitute MCA syndromes.

Family histories
of MCA cases and
consanguinity data
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identify
Mendelian
MCA entities ...

After the delineation of new MCA syndromes and MCA associations, and the identification of previously delineated and recognizable MCA syndromes and MCA associations, the balance corresponds to the so-called random combination of CA which are a chance concurrence of two or more different CA.

Of the 651 multi-malformed cases, 58 (8.9%) were identified as previously delineated MCA syndromes. Among 23 (3.5%) Mendelian CA entities, the majority were EEC, OFD II, Meckel and Roberts syndromes. Of 31 (4.8%) chromosomal syndromes, 29 cases were affected with trisomy 13. All four (0.6%) MCA caused by teratogens were identified as fetal hydantoin syndrome. CL and CP were not differentiated among these MCA entities because they occurred alternatively among the cases. Only one delineated MCA association had CL or CP. Of 130 MCA cases with schisis association, 73 (11.2%) had either CL (55) or CP (18).

The numbers of unidentified MCA cases including CL or CP were 351 (53.9%) and 169 (26.0%) respectively. The majority of MCA cases were not identified; on the contrary, that random combination may explain only 12.1% of the study material. Clearly, the proportion depends on the number of component CA:

2 = 16.7% (1 in 6);
3 = 0.4% (1 in 225), and
4 or more = 0.0% (1 in 14 000).

It is an important task to decrease the proportion of unidentified MCA entities and delineate further MCA entities including CL and/or CP. The hope is that this population-based data set will stimulate experts to attempt to identify either previously delineated or new MCA entities.

Finally, it is necessary to obtain the family histories of MCA cases and consanguinity data of the parents as this information may help to identify Mendelian MCA entities. The advances made in CFA research have given medical doctors greater understanding and expertise in identifying previously delineated MCA entities. "Diagnosis" of MCA entities is the task of the clinicians who see and examine the cases so it is helpful to adopt registry diagnoses to identify well-defined, previously delineated MCA entities. The validity of these diagnoses will, however, need to be further checked. The progress in gene mapping will drastically facilitate identification of newly recognizable MCA entities.

Table 2: Diagnostic criteria of MCA entities (MCA syndromes): registry diagnosis

CA syndromes	Obligatory CA	Additional CA
Acrocephalosyndactyly type I	Craniosynostosis	*
Apert syndrome	Syndactyly	-
Asplenia with cardiovascular CA	Asplenia-polysplenia	*
Ivemark syndrome	Cardiovascular CA	-
Congenital rubella	Cataract; Cardiovascular CA	Microcephaly supports the diagnosis
Cryptophthalmos with other CA	Cryptophthalmos	*
Fraser syndrome	Syndactyly	-
EEC	Split hand and/or foot; Orofacial clefts	Ectodermal dysplasia confirms the diagnosis
Ellis-van Creveld	Achondroplasia; Polydactyly	Cardiovascular CA confirms the diagnosis
Wiedemann-Beckwith syndrome	Omphalocele; Macrosomia-macroglossia	*
Holt-Oram	Septal heart CA; Radial-type limb reduction	Vertebral CA, anal atresia-stenosis, oesophageal atresia-stenosis and renal agenesis exclude the diagnosis
Klippel-Trenaunay-Weber	Unilateral limb hemihypertrophy ; Haemangioma	*
Meckel	Occipital encephalocele; Cystic kidney	Orofacial clefts, polydactyly and hypo-genitalism confirm the diagnosis
Mohr (OFD II)	Cleft palate; Polydactyly	*
Poland	Syndactyly; Pectoral muscle hypoplasia	In general unilateral
Roberts	Orofacial clefts; Phocomelia	*
Ullrich-Turner	Congenital lymphoedema ; Pterygium colli	*

* With or without some other characteristic CA; however, the occurrence of other non-characteristic CA excludes the diagnosis.

Table 3: Diagnostic criteria of MCA entities (MCA associations): registry diagnosis

CA-associations	Obligatory CA	Additional CA
Postural	Two or more postural type CA (club-foot, dislocation of the hip and torticollis)	*
Schisis	Two or more schisis-type CA (neural-tube defect, orofacial cleft, omphalocele and/or diaphragmatic CA)	*
Vacterl	Three or more VACTERL-type CA from the following six: specified vertebral CA, anal atresia-stenosis, cardiovascular CA, tracheo-oesophageal atresia-stenosis, renal agenesis or dysplasia, radial type limb reduction or polydactyly	*

* Other major CA exclude the diagnosis.

2.4 Example of epidemiology of hereditary syndromes with CFA in the former Soviet Union

The diversity of hereditary syndromes with CFA in the population of the former Soviet Union was broad ...

The prevalence of Mendelian hereditary diseases was studied among the populations of the former Soviet Union over the last 20 years, as follows:

- **Step 1:** A special form that included the symptoms of different hereditary disorders (neurological, ophthalmological, dermatological, skeletal, etc.) was distributed to local medical professionals for them to enter information on all families they had encountered with such symptoms. The form allowed for the recording of at least 500 different hereditary diseases, autosomal dominant, autosomal recessive and X-linked recessive, in approximately the same proportion as they are presented in Victor McKusick's *Catalogue for Mendelian Phenotypes in Man* (McKusick, 1998).
- **Step 2:** A professional team personally investigated the data submitted by the local medical staff and also collected from other sources. Team members visited every family, excluding those where cases were evidently nonhereditary; the team subsequently compiled the genealogical trees of the affected families.
- **Step 3:** Specialists from Moscow's medical institutes investigated the most recently recorded cases. Finally, the study revealed the prevalence rates for autosomal dominant, autosomal recessive and X-linked recessive disorders, as well as the spectrum of hereditary diseases in the population that had been investigated.

In 1976-1984, a similar study was conducted on a population of almost one million people in the Central Asian Republics of the former Soviet Union. The same methodology was used and more than 420 families, with 1114 people affected with different hereditary disorders, were revealed in the course of the study.

In 1985, further studies were conducted in Northern, Central and Southern regions of the European part of the former Soviet Union. A study that included other ethnic groups, namely Adigean, Chuvashian and Mari, investigated a population of more than 1.5 million people. During the course of this study the following statistics were revealed:

- 1723 patients from 884 families with 111 different autosomal dominant disorders;
- 942 patients from 707 families with 111 different autosomal recessive disorders; and

- 223 patients from 169 families with 36 different X-linked recessive disorders.

The prevalence rates for autosomal dominant, as well as for recessive disorders, were approximately two times higher in rural populations than they were in the urban populations of all the territories investigated, except for Krasnodar Province. Prevalence rates for X-linked pathology were approximately equal in both urban and rural populations. It should be mentioned that values of prevalence rates for hereditary pathology of rural populations in the study were close to the values of the frequencies of Mendelian disorders in the highly respected Register for Handicapped Individuals of British Columbia.

The spectrum of hereditary syndromes and diseases, including CFA, detected during the medical genetic study of populations of the former Soviet Union is shown in the Tables 4 and 5. There were more than 30 autosomal dominant syndromes with CFA. Only four of them had a relatively high prevalence rate ($p > 1:100000$). Among those, Marfan syndrome and trichorhinophalangeal syndrome type 1, showed local accumulation, the latter among the Adigean population. Three syndromes, namely Noonan syndrome, EEC syndrome and Waardenburg syndrome, had a prevalence rate of approximately 1:150 000; EEC syndrome showed local accumulation in the Mari population. All other autosomal dominant (AD) syndromes had a low, or extremely low, prevalence rate but, in spite of this, Moebius syndrome, Saethre-Chotzen syndrome and frontonasal dysplasia showed local accumulation. Eleven autosomal recessive syndromes with CFA were detected during the study; prevalence rates for most of them were extremely low. There were no cases of local accumulation for autosomal recessive syndromes. Several X-linked recessive syndromes and one X-linked dominant syndrome with CFA were registered, such as oto-palato-digital syndrome, type II, Coffin-Lowry syndrome and Aarskoga syndrome.

Conclusions based on the study:

- 1) The diversity of hereditary syndromes with CFA in the population of the former Soviet Union is broad.
- 2) On the contrary, the proportion of common hereditary syndromes with CFA is low.
- 3) The prevalence of hereditary disorders in populations of the former Soviet Union depended on genetic structure.
- 4) Some ethnic characteristics in the distribution of hereditary pathology should be expected in the population of the former Soviet Union.

Table 4: Spectrum and prevalence rates ($\times 10^{-5}$) of autosomal dominant syndromes with orofacial anomalies in the population of the former Soviet Union

Syndrome	Populations						Prevalence rate
	Mari	Russians in Mari El	Adigi	Kostroma	Krasnodar	Kirov	Briansk
1. Achondroplasia	1.16±1.82	-	1.66±1.66	1.57±0.59	0.93±0.46	1.88±0.84	-
2. Multiple osteochondromatosis		2.25±1.59		0.44±0.31	2.81±0.81	1.13±0.65	-
3. Marfan syndrome	3.49±1.42	(5.63±2.51)	1.66±1.66	0.67±0.38	1.40±0.57	0.75±0.53	-
4. Trichorhinophalangeal syndrome, type 1	0.58±0.58	-	(13.33±4.71)	0.44±0.31	0.23±0.23	1.13±0.65	3.40±1.96
5. Noonan syndrome	1.74±1.00	-	-	-	0.70±0.40	1.51±0.75	1.13±1.13
6. EEC syndrome	(4.66±1.64)	-	-	-	0.23±0.23	0.37±0.37	-
7. Waardenburg syndrome	1.74±1.00	-	-	1.57±0.59	-	-	-
8. Pseudoachondroplastic dysplasia	0.58±0.58	-	-	0.44±0.31	0.23±0.23	-	-
9. Goldenhar syndrome	-	-	-	-	0.93±0.46	-	-
10. Cleidocranial dysplasia	-	-	-	0.89±0.44	-	-	-
11. Williams syndrome	0.58±0.58	1.12±1.12	-	-	0.46±0.32	-	-
12. Crouson craniofacial dysostosis	-	-	-	0.22±0.22	0.46±0.32	0.75±0.53	-
13. Moebius syndrome	1.74±1.00	(2.25±1.59)	-	-	-	-	-
14. Saethre-Chotzen syndrome		1.12±1.12	-	-	0.23±0.23	0.37±0.37	(2.26±1.60)
15. Treacher-Collins syndrome	-	-	-	0.89±0.44	-	-	-
16. Acrodyostosis	-	-	-	-	0.46±0.32	-	-
17. Frontonasal dysplasia	-	(2.25±1.59)	-	-	-	-	-
18. Chondrodysplasia punctata	-	-	-	-	0.23±0.23	-	-

(continued)

Table 4 (continued)

Syndrome	Populations						Prevalence rate
	Mari	Russians in Mari El	Adigi	Kostroma	Krasnodar	Kirov	Briansk
19. Cornelia de Lange syndrome	0.58±0.58	-	-	-	-	0.37±0.37	-
20. Apert syndrome	-	-	-	0.22±0.22	-	-	-
21. Van der Woude syndrome	-	-	-	-	-	1.13±0.65	-
22. Coffin-Siris syndrome	0.58±0.58	-	-	-	-	-	-
23. Langer-Giedion syndrome	-	-	-	-	-	0.37±0.37	-
24. Marshall syndrome	-	-	-	-	0.46±0.32	-	-
25. Acrocephalosyndactyly, type V	-	-	-	-	0.23±0.23	-	-
26. Cloverleaf skull syndrome	0.58±0.58	-	-	-	-	-	-
27. Femoral-facial syndrome	-	1.12±1.12	-	-	-	-	-
28. Goldenhar syndrome	1.16±0.82	-	-	0.22±0.22	0.23±0.23	-	-
29. Beckwith-Wiedemann syndrome	-	1.12±1.12	-	-	-	0.38±0.38	-
30. Townes-Brocks syndrome	-	-	-	0.89±0.44	-	-	-

Legend:

- = no information exists.

(italics) = not included in calculation of overall prevalence rate.

Table 5: Spectrum and prevalence rates ($\times 10^{-5}$) of autosomal recessive syndromes with orofacial anomalies in the population of the former Soviet Union

Syndrome	Populations							Prevalence rate
	Mari	Russians in Mari El	Adigi	Kostroma	Krasnodar	Kirov	Briansk	
1. Cockayne syndrome	0.58±0.58	-	-	-	0.45±0.33	-	-	1: 526 315
2. Dubowitz syndrome	0.58±0.58	1.12±1.12	-	-	-	-	-	1: 526 315
3. Cohen syndrome	-	-	-	0.22±0.22	0.22±0.22	-	-	1: 769 230
4. Larsen syndrome	1.16±0.82	-	-	-	-	0.38±0.38	-	1: 526 315
5. C Trigoncephaly syndrome	0.58±0.58	-	-	-	-	-	-	1:1 544 371
6. Oral-facial-digital syndrome, type III	-	-	-	-	0.22±0.22	-	-	1:1 544 371
7. Russell-Silver syndrome	-	-	1.16±0.82	-	0.22±0.22	0.38±0.38	-	1: 526 315
8. Roberts syndrome	-	1.12±1.12	-	-	-	0.38±0.38	-	1: 769 230
9. Robinow syndrome	1.16±0.82	-	-	-	-	-	-	1: 769 230
10. Smith-Lemli-Opitz syndrome	-	-	-	-	0.22±0.22	-	-	1:1 544 371
11. Ellis-van Creveld syndrome	-	-	-	-	0.22±0.22	-	-	1:1 544 371

Legend:

- No information exists.

2.5 Example of ascertainment and registration of birth defects: Atlanta, USA

Surveillance systems in the USA collect information on the race and ethnicity of yearly births ...

Birth defects are the leading cause of infant mortality and contribute substantially to illness and long-term disability. Given the public health importance of birth defects, it is necessary for birth-defect surveillance systems to monitor and detect trends in birth defects, provide data for etiologic studies of birth defects, and provide the basis to plan and evaluate the effects of prevention activities. These purposes are best accomplished through surveillance systems that use multiple data sources, possess accurate and precise diagnostic criteria, perform timely data analysis, provide timely dissemination of the data, and use personal identifiers for follow-up and data linkage.

The population covered by the surveillance system needs to be specified in terms of the geographical area, number of yearly live births and stillbirths to area residents and the hospitals in the study area where births are delivered and children undergo medical evaluations. Surveillance systems in the USA also collect information on the race and ethnicity of the yearly births. It is important to collect this information given the variation in these characteristics and in the prevalence of some birth defects (e.g., the prevalence of oral clefts varies by race/ethnicity). One example of a population-based, intense birth-defect surveillance system is the Metropolitan Atlanta Congenital Defects Program (MACDP) sponsored by the CDC. The MACDP serves as a case registry for epidemiological studies, a prototype for other birth-defect surveillance systems, and a “laboratory” for testing new surveillance methodologies. The CDC also established eight Centers for Birth Defects Research and Prevention. The major activities of these centres are to participate in the National Birth Defects Prevention Study and expand and improve the birth-defect surveillance systems in their respective states.

The CDC is also actively engaged in efforts to improve birth defect surveillance across the USA. For example, 36 cooperative agreements have been awarded to enhance state-based birth-defect surveillance activities. These cooperative agreements provide the opportunity for state-based birth-defect surveillance systems to share data and increase the information on rare birth defects and geographical variation. The state birth-defect surveillance programmes that provide data on oral clefts vary in several respects, including:

- case ascertainment methods,
- definition of birth defects,
- coding systems,

- the inclusion of stillbirths and pregnancy terminations in counts of the occurrence birth defects, and
- the population coverage.

Hence, state surveillance data on the prevalence of OC cannot be combined to give a reliable overall national rate for the USA or used to make meaningful comparisons between states. Although differences between each state's approach for birth-defect surveillance systems sometimes creates such limitations, the diversity of approaches serves as a useful resource for guiding the development of surveillance systems for other childhood conditions.

2.6 Frequencies for oral clefts: global literature review

After a thorough critical revision and discussion of more than 150 published sets of data on the frequency of OC, Peter Mossey and Julian Little (2002), reached the following conclusions:

- 1) Cleft lip with or without cleft palate (CL/P), and cleft palate only (CP) are two different nosological entities. Furthermore, distinct subgroups within these conditions seem to exist according to severity, sidedness, and associated anomalies.
- 2) There is a large geographical variation in the birth prevalence rates of OC, which is more marked for CL/P than CP.
- 3) The proportion of OC cases with additional CA and syndromes is quite variable.
- 4) Migrant groups seem to retain rates of CL/P similar to those of their area of origin.
- 5) There is no consistent evidence of time trends, variation by socioeconomic status or seasonality, but adequate studies are still lacking.
- 6) There is large international variation in the reported birth prevalence rates of OCs, but part of that variation seems to be based on differences in source population (hospital versus population), time period, method of ascertainment, inclusion/exclusion criteria and sampling fluctuation.
- 7) Data on OC frequency are still lacking for many parts of the world, in particular parts of Africa, Asia and Eastern Europe.

2.6.1 Basis for the differences

Registries involved in birth-defect monitoring and other forms of surveillance know well that OC seldom produce an alarm or a suspected epidemic (ICBDMS, 1991) and do not experience cyclic periodical variations (Saxén & Lathi, 1974; Castilla et al., 1990) or changing secular trends (ICBDMS, 2000; EUROCAT, 1996). The only exception to the latter is the increasing trend reported by the Finnish national registry for both CL/P and CP (ICBDMS, 2000).

It is clear that, when very large time periods are considered, time increases or decreases can be found (Mossey and Little, 2002) – time increases are due to better reporting and survival; time decreases are due to prenatal diagnosis followed by unregistered terminated pregnancies, mainly in the syndromic forms of OC.

As can be seen in the following table (extracted from ICBDMs, 2001), OC seldom present an alarm during quarterly or yearly monitoring of prevalence rates, if compared with the four other frequent and well-known congenital anomaly types.

Table 6: Summary of the results of observed to expected ratios in 1999 births

Malformation	Observed to expected ratio *	
	Number	Statistically significant
CP	27	2
CL/P	27	3
Anencephaly	28	3
Spina bifida	27	4
Down syndrome	27	6
Hypospadias	25	7

* The total number of ratios was 1078. The reasons the number of ratios was different, malformation by malformation, were that several registries did not contribute data for a few malformations and some expected ratios were not computable. The number of computed ratios was very high so a certain number (about 5%) of significant ratios can be expected by chance.

There is no
clear evidence
that under-
ascertainment
of CP is greater
than that
of CL/P ...

- **Differences:** Differences in ascertainment rate do not seem to play a major role. In comparison with other congenital anomalies, OC are rather conspicuous, severe anomalies, rarely overlooked at birth because they are external and obvious and cause typical changes in crying pitch and sucking ability. CL/P is more obvious than CP and severe forms, such as complete bilateral cleft of the lip and palate, are more obvious than mild forms, such as incomplete cleft of the soft palate. However, in spite of this clinical logic, there is no clear evidence for a greater under-ascertainment of CP than of CL/P.

Obvious under-reporting exists for the microforms such as “healed” or “fruste” CL (Castilla & Martínez Frías, 1995), sub-mucous CP, and notched gums (clefts of the alveolar ridge). However, except for sub-mucous CP, these forms are too rare to be reflected in the total registered number of cases (Christensen & Fogh-Andersen, 1994).

- **Variability:** The largest source of variability among populations seems to be genetic predisposition rather than environmental differences or differences in ascertainment. This statement is mainly supported by the above-mentioned inter-ethnic differences and stable time trends.

Ethnicity must be considered in its macro as well as its micro components. Macro-ethnicity was already summarized as having maximal OC frequencies in the Mongoloid races, minimal in Africans, and intermediate in Caucasians. Furthermore, micro-ethnicity could be responsible for reported geographical clusters, such as the Cumaná cluster on the Caribbean coast of Venezuela, apparently due to a single mutation-producing, non-syndromic CL/P (Sözen et al., 2001).

Some situations could even be intermediate between the above-mentioned macro- and micro- ethnicity, as for instance those of Finland (Saxén and Lathi, 1974) or the Philippines (Murray et al., 1997).

The major role of genetic factors in the etiology of OC was recently updated by Calzolari (2001) with EUROCAT data.

BOX 12**ICBDMS experience**

When summarizing 15 years of experience in the book *Congenital malformations worldwide* (ICBDMS, 1991), the ICBDMS made the following statements:

“Cleft lip with or without cleft palate: This is one of the most stable malformations among those studied, probably because it is a condition easily observed and described. Some temporal changes can be noted, however. Up to 1982, the rates of Canada-National and Atlanta were virtually identical, but since that time the Canadian rate increased and the Atlanta rate decreased slightly. A slightly increasing trend is seen in the Tokyo programme. More remarkable is the difference among programmes. Programmes in southern Europe and Israel have rates around 6 per 10 000, while the Scandinavian, and the Asian programmes, as well as Canada have rates twice as high. The rate of total cleft lip apparently differs in different populations, and it is likely that genetic factors play a decisive role for this difference.

“Cleft palate: In most programmes, the rate is around 5 per 10 000 births, and remains reasonably constant during the observation period. Some remarkable exceptions can be seen. In England-Wales, Japan, and Atlanta very high rates existed at the beginning of the observation period followed by a marked decrease down to the approximate level of most other programmes. High and increasing rates are seen in Finland. A tendency to an increase is seen in Sweden, France-Strasbourg, and perhaps to a lesser extent in some other programmes. Although such changes might have arisen by an increased inclusion of mild cases, a special study made at ICBDMS on this problem yielded no convincing evidence that this was a major cause of the observed changes.”

3

Registration of targeted craniofacial anomalies in geographically defined areas

3.1 Birth defect registration in the Philippines

In the Philippines, CA rank among the top 20 causes of death across the life span and are the third leading cause of death in the infancy period. Despite the magnitude of the problem, no formal systematic registration of birth defects was practised in the Philippines until 1999. Various attempts to gather data were made by study groups but there was no formal attempt to consolidate the information. However, hospitals now use the WHO *International Statistical Classification of Diseases* (ICD) and the Related Health Problems system, ICD-10 having been implemented in 1999.

- **Philippine Birth Defect Registry Project:** This is a joint project conducted by the Department of Health and the Institute of Human Genetics of the US National Institutes of Health (NIH). It started in February 1999 with 79 hospitals nationwide participating. For 1999-2000, the project collected reports from 191 576 deliveries. This represents approximately 6.3% of the annual births in the country. A total of 1240 cases of birth defects have so far been tallied, the top 12 of which include:
 - multiple congenital anomalies,
 - congenital malformations of the tongue, mouth and pharynx (e.g., ankyloglossia),
 - cleft lip and palate,
 - Down syndrome,
 - congenital deformities of the feet (e.g., talipes equinovarus),
 - other congenital malformations of the face and neck (e.g., preauricular skin tags),
 - anencephaly and similar neural tube defects,
 - congenital malformations of the musculoskeletal system not elsewhere classified (e.g., diaphragmatic hernia, gastroschisis),
 - hypospadias,

- congenital hydrocephalus,
 - polydactyly and syndactyly, and
 - cleft lip only.
- **Prenatal Inventory and Neonatal Outcome Study Group:** This group was formed to determine the accuracy of detection and the effectiveness of perinatal and neonatal interventions on congenital anomalies. For the period 2000-2001, 73 mothers were enrolled after routine obstetric ultrasound examinations detected congenital anomalies on the fetus. Postnatal verification of the anomalies was assessed and 65.7% had confirmed abnormalities. The six top congenital anomalies were:
 - multiple congenital anomalies,
 - congenital hydrocephalus,
 - neural tube defects,
 - cleft lip and/or palate,
 - hydrops foetalis, and
 - congenital heart disease and omphalocele.
- **Hospital pathology reports:** Autopsy reports from 1995-1999 were reviewed at the Department of Pathology of the College of Medicine, University of the Philippines, Manila. A total of 68 cases were reported to have congenital malformations. The three most common malformations were:
 - congenital heart disease (mostly patent ductus arteriosus),
 - multiple congenital anomalies, and
 - Down syndrome, with or without other congenital anomalies.
- **Hospital in-patient and out-patient records:** The Philippine General Hospital (PGH) is the largest tertiary government hospital in the Philippines. In 2000, it serviced 639 760 patients either as in-patients, out-patients, or emergency patients. The hospital offers more than 1400 beds distributed throughout 12 departments. A review of records from 1996-2000 at the PGH revealed a total of 6742 cases with diagnoses of birth defects. The top 20 were:
 - congenital malformation of the heart, unspecified,
 - Hirschsprung's Disease,
 - congenital absence, atresia, and stenosis of anus without fistula,
 - unspecified CLP, bilateral,
 - congenital hydrocephalus, unspecified,
 - cleft lip and palate,
 - CL and multiple congenital malformations, not elsewhere classified,
 - patent ductus arteriosus,

- spina bifida, unspecified,
 - congenital cataract,
 - hypospadias, unspecified,
 - CP, unspecified, unilateral,
 - CP,
 - atresia of bile ducts,
 - Down syndrome, unspecified,
 - CL, unilateral,
 - undescended testicle, unspecified,
 - talipes equinovarus,
 - encephalocele, unspecified, and
 - peripheral arteriovenous malformation.
- **Community outreach programmes:** To augment health services in the country, voluntary medical and surgical missions are conducted all year round. Operation Smile is one of the organizations that has been conducting free surgical missions with the main purpose of repairing oral clefts in various provinces of the Philippines since 1992. As of 2000, Operation Smile had served 1633 Filipino children aged 10 years and below. Data from Operation Smile indicates that the Philippines has one of the highest rates of oral clefting in the world, with an incidence of 1:500. Studies are under way to determine the genetics of oral clefting in the Philippines.

3.2 Monitoring craniofacial anomalies in South Africa

In 2001, for the first time in the country's history, the South African National Department of Health released *Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disability*. One of the stated objectives of these guidelines is the establishment of a national monitoring and evaluation system for genetic disorders and birth defects. Cleft lip and palate (CLP) is one of the six priority conditions listed for monitoring. It appears that the present would be a suitable time to consider the establishment of (at least) a CLP monitoring and registry system in South Africa.

Other circumstances that support this view are the fact that:

- there are only limited epidemiological data available for CLP in sub-Saharan and South Africa, and
- the recent documentation in South Africa shows a very high prevalence of fetal alcohol syndrome (FAS) in the urban populations of Africans and South Africans of mixed ancestry.

Surveillance of
genetic disorders
and birth defects
in South Africa ...
have been
successfully
undertaken ...

Cleft palate is an occasional feature of FAS, but only limited information is available on the association between the two conditions. South Africa would be the ideal situation to study this relationship.

The surveillance of genetic disorders and birth defects in South Africa, including the ongoing studies on the prevalence of FAS, have been successfully undertaken in rural and urban situations. The next phase in this research is a prevention programme in geographically isolated communities; this will include a population-based study of the birth prevalence of FAS. The monitoring of CLP within this study is imminently possible. Within the country's major cities, most of which have academic medical facilities, CLP surveillance of newborns in large hospitals and the ascertainment of other patients through the craniofacial/CLP surgical units are possible. Thus a registry, that may be regional initially, will have the potential to be national.

The pitfall within the contemplated scenario is that, due to the increasing pressures that the country's health services are experiencing because of the current HIV/AIDS pandemic, such an undertaking would initially – and possibly for some time – have to be an academic endeavour, financed and undertaken from outside the health service, but working in collaboration with it. Such partnerships are welcomed by the South African Department of Health.

3.3 Registration of targeted craniofacial anomalies in India

- 1) Three multi-centre studies in India have provided almost similar frequency of CFA: meta-analysis of 25 early studies from 1960-1979, involving 407 025 births, showed:
CL/P = 440 cases, 1.08 per 1000 births,
CP = 95 cases, 0.23 per 1000 births.
- 2) A prospective national study of malformations in 17 centres from all over India from September 1989 to September 1990 involving 47 787 births showed:
CL/P = 64 cases, 1.3 per 1000 births,
CP = 6 cases, 0.12 per 1000 births.
- 3) The latest 3-center study, conducted in 1994-1996, involved 94 610 births in Baroda, Delhi and Mumbai, and showed a frequency of:
CL/P = 0.93 per 1000 births,
CP = 0.17 per 1000 births.

This was the most rigorously conducted study and it found the number of infants born every year with CLP to be 28 600; this means 78 affected infants born every day, or 3 infants with clefts born every hour!

Table 7: Number of infants with common malformations born every year in India

Malformation	Rate per 10 000	Total number per year
Neural tube defects	36.3	88 935
Talipes equinovarus	14.5	35 525
Polydactyly	11.6	28 420
Hydrocephalus alone	9.5	23 275
Cleft lip with cleft palate (CLP)	9.3	22 785
Congenital heart disease	7.1	17 395
Hypospadias	5.0	12 250
Cleft palate alone (CP)	1.7	4 145

CFA are disfiguring and cause a tremendous social burden ...

CFA are not lethal, but they are disfiguring and thus cause a tremendous social burden. However, these disorders have an excellent outcome if surgical repair is carried out competently. Recent information regarding the etiology of CFA provides the means to carry out primary or secondary prevention. Maintaining a registry would be very useful as a benefit to the community and in reducing the burden of these anomalies, either by prevention or surgical repair.

Another reason why a registry would be desirable is the changing pattern of morbidity and mortality in India emerging as a result of the achievements in immunization, the success in providing primary health care and the existence of a well-developed health infrastructure. In many university and city hospitals congenital malformations and genetic disorders have become important causes of illness. All these reasons show that starting a registry of these disorders deserves high priority in India.

3.3.1 Existing epidemiological data on CFA

The epidemiological information that exists on CFA anomalies in India needs to be examined to decide what data should be collected for the registry:

- 1) Higher frequency of CL + CP among Indian males is similar to that observed among Caucasians. The ratio is more than that observed in Africans and Japanese.

- 2) The higher prevalence of CL+CP as compared with CL among Indians is like that observed in Africans, and is more than that observed in Caucasians.
- 3) Children born prematurely are more frequently affected in India, as elsewhere.
- 4) About 10.9 % of 459 cases of all clefts are syndromic in Madras. Of these, about 50 % are due to single-gene disorders, about 18 % due to chromosomal disorders, and the rest due to undetermined causes. Chromosomal studies would be desirable in cases with associated abnormalities.
- 5) Syndromes are more commonly associated with CP than with CL, as elsewhere.
- 6) Lateralization (more clefts on the left side) in India is similar to that observed in other races.
- 7) In one study in India, the intake of drugs was observed in 18 % of the parents – mostly steroidal compounds (progestogens as tests for pregnancy).
- 8) A greater history of terminated pregnancies has been observed among cases, as compared with controls.
- 9) History of severe vomiting has been observed to be about six times more common among case mothers than among controls.
- 10) There is some difference in frequency of OC in different states in India; this needs verification however. The state of origin (or mother tongue) of the parents should be recorded.
- 11) Clefts are more commonly found in certain caste groups among Hindus.
- 12) In India CP has less frequency in those with blood group A, while CL occurs more in those with group O and AB.
- 13) Association of clefts with certain HLA types has been documented in India.
- 14) In a study in Chennai, significantly more consanguinity was observed among couples having children with clefts as compared with controls.

3.3.2 Data collection for birth defect registries

Based on the experience of the author in a number of multi-centre studies and two large-scale studies on congenital malformations in India, the following comments highlight the difficulties encountered in low- to middle-income countries, and suggest how these can be surmounted:

- 1) If the aim is to collect data on a large number of subjects, the minimum amount of information should be collected, otherwise a large workforce will have to be employed.
- 2) Often, in some communities, the date of birth is not known so the age is approximate.
- 3) Many women do not remember the date of their last menstrual period.
- 4) Addresses are often not precise, so follow-up may not be possible. This makes it necessary to collect all the data that is needed while the mother and child are in hospital.
- 5) Hospital-based studies are more feasible, but home-born babies are missed by this approach. However it is likely that, in the first phase in low- to middle-income countries, only studies among hospital-born babies will be possible.
- 6) Diagnosis of external abnormalities is not difficult and may even be performed by the primary health workers.
- 7) Studies on stillbirths and post mortems on neonatal deaths are difficult, so collection of data on internal anomalies is neither easy nor accurate. In one study conducted by the author, where post mortems were successfully carried out in the majority of deaths in newborns, it was observed that 31% of stillborns with malformations did not have any external abnormalities and their congenital abnormalities (such as those of the gastro-intestinal tract or the renal or cardiovascular systems) were detected only when autopsy was performed (Puri, Verma, and Mahadevan, 1978).
- 8) Collection of information on socioeconomic status is notoriously unreliable. People often declare less income, fearing they will have to pay more for the treatment.

In low- to middle-income countries it would be better to collect data on all birth defects rather than on clefts only. As per the recommendations of the WHO report, *Primary health care approaches for prevention and control of congenital and genetic disorders* (WHO, 2000), the registry in India could collect data as a pilot study in seven centres – Ahmedabad (Gujarat), Amritsar or Ludhiana (Punjab), Chennai (Tamil Nadu), Cochin (Kerala), Delhi, Mangalore (Karnataka), Mumbai (Maharashtra) and Srinagar (Kashmir) – based on geographical location, presence of consanguinity and high and low incidence areas, as noted in previous studies. After gaining experience in these seven centres, the registry could be extended to another seven centres in other states and, subsequently, in stages, to all the 26 states and 6 Union territories in India. Finally each state should have at least one centre, while the larger states could have

Collection of
blood samples
on Guthrie cards
would be
very useful
data ...

more than one. In each centre it would be ensured that about 15 000-18 000 births per year would be covered, so that each centre would evaluate about 50 000 births over a 3-year period.

Collection of blood samples on Guthrie cards would be very useful data that is currently not available, and inborn errors of metabolism and congenital hypothyroidism could be detected from this data. Furthermore, the samples could be used for the study of polymorphisms of the genes involved in folic acid metabolism.

It would also be a good idea to start a web site for the registry, with a description of its mission and objectives, the composition of its advisory committee, various constituents and participating units, and giving clear information to the public and professionals on various aspects of birth defects.

3.4 South-East Asian collaboration for treatment and research in craniofacial anomalies

Since 1986 the group study combined research with efforts on the treatment of congenital anomalies, especially on CL and CP patients. The group concentrated in several regions in two provinces, East Java and Nusa Tenggara Timur (NTT), that have different racial groups, culture and environment. During the 14-year period (1986-2000) the group collaborated with other countries, such as Japan, the Netherlands and Singapore, in the areas of both treatment and research (Hardjowasito and Hidayat, 1992-1996; Hardjowasito, Pardjianto and Hidayat, 1996; Hidayat, Ali and Hardjowasito, 1997; Hardjowasito, 1998; Sutrisno, 1999).

3.4.1 Highlights of cleft research

Morphometric study: Through assessment, the group investigated differences between cleft and noncleft families from two racial backgrounds (Proto Malayid and Deutero Malayid) in the former East Timor (District TTS) and East Java (District Blitar). In District TTS there was a significant difference in the bigonial measurement of the fathers of cleft children and those of non-cleft children – the measurement being significantly higher in fathers of cleft children (Loekito, 1995). In Blitar, with a Deutero Malayid background, there was also significant difference in the bigonial measurement, but here the width was greater in fathers of the non-cleft families (Loekito, 1997).

Zinc deficiency: In 1988 the group began looking at the implications of a zinc micronutrient deficiency. Inland, in the former East Timor, they found that zinc concentration in drinking water was indeed much lower

The family of a child with birth defects needs the support of the medical staff involved in the child's treatment ...

than the norm; in many places it was even zero. In 1990 they proceeded to examine pregnant women in District Soe, Timor Island. The study showed that about 39.2% of the cases were suffering from zinc deficiency, with a serum concentration of less than 11 μMol per litre. At present, major health problems in Indonesia also include nutrition and infection. In the province of NTT where these factors were more prominent, the maternal and infant mortality rates were high compared to those in other places in Indonesia; the Indonesian national figures being among the highest in ASEAN countries. In NTT one of the trigger nutritional factors was the micronutrient zinc deficiency (Hidayat, Ali and Hardjowasito, 1997; Hardjowasito and Loekito, 1998; Hidayat et al., 1999). In West Timor it may be that zinc supplementation could decrease the prevalence of clefts and morbidity during pregnancy. Interaction between genetics and environment (zinc deficiency) might explain the high prevalence of clefts in West Timor.

Consanguinity: The indigenous population of the former East Timor still practices inter-family marriage (between cousins), a cultural custom in certain regions. Many families therefore have the same surnames and this allows them to trace their pedigrees more easily. Cross-cousin marriage among the Proto Malayid native population in the former East Timor was found to increase CL/P. The interaction of micronutrient deficiency and genetic background has been under intense investigation (Hidayat, Ali and Hardjowasito, 1997; Hidayat et al., 1999).

3.5 Focus on the family situation of patients with craniofacial defects in Brazil

It has been suggested that the birth of a malformed child is accompanied by ruptures in the parents' marriage. The families of children with birth defects need the support of the medical staff involved in the children's treatment to assure the preservation of self-esteem and positively influence the parents' role. It is important for the health team to know the profile of the families and to verify their situations.

A hospital-based survey at the Hospital of Craniofacial Anomalies of Baurú, USP (HRAC) examined 34 480 probands with CFA. Of these, 92 % had clefts, 61% of which had CL/P. There was slight prevalence of the masculine sex (57 %) and the age varied from 0.01 to 45 years with most (53 %) less than 1 year of age. Only 9 % of the patients were older than 18 years. The age of the mothers at patient's birth varied from 12 to 50 years, with an average of 25 and the parents' average age was 29.5 years. Adolescent mothers accounted for 26 % with 12 % being younger than 18 years. The adolescent fathers were in smaller proportion, 12 %.

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Low socioeconomic class families accounted for 86 %; if the mother was uneducated, the socioeconomic status was lower. No cases from middle or high class backgrounds were registered. Parents of the patients were found to have had limited education and most hadn't completed elementary school. The adolescent mothers had less education compared with the adult mothers. To complete the family picture, in 21% of the families the parents were separated and in only 34 % of the families were the mothers contributing economically to the family income.

Such family conditions make it extremely important that team members are attentive and can relate to the young families and their problems; otherwise the process of collecting information can be very difficult for assistants and research staff.

3.6 Craniofacial anomalies registered in Belarus

Congenital malformations (CM) of bone and soft tissues of the cranium and the face are subdivided into isolated (single) anomalies and those that are part of multiple congenital malformations (MCM). In Belarus CL/P, as one of the most common CFA, has been regularly registered since 1979 by the Institute for Hereditary Diseases (National Registry of Belarus). These anomalies, being a part of MCM, are also registered by the Registry of MCM Syndromes. About 150 anomalies are recorded annually; two-thirds of which are isolated.

The National Registry System records all cases that are either diagnosed within the first seven days of an infant's life or revealed at autopsies of infants who die in the perinatal period; it also records the anomalies found in medical abortuses obtained after termination of pregnancies for genetic reasons. Primary information on paper cards is filled in at the maternity houses, then sent to the regional medical genetic centres. After the diagnosis has been verified the information is recorded by the National Registry. The National Registry contains information on 2322 cases of isolated CFA, including 2211 CL/P, 105 anotias-microtias, 6 choanal atresias and 1107 CFA that are part of MCM. MCM are presented by syndromes (933 cases) and non-classified complexes. The data on the syndromes has been obtained not only from Belarus, but also from other areas of the former Soviet Union.

Syndromal diagnosis of MCM, including the accompanying CFA, is performed using sophisticated computer software at the Belarus Institute for Hereditary Diseases (only). At the regional medical genetic centres more simple programmes are used in the diagnosis. At maternity houses and childrens' hospitals the syndromes with CFA are rarely diagnosed. The registry of MCM contains 326 syndromes accompanied by craniosynostosis, and 607 syndromes accompanied by CL/P.

There can be
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model that
has universal
applicability
for a registry ...

The information on CFA frequency due to the Chernobyl accident could be of special interest. However, since the registration of CFA as part of the syndromes is not complete and is mainly selective, assessment of CFA dynamics resulting from the Chernobyl accident can be made only from information on CL/P registration. In these data no significant differences have been found in CL/P frequency between contaminated and “clean” areas. The average annual frequencies are 9.7:10 000 births.

Tasks requiring urgent solutions are concerned with:

- preparation of clear definitions for a glossary and nosology of CFA,
- development of CFA classification taking into account the current knowledge on CFA,
- search for markers for prenatal diagnosis, especially during the first trimester of pregnancy,
- discussions on the possibility of creating international centres, where it will be possible to perform molecular studies of CFA, and
- development of a protocol of clinical genetic data to perform molecular studies of CFA.

3.7 Variability among registries – merits and drawbacks

Existing registries vary widely in structure, administration, coverage base (population or hospital), coverage units (municipal, state, national or regional), coverage size (from a few thousand to many millions of births per year), statutory systems or non-institutional projects, governmental or non- governmental research projects, sources of ascertainment (single or multiple), information collected on exposure, available background information, exclusion criteria, registration criteria, inclusion (or not) of pregnancies terminated after prenatal diagnosis, methods of ascertainment, age limit for registration, definitions of major and minor anomalies, definitions of isolated and associated anomalies, interpretation or identification of syndromes.

All these factors result in variability in the registration systems and, inevitably, in the quality of data. Differences among programmes must be recognized and accepted, with the understanding that there can be no single ideal model that has universal applicability for a registry. When planning joint research projects, these variabilities must be taken into account, but difficulties in comparing data are compensated by the value of diversity itself, in providing clues for the identification of risk factors (Källén et al, 1992).

4

Establishment of a system of registration for craniofacial anomalies: problems, pitfalls and potential

4.1 Guidelines for population-based birth-defect registries at a national and regional level

To implement a registry of birth defects with a guided system to help health personnel involved in different fields follow a methodology that has been formalized and standardized, the following four basic “w” questions need to be considered:

- **Why** to register?
- **Who** must be registered?
- **When** to register?
- **Where** to register?

Guidelines and recommendations represent an operative tool derived from the best and most recent scientific know-how e.g., evidence-based medicine (EBM), and the practice in congenital malformations (CM) management, registration and surveillance settings. In the field of CM registration and surveillance, an evidence-based system (EBS) can be defined as a set of indicators that are both theoretical and empirical, to each of which a different value can be assigned, according to the indicator’s reliability and strength.

The main features of a CM registration system are its effectiveness and ability to adapt to the social and health settings in terms of clinical activities, epidemiological surveillance, public health organization and research. Therefore, the crucial feature of the guidelines must be a focus on adaptability to different situations. The guidelines have to be both formal and flexible at the same time. In fact, the guidelines should not be a rigid protocol to be applied wherever and whenever, but a reasoned set of rules that provide the best assistance for setting up a registry. General knowledge and guidelines are closely connected and play an important role in the decisional process in setting up a registry. It is important to consider that:

- by definition, general knowledge covers a greater area than that of guidelines since guidelines are defined on the *basis* of general knowledge, and
- the ratio of general knowledge to guidelines that is informative for decision-making depends directly on the main purpose of the registry (surveillance, public health and/or research).

The aim in creating guidelines is to streamline the decision-making process of the different stages and make it as objective as possible, to promote quality assessment of registration, to improve cost-effectiveness of the public health services involved, and to set up indicators that are able to control all procedures. Theoretically, from a methodological point of view, the adoption of good quality guidelines is important because:

- they limit behavioural variability in dealing with analogous problems;
- they provide standards that reduce differences in activities such as classification, codification and variables aggregation; and
- they facilitate the production of useful training tools for physicians and assistants, as well as for public health service managers.

The priority goals of guidelines for a CM registry are to provide a useful tool for those who want to implement a birth-defect registry, by defining a methodological standard by which to assess registries already in place or to reset or revise unsatisfying situations, and to contribute to the development of an assessment methodology of the guidelines themselves.

BOX 13**Criteria to be used in preparing the guidelines**

- Define of the area of interest, evaluating the impact of selected anomalies in terms of mortality, morbidity, prevention, costs (not only social and economic, but also in terms of health care and human suffering).
- Create a multidisciplinary panel at the preliminary and review stages.
- Identify an independent panel to certify and control activities undertaken with respect to guidelines.
- Review the evidence in literature.
- Consider issues in defining a “gold standard” and a “golden range”.
- Make recommendations based on the strength of both practical and theoretical evidence (i.e., based on the knowledge of running a registry).
- Establish a flexible structure that will allow for the guidelines to be updated.
- Make allowances for different alternatives to be selected if different priorities are chosen (this should relate to cost-effectiveness and risk/benefit assessment).

4.1.1 Guideline assessment by indicators

Indicators of guideline evaluation must concern: scope, objectives, involvement of active subjects (including media, stakeholders, decision-makers), involvement of users/persons/associations, rigorous development in terms of relevance and appropriateness, technical and scientific validity, clarity and simplicity of presentation (user-friendly presentation), applicability and repeatability, social and health impact, independence (interest conflict) and ethical issues.

Processes or structures covered by the guidelines are: objectives, resources, procedures, observation stage, registration, validation (ascertainment of full cases), confirmation (by linkage with other sources), classification, analysis, interpretation, presentation and output (communication, reports, etc).

4.1.2 Setting up the registry

Guidelines must provide the following flow-chart:

- 1) **Definitions and selection of birth defects** to be registered (terminology, naming and operational definitions, classification and coding), with an explanation of reasons and criteria for selection; changes of definitions and completeness of diagnoses (from prenatal to infant period) must be considered over time.
- 2) **Definitions of the type of fetus/birth** to be registered (spontaneous abortion, terminated pregnancies, stillbirths, live births).
- 3) **Definitions of the registration periods** (early prenatal period, prenatal, neonatal, post neonatal, infant), depending on the level of resources available and possibility to link with other information systems.
- 4) **Definition of the registration base** (hospital versus population).
- 5) **Ascertainment features** (active case-finding and use of multiple sources of information).
- 6) **Coding and classification procedures** to be followed; specification of the person/s who will be in charge and responsible for the coding activities; recommendations to regulate specific and more detailed classifications that are different from standard systems (e.g. for CFA).
- 7) **Clear indication of the person/s in charge of the codification** of congenital malformations (e.g. physicians, expert on CM or nurses where the diagnosis is made, panel of experts working in the postnatal period on the basis of the description of anomalies).

- 8) **Listing of any further variables** on reproductive history, delivery, babies and parents (e.g. previous pregnancies; parents' occupation and exposures, use of drugs, lifestyle, etc).

The above factors will be strongly influenced by the kind of collection. The need to collect a wide and detailed core of information must be balanced with the difficulties in obtaining valid data (e.g., interviews).

Collected data can be used to:

- carry out investigations when excesses, trends, patterns or clusters are reported by the surveillance system or health personnel;
- design and implement new etiologic studies, including GEI studies;
- obtain information on exposure by linkage with other sources (e.g. envirovigilance data).

It is essential
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health system ...

Collection of data must be planned in view of different study design needs (e.g. level of exposure – in particular for individual or community measures, selection of healthy or sick controls, availability of parental data for triad designs). The registration form must take all these needs into account. It is essential that a birth-defect registry can be integrated into the public health system at the same administrative level (regional, national) so that results can be effectively used in the setting that has produced the information.

The general guideline methodologies and procedures will focus on a CFA registry, presenting performance indicators of the CFA registration activity.

4.2 ICBDMS: interregional experience

The International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) was established in 1974 to encourage an international exchange of data and collaborative research in the field of birth defects. It is an independent, non-profit organization, accepted in 1986 as an NGO in official relations with WHO.

The International Centre for Birth Defects (ICBD), located in Rome, Italy, serves as the headquarters for ICBDMMS, coordinating its monitoring activities and collaborative studies, regularly producing an annual report, newsletters and reports on monitoring.

The major activity of the ICBDMMS is to monitor changes in the prevalence of birth defects and, with all its participating programmes combined, to monitor a very large population with almost three million births each year. At present (2002), there are 36 participating programmes, representing 34 countries spread across the five continents. One programme (in South

America) includes hospitals in 12 different countries, while several countries – Canada, China, France, Italy and the USA – are each represented by two or more programmes.

The ICBDMs performs international collaborative research on a very large scale; the problems it faces because of the heterogeneity of the various registries are counterbalanced by the beauty of diversity. The final results are regularly published in international scientific journals.

Further information on the ICBDMs can be found at www.icbd.org.

4.3 ECLAMC: the Latin American experience

This description of the Latin American Collaborative Study of Congenital Malformations (ECLAMC) concentrates on the present pitfalls to function as a registry of OC, in an attempt to identify possible solutions for the future. ECLAMC is a hospital-based, non-institutional, non-governmental, voluntary, collaborative research project for congenital anomalies and has operated in about 100 South American maternity hospitals since 1967.

4.3.1 Oral clefts epidemiology and the DNA bank

The epidemiology of oral clefts in ECLAMC can be summarized as follows:

- **For both CL/P and CP:** stable secular trends over the 33-year period (1967-1999) for isolated cases, and significantly rising trends for syndromic cases.
- **For CL/P:** a significant association with high altitude (above 2000 metres), male sex, twinning, low socioeconomic class, maternal illnesses, self-medication and parental consanguinity.
- **For CP:** a significant association with the female sex, twinning, low socioeconomic class and self-medication.

Since January 2000 ECLAMC has maintained a DNA bank for all major malformations, as well as for a randomly selected sample of non-malformed newborns. Until July 2001, the stored material included DNA samples from 7546 healthy newborns and 1447 malformed newborn/mother dyads, including the following CFA:

- 336 cleft lip, with or without cleft palate,
- 73 cleft palate,
- 40 microtia, and
- 46 holoprosencephaly cases.

4.3.2 ECLAMC – pitfalls as a registry

Hospital-based
systems fail
to cover real
populations ...

Incomplete coverage: Hospital-based systems are best applied in low- to middle-income countries where statutory statistics are unreliable or missing. However, unlike their counterpart (population-based systems) they fail to cover real populations. In South-America, the ± 100 reporting hospitals that are scattered over 9 of the 10 participating countries failed to identify 3 known geographical clusters for OC. Those were:

- the Baurú syndrome in São Paulo state, Brazil – where this meeting took place (Gorlin, Cohen & Hennekam, 2001) ;
- non-syndromic CL/P associated with a mutation of PVRL1 in Margarita Island and the Cumaná seaside in Venezuela (Sözen et al, 2001); and
- a high prevalence rate for OC, based on a longstanding “rumour”, in Patagonia (Castilla & Sod, 1990).

Under-ascertainment of minor forms: In spite of the fact that ECLAMC registers minor defects including birthmarks on the skin, some microforms of oral clefts are under-ascertained. These include sub-mucous CP, uvula bifida, and notched gum at the maxillary-palatal junction level. Registered birth prevalence rates per 100 000 are:

- sub-mucous CP: 0.6,
- uvula bifida: 1.2, and
- notched gum: 1.1.

Even though some of these microforms may be unrelated to typical OCs, actual evidence is still needed, as shown by the following findings on congenitally “healed” cleft lip. The epidemiology of congenitally “healed” or “frustre” cleft lip was first reported in the combined material of ECLAMC and ECEMC (a similar Spanish study). Twenty-five cases were ascertained from four million observed births (1/160 000 births). The lack of previously published figures caused difficulty in establishing the ascertainment rate for this defect, but under-registration was likely. This anomaly could be a variant of CL, as suggested by its preponderance in the male sex and on the left side. The combined data also had a record of two families with joint segregation of open CL and healed CL. The existence of ipsilateral notched vermilion and collapsed nostril favours the pathogenesis of an intra-uterine spontaneously repaired cleft (“healed” in the English literature), rather than an incomplete cleft (“frustre” in the French literature) (Castilla & Martínez Frías, 1995).

Under-ascertainment of syndromes: Most of the nearly 300 recognized syndromes, including OCs, are seldom registered by ECLAMC in newborn infants.

Incomplete family histories: Even though ECLAMC records complete family histories for all malformed and matched control infants, relatives are not examined by the reporting physician. Thus, there is no careful examination of the lower lip or searching for bilateral pits even in the mother who is present during the history-taking before discharge from the maternity hospital. As a result, only four cases of van der Woude syndrome have been recorded among the four million examined births. This is considered to be under-registration for such a well-known syndrome.

4.3.3 Possible solutions

Some of the above-mentioned pitfalls in the ECLAMC system could be reduced by implementing the following strategies:

- **A malformation-specific registry** could be nested into the ECLAMC system. An OC registry could easily extend its geographical coverage in this way, following up cases and families for a minimum period of two years and interacting with the community (support organizations) and local health authorities for the benefit of patients and their families.
- **Oral physical examination of the newborn**, a no-man's land lying between the responsibilities of medicine and dentistry, is frequently disregarded. Participant paediatricians should be trained in transillumination and digital palpation of the palate, careful observation of the gum, gum-labial bands, tongue ties, lower lip pits and fistulas, both in the newborn and in the mother.
- **A postnatal follow-up** would greatly improve the detection and identification of syndromes for the benefit of families through sound genetic counselling. Follow-ups can be ensured by OC registries since they exist with other registries (congenital heart diseases, cytogenetics, cancer, twins, etc.) (Last, 1995). Such other registries may easily overlap with pre-existing birth-defect surveillance systems (Källén & Winberg, 1979) or could even become the bases for future systems if there were none in the area.

4.4 EUROCAT: European experience

The EUROCAT project, supported by the European Union, represented by the Commission of European Communities, focuses on the epidemiological surveillance of congenital anomalies in Europe. Surveillance is based on a network of regional registries coordinated by a central registry. The participating registries use the same epidemiological

methodologies and their general characteristics have been described elsewhere (De Wals, Weatherall & Lechat, 1985). The EUROCAT database provides the opportunity to perform a large descriptive epidemiological survey on OC throughout Europe and obtain further insight on OC epidemiological and genetic features.

Further information on EUROCAT can be found on its web site: www.eurocat.ulster.ac.uk.

BOX 14**Aims of the EUROCAT Registry**

- Provide essential epidemiological information on congenital anomalies in Europe.
- Facilitate the early warning of teratogenic exposures.
- Evaluate the effectiveness of primary prevention.
- Assess the impact of developments in prenatal screening.
- Act as an information and resource centre regarding clusters or exposures or risk factors of concern.
- Provide an established collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children.
- Act as a catalyst for the setting up of registries that will collect comparable, standardized data throughout Europe.

4.4.1. The EUROCAT Oral Cleft Project

The 1980-1996 EUROCAT database includes 9553 cases with CP, or CL/P collected by 31 registries. This European network of population-based registries for the epidemiological surveillance of congenital anomalies, covers more than 900 000 births per year. It also comprises data on terminated pregnancies, in accordance with the EUROCAT guidelines. Validation and classification procedures have been performed on a sub-file that includes all eligible OC cases provided by the EUROCAT central database. Each individual record is classified into isolated, multiple congenital anomalies, chromosomal anomalies, sequence, syndromes and/or recognized conditions.

BOX 15**Objectives of the EUROCAT OC Project**

- Assess quality of data, i.e., completeness, validity and homogeneity amongst registries.
- Split cases into isolated, associated or recognized conditions.
- Describe the variation of the different types of OCs with regard to geographical patterns and temporal trends.
- Produce an epidemiological description of the different OC types according to selected variables, such as sex ratio, birth weight, gestational length and maternal obstetrical history.

The relevant heterogeneity highlights the need to analyse data of the different OC types ...

4.4.2. Results and comments

A total of 9553 oral cleft cases were recorded among 6 242 763 live births and stillbirths in the EUROCAT database. Among these cases, 65.7 % occurred as isolated anomalies. Among the isolated cases, 73.5% were CL/P. Isolated atypical clefts were diagnosed in four cases. In 1732 cases (18.1 %), an OC occurred with a recognized condition, and in 1610 cases (16.1 %) it occurred with multiple congenital anomalies of an unknown nature. OC in chromosomal aberrations were observed in 1542 cases (16.1%). The birth prevalence rate of all OC cases was 15.3 (CL/P = 9.0 and CP = 6.2) per 10 000 births.

The proportion of terminated pregnancies following prenatal diagnosis was small (4.5 % for CP; 11.8 % for CL/P), and generally related to more severe anomalies associated with OCs. The detection rate diagnosed by ultrasound was 27% for CL/P and 7 % for CP.

The relevant heterogeneity observed among centres highlights the need to analyse data of the different oral cleft types, taking into account the available knowledge of genetics, genetic susceptibility and environmental conditions in the different European areas, particularly with reference to the distribution of gene variants and nutritional habits.

4.5 NBDPN: North American experience

The National Birth Defects Prevention Network (NBDPN) is a group of individuals involved in birth-defect surveillance, research and prevention. The need for such a group was originally discussed in an informal meeting of interested individuals, held in conjunction with the CDC's Maternal, Infant, and Child Health Epidemiology Conference in Atlanta in December 1996. As a result of that meeting, Charlotte Druschel, MD, and

Russell Kirby, PhD, agreed to co-chair the NBDPN during its start-up phase.

Subsequently, in February 1997, several individuals who had expressed interest in serving on the planning workgroup for the NBDPN met at CDC to establish a mission statement and objectives for the new organization. In addition, several committees were formed and a number of priority activities for the network were outlined. To date the NBDPN has held four annual meetings which involved plenary sessions, concurrent workshops and business meetings to elect committee chairs and conduct committee business.

Further information on NBDPN can be found at www.nbdpn.org.

BOX 16

Aims of the NBDPN project

- Improve the quality of birth-defect surveillance data.
- Promote scientific collaboration on the prevention of birth defects.
- Provide technical assistance for the development of uniform methods of data collection.
- Facilitate the communication and dissemination of information related to birth defects.
- Collect, analyse and disseminate state- and population-based birth-defect surveillance data.
- Encourage the use of birth-defect data for decisions regarding health service planning (secondary disabilities prevention and services).

4.5.1 NBDPN results

Based on the experience of the NBDPN, Larry Edmonds from the National Center on Birth Defects and Developmental Disabilities, CDC, presented a comprehensive analysis of the costs involved in registering oral clefts by different systems (Edmonds, 2001).

Birth prevalence rates per 10 000 live births of OCs obtained from various data sources show the expected under-registration of statutory and mandatory systems, as compared with active search for cases. However, the range is minimal, probably due to the conspicuousness of this type of congenital anomaly.

Table 8: Summary of birth prevalence rates

Type of source	Source	Rate
Linked data sources	Colorado, 1990-1991	10.0
Active hospital surveillance	MACDP*, 1990-1991	9.9
Hospital discharge data	BDMP**, 1990-1991	8.6
Birth certificates	1990-1991, excludes 5 States	8.5
Mandatory hospital reporting	New York, 1990-1991	7.8

* MACDP: Metropolitan Atlanta Congenital Defects Program, started 1968.

** BDMP: Birth Defects Monitoring Programme, started 1974.

The estimated costs of birth-defect surveillance (in US dollars) by different methods are summarized in the following table. However, it should be noted that these are *estimates* and can vary greatly depending on the particular methodology used.

Table 9: Costs of birth-defect surveillance by different methods

Method	Quality of data	Cost per live birth	Cost* per case	Cost* for 50 000 births/year
Birth certificates	Poor	None	None	None
Mandatory hospital reporting (no follow-up)	Fair	1-5	25-125	50 000-250 000
Mandatory hospital reporting (with follow-up)	Good	5-10	125-250	250 000-500 000
Intensive surveillance	Best	10-30	250-750	500 000-1 500 000

* Cost in US dollars.

Source: Larry Edmonds, NDBPN

It is clear that the best quality data are obtained from the more expensive, active systems. The ideal source/s of data must be decided upon for each planned study according to aims and resources.

5

Data collection aimed at supporting research

5.1 The European Science Foundation Project

For CFA research, consistent protocols across populations are fundamentally important. The following summary contains a proposal for the use of the “European Science Foundation (ESF) Common Core Protocols Project – Minimum Data Sets” for ongoing GEI research, tailored towards a case triad study design. This will provide guidelines on the core information required in eight different areas and will provide some rationale for the recommendations. Apart from the core data, information on the development of further desirable and/or optional data will also be provided where applicable.

It is noteworthy that a complimentary and collaborative group of international scientists based in the US, the International Consortium for Oral Clefts Genetics, also produced a document entitled *Guidelines for the design and analysis of studies on non-syndromic cleft lip and cleft palate in humans*. The report of this was published in the *Cleft Palate Craniofacial Journal* (Mitchell et al, 2002).

The following is a summary of the deliberations of the ESF Special Interest Group on Cleft Lip and Palate.

5.1.1 Case ascertainment: recommendations for core information

Orofacial clefting (OC) is a heterogeneous group of defects with a considerable range of severity so there is, inevitably, variability in the ascertainment rates. The information collected should be divided into essential, desirable and optional.

BOX 17

Core information recommended for case ascertainment

Essential information:

- Base ascertainment of congenital anomalies and precise diagnosis on multiple sources of information.
- Make it clear if terminations and fetal deaths are included and, if so, describe the inclusion criteria and methods used.
- Include multiple anomalies and syndromes.
- Present all epidemiological and genetic data by specific cleft type.
- Differentiate between CP and CL/P and, where possible, subdivide CL and CLP.
- Subdivide each cleft type by the presence or absence of associated congenital malformations.
- Separate syndromic cleft cases from non-syndromic cases.

Desirable information:

- Record the type of classification and how this was done for syndromic cleft cases that are separated from non-syndromic ones, for example, where classified by a dysmorphologist.
- Tally birth prevalence statistics for clefts separately for familial and sporadic cases; this will further benefit risk-factor studies.
- Record late-diagnosed cases.
- Code congenital anomalies, minor anomalies, and give precise diagnoses.

Optional information:

- Diagnose all degrees of cleft expression (including sub-mucous clefts) to prevent under-ascertainment.
- Where possible, present data within countries by ethnic group.
- (Ideally) collect data sets containing core information agreed by consensus; additional information can be collected for studies in suspected high-risk population subgroups.
- In preparing incidence data to support genetic and other etiologic studies, include all terminated pregnancies and stillbirths or make appropriate adjustments.
- Make diagnoses more specific as further investigation is performed.

5.1.2 Clinical assessment of oral clefting: recommendations for core information

- 1) Record basic demographic information, including basic lifestyle data.
- 2) Follow guidelines for recording of baseline (neonatal) minimal-record data sets.
- 3) Take photographic records; if possible standardized extra-oral and intra-oral views.
- 4) Have access to clinical dysmorphology expertise, if possible a clinical geneticist/dysmorphologist.
- 5) Use an internationally recognized system of coding and subsetting for CFA.
- 6) Use an internationally recognized system for cleft classification.
- 7) Record pre-natal diagnosis, ultrasound or maternal serum screening.
- 8) Diagnose isolated CP subsets, e.g., 22q11 deletions; and, where applicable, cleft lip and palate subsets. (*See also Box 17 above.*)

5.1.3 Nutritional factors and food frequency questionnaires: recommendations for core information

Nutrition remains one of the most eligible aspects of orofacial clefting research.

- 1) For core nutritional data, compile a food-frequency questionnaire to assess total energy intake.
- 2) Report nutrient intake.
- 3) Make the questions population-specific.
- 4) Validate data by comparing it with relative ranking obtained by another method, such as diet, diary or weight record.
- 5) Include vitamin supplements and food fortification.
- 6) Consider whether food-frequency questionnaires are the optimum method to obtain nutritional data. Minimum requirements might include food fortification, and multivitamin supplements.
- 7) Use food-frequency questionnaires only for relative ranking of reported intake and not as a measure of absolute intake.

5.1.4 *Lifestyle and environmental factors: recommendations for core information*

- 1) Collect data on lifestyle exposures, such as smoking and alcohol, during pregnancy (first trimester); regard these as core data.
- 2) Include occupational exposure and recreational drugs when examining congenital abnormalities; these are desirable and optional additional data but are difficult to collect and analyse consistently.
- 3) If socioeconomic status is to be examined, consider what the most consistent measures of this would be – education, housing, postal code, occupation, other lifestyle factors, a combination of these or something else?

5.1.5 *Obstetric and medical history: recommendations for core information*

- 1) Include illnesses and medications in the first trimester as minimum data.
- 2) Record the obstetric history.
- 3) Enter date of conception.
- 4) Describe birth-control methods.
- 5) Record timing of awareness of pregnancy.
- 6) Ask if the mother suffered from morning sickness.
- 7) Record medical history of illnesses, including common ailments such as colds and influenza, as well as any specific medical conditions that may have implications for birth defects.
- 8) Note any drug therapy as this would be related to the medical conditions.
- 9) Tailor the questions on drug therapy to the hypothesis, such as anti-convulsants; also record epilepsy/anti-epileptics, radiotherapy or X-ray exposure.
- 10) Tailor hypothesis e.g., folate and the folate antagonist drugs, such as methotrexate, anti-malarials etc.
- 11) Record other aspects of medical history specifically related to the hypothesis being tested, e.g. vitamin A teratogenesis, accutane, etc.
- 12) Record previous obstetric history in terms of number of siblings, previous stillbirths or other related congenital abnormalities.

5.1.6 Biochemical assays: recommendations for core information

There are four main issues that relate to the methods of **sample collection, processing, storage, and analysis**. These are dependent on the hypothesis under test and/or the purpose for which blood or other tissue samples are being collected. As an example, where the study proposes to investigate nutritional biochemistry, the core data set in OC should include:

- full blood count,
- red cell folate,
- plasma folate, plasma vitamin B 12, plasma homocysteine,
- other assays, plasma vitamin B2 and B6,
- methylmalonic acid,
- genetic analysis,
- vitamin A and other nutrients,
- immortalized cell lines obtained from lymphocytes.

5.1.7 Genetic protocols and assays: recommendations for core information

Molecular genetic factors in OC, DNA, polymorphisms, adjacent to or within the candidate genes aim at identification of etiologic genetic loci. Case-control triads remain the “gold standard”, case-only design has limited usefulness, but nuclear triads have several advantages (and a few drawbacks).

- 1) For congenital birth defects such as OC, a common core protocol should pursue case triads and the subsequent genetic analysis protocols should include:
 - transmission disequilibrium test (TDT),
 - parent of origin, effects and imprinting,
 - chromosomal deletions,
 - uni-parental disomy.

Information should also be included on:

- 2) Method of collection of samples, alternative methods:
 - buccal cells via saliva samples, cytology brushes or cotton swabs,
 - dried-blood spots (Guthrie cards),
 - blood samples.
- 3) Candidate genetic loci for OC – five overlapping categories:
 - genes expressed during palatogenesis with temporal and spatial specificity to clefting,

- chromosomal deletions, duplications or translocations causing OC,
- genes or loci identified in animal models,
- genes that possess or control specific biological activities that may explain orofacial clefting,
- genes at genome locations identified by genetic linkage.

5.1.8 Family history: recommendations for core information

Core information could be subdivided as follows:

- 1) **Minimal information (compulsory):**
 - for the family history include immediate family as first-degree relatives, i.e. grandfather and grandmother on both sides; all fathers' siblings and paternal first cousins; all mothers' siblings and maternal first cousins;
 - record malformations in the family;
 - design the questionnaire so that, to maintain confidentiality, nominal information will be collected but not computerized.
- 2) **Complete family history:**
 - a desirable option is to employ an interviewer, trained in family investigation, to obtain greater detail using a more complete, in-depth family-history questionnaire on both maternal and paternal sides, plus information on other CA and familial diseases.
- 3) **Blood samples:** Collect blood samples from relatives to enable genetic analysis to be performed, including:
 - all siblings, whether affected or not;
 - affected relative/s (other than parent or sibling);
 - blood sample/s from any relative/s in the affected branch of the family.

5.1.9 Bio-ethical issues: recommendations for core information

- 1) Include minimum data on legal requirements and guidelines with respect to informed consent, confidentiality and the principles of medical research espoused in the Declaration of Helsinki.
- 2) For multi-centre international collaborative research that involves genetics, specific areas of ethics and confidentiality need to be applied.

6

Setting up a global web-based database: is it feasible?

6.1 How to create a global database

In order to learn more about the possible genetic and environmental causes of CFA (and their interactions), comparable population data sets, collected over similar time periods and from many different geographical localities, need to be analysed. Storing and exchanging this data via a global database is desirable. However, there are a number of questions that need to be answered in order to create such a database. The potential answers to these questions will have to be examined and the remaining gaps in our knowledge on how to construct the database identified.

First, the most fundamental requirement in planning the database is to have access to people with training and skills in both biological/medical and computational/programming methods. Without such people on the design team, there will be a real risk that simple misunderstandings of terminology could lead to poor design and/or implementation of the database.

Second, the experience of some research teams working with global data on cancers in children (Dr Jim Kepner, Children's Oncology Group, Florida, USA) and in adults (Professor Bruce Armstrong, New South Wales Cancer Council, Australia), has confirmed the existence of two major problems:

- to have access to record linkage software, and
- to ensure the integrity of database queries.

Without adequate record-linkage software, important sources of historical, clinical and environmental exposure data may not be available. Geo-coding of current address data may not be possible so important spatial information on the distribution of cases can be lost. Even with the best designed databases, human misunderstandings and errors may lead to the unintentional extraction of data files that are not validly comparable between the participating research teams.

Any endeavour
to create a
global database
will demand
adherence to
strict security
measures ...

It is desirable to include DNA samples within the collection and to have access to the best gene-sequence and protein databases. Modern micro-array analysis of DNA creates large multidimensional data structures. However, the data analysis software supplied with commercial micro-array equipment does not usually offer the full range of statistical analysis tools required by research teams. It is highly desirable that computing software and hardware interfaces easily with the laboratory equipment. With such an interface, data files can be analysed by common statistical packages such as SPlus, SPSS, BMDP and SAS. Analysis using neural network software may also be useful in situations such as CFA research where the causes of the defects are thought to be multi-factorial in nature.

Once established, the database may be used for the registration of clinical trial participants (requiring randomization in real time) as well as for collaborative research on existing data. Existing data collections may need to be imported via a batch-loading process, with complex rules applied prior to importation in order to ensure the integrity of the data. Other issues of relevance to the design of the database include resources available for funding and maintenance, authentication of users, local versus central coding of data, identification of duplicate entries, and tracking participants over time and across centres.

In conclusion, any endeavour to create such a database will demand adherence to the strictest security measures possible in order to safeguard the highly sensitive personal data. If the data were to be exchanged via the Internet, the need for security and ease of access would have to be balanced by the need to ensure that the performance of the database allows quick access to data and information for all collaborators.

6.2 Linking bioinformatics to a proposed web site

In order to gain experience in the field of web site design and development and, in particular, in the linking of bioinformatics facility to a proposed web site, expertise was sought from those involved in the creation of facilities in two exemplar projects:

- Dr Olivier Cohen (*see Section 8, List of participants*) has been developing a bioinformatics platform dedicated to medical genetics in France to allow statistical information to be extracted from the database and to make it available to the medical and research communities through a web site.
- Dr Douglas Bratthal, (*see Section 8, List of participants*) is Director of the WHO Oral Health Country/Area Profile Programme (CAPP) created in January 1996, the purpose of which is the presentation of

a wide range of information on the Internet on dental and oral diseases.

6.2.1 *A web site based on an international human genetic database*

Dr Olivier Cohen has been developing a generically secured bioinformatics platform dedicated to medical genetics in France. The aim of this platform is to allow statistical information to be extracted from the database and to make it available to the medical and research communities through a web site. This information includes genetic nomenclatures and the patient data are described according to the familial genealogy. The database takes into account the different facets of the genetics, such as the clinical, chromosomal and gene aspects.

The web site provides users with information and anonymous data, related to genetic diseases, from the database. International nomenclatures are the basis for describing the chromosomal and gene-mutation features. The *London Dysmorphology Thesaurus* generates descriptions of clinical features from a list of syndromes and symptoms, according to a standard procedure.

The platform was initially dedicated to familial structural rearrangements of chromosomes that concern about one couple in 200. For a given chromosomal anomaly, the web site provides geneticists with assistance in diagnosis and genetic counselling. In real time, the user can get an ideogram of the rearranged chromosome according to international nomenclature (ISCN 1995), the assessment of the risk of imbalance at birth with a confidence interval, and specifically related papers. For research workers, interfaces exhibit the distribution of chromosomal breakpoints and genome regions observed at birth in trisomy or monosomy. These interfaces are interactive and allow the user to make contact in real time; 1000 contacts from about 50 different countries are currently users.

Impact at an individual level: The definition of individual risk factors is of a great importance. Indeed, each carrier has specific risks of imbalance at birth and miscarriages, varying from 0 % to approximately 80 %. Concurrently, different prenatal diagnostic strategies could be proposed, such as amniocentesis or chorionic villus sampling (CVS). The knowledge of the risk of imbalance at birth for each carrier allows for the proposal of a strategy based on objective reasons. Many factors have to be taken into account but, specifically considering the level of risk of imbalance at birth, the best strategy is that for which the risk of imbalance is greater than the iatrogenic risk.

The aim is to make statistical information available to medical and research communities through a web site...

Impact at population level: Since familial structural abnormalities of chromosomes are frequent, the impact of a risk assessment at population level is also very high. An initiative to conduct risk assessment could lead to better patient management with a consequent decrease of:

- handicaps prevalent in children (i.e. handicaps linked to the unbalanced chromosomal abnormalities);
- maternal morbidity (linked to repetitive reproduction failures or late pregnancy terminations);
- iatrogenic fetal loss (linked to CVS carried out when low risk of imbalance exists).

Giving more accurate information to the carriers should increase the understanding of their respective families – who are the actual targets of prevention. Indeed, it is only the patient who can inform his or her direct family members that each of them could be a carrier and can request a simple blood karyotype for screening. The importance of familial investigations is currently emphasised in genetic counselling consultations, but an educational initiative dedicated to the carriers and their families should increase targeted screening with a minimal cost-efficiency ratio.

Monogenic diseases: Using the MIM nomenclature, monogenic diseases can be considered. After registering the individual phenotypic expressions, the chromosomal status and the gene mutation description, the user can send data including the pedigree, through the Internet.

Increased security with smart cards: Each user needs a dedicated smart card to access genetic records. The smart card permits formal authentication by checking with a central electronic directory that certifies the user's identification and qualification.

Thematic networks: In order to improve collaborative networking, which is particularly useful in case of rare diseases, each user can ask for a thematic network to be opened. After agreeing on a charter of use, validated by legal experts, the user becomes the coordinator of that particular network. A diagnostic validation committee controls the quality of the records provided by users who have decided to share their data through the network.

6.2.2 Planning and managing the WHO Oral Health database

Considering the wealth of information available in the oral health field in the early 1990s, there was an urgent need to share it via the Internet in a standardized format that would make the data instantly available to thousands of users. The WHO Collaborating Centre at Lund/Malmö University in Sweden, that not only had wide experience in epidemiology

The main purpose of the CAPP web site is to present information on dental and oral diseases ...

and electronic communications, but was already an established Internet server, was approached for assistance in building, developing and implementing a pilot programme for such a database. The Centre responded positively and several proposals were presented and discussed. Finally, a model that included maximum input and participation from different sources was agreed upon and presented to other collaborating centres and organizations involved in the oral health project. A server to focus on periodontal diseases was simultaneously established at Niigata University, Japan.

Thus conceived, the WHO Oral Health Country/Area Profile Programme (CAPP) was created in January 1996; its main purpose being the presentation of information on the Internet on dental and oral diseases, including data for every country on the availability of its oral health services, dental education and manpower. To avoid a massive build-up of data sets over time, the programme structure was designed so that it would be easy to find and update data and images. Also, to facilitate access from computers with low or moderate capacity, a simple, “non-fancy” design was chosen for the web pages. Most importantly it was decided that, in order not to be dependent on outside expertise, all programming would be done by the WHO department involved.

The Home Page (<http://www.whocollab.od.mah.se/index.html>) of the CAPP has five sections:

- Main CAPP pages,
- About and Help,
- Links,
- Projects and Reports,
- Messages.

In the *Main CAPP pages* section, the user can select a country by either clicking on the list of countries arranged in alphabetical order or by selecting the list compiled on the basis of the WHO regions. Once a country is selected, a page specific for that country appears, showing the topics of the data available, such as:

- general information on the country, e.g. gross domestic product (GDP) and life expectancy,
- oral diseases including caries, tooth mortality and fluorosis,
- oral health manpower,
- dental education,
- oral health care system and services and, lastly,
- information relevant to oral health and care.

This means that each country has several pages of information under different topics. Another section includes *Methods and indices* – a much-used source of information for users who are planning and/or performing studies.

Topics such as oral mucous-membrane diseases or CFA, which are usually not routinely included, can also be presented when standardized study data are available. The ease with which the format and presentation of the data can be modified, and the programme instantly updated and made available to Internet users all over the world, is a major advantage of the CAPP. Furthermore, an active exchange of ideas, questions and comments from users is available through the e-mail service provided on CAPP's home page.

The presentation of CAPP on the Internet has made oral health information available globally. CAPP data can be updated on a daily basis. Information and further clarification is requested by many users of CAPP, including government bodies, universities, companies and private individuals. According to the log, the server was approached during its first year (1996) by more than 15 000 different computers (hosts) and from October 2000 to October 2001, more than a million requests for information from about 70 000 hosts were received. These figures clearly illustrate the growing need for this database and its usefulness all over the world. The number of individual requests recently exceeded 3000 per 24 hours – indicating the future scope and potential of CAPP.

7

Proposal and practicalities for a global registry and database on craniofacial anomalies

7.1 A global registry for craniofacial anomalies

The basic idea, as discussed at the Baurú meeting, is to create a master database – or registry of registries - that maintains the individuality and independence of each of the contributing programmes with all their valuable diversities and flexibilities, and is capable of being adapted to cover the large variety of different social, economic, political and cultural situations. In spite of the diversities, a common core of similar standard data on clefting and other craniofacial birth defects can be found and successfully shared in a central pool for the purpose of global research.

7.1.1 *Rationale and aims*

The rationale for the registry is that it will identify global variability in the prevalence of craniofacial birth defects, estimate the burden of need for public health services, identify priorities and underpin research initiatives that will address primary and tertiary prevention.

This proposal can be envisaged as a disease-specific “registry of registries”, or a global coordinating registry, dealing with craniofacial congenital anomalies in general, but starting specifically with the most frequent and relevant anomalies: OC, including CL/P, and CP. Other CFA could be added in the future.

BOX 18

Aims and objectives of a CFA registry

The general objective of a global registry for CFA is to systematically “register” CFA cases within the classical definition of a register, namely, to detect, enlist and follow up (Last, 1995), in order to build a worldwide collaborating network and an active database, capable of providing material and coordinating the following activities:

- **Surveillance:** Monitoring, searching for geographical clusters, etc.
- **Promotion:** Creating, helping and supporting local registers and centres.
- **Expertise:** Providing expertise from a worldwide net of experts and an available task force.
- **Prevention:** Creating, recommending and conducting public health activities.
- **Community outreach:** Actively interacting with support organizations.
- **Education and training** with worldwide coverage.
- **Research:** Assisting with research, such as temporary activities aimed at specific objectives.

7.1.2 Structure

Based on the principle that no ideal registry exists, the main characteristic should be *flexibility* in order to benefit from the existing diversity of methodologies of registration, allowing for better adaptation to the range of economic development worldwide, different cultures, and levels of interest in this type of disease (Källén et al., 1992).

The global registry could enrol participating members into different levels of activities, with the understanding that a given participant may be suitable for only particular activities. Several levels of participation could be established.

BOX 19**Possible levels of participation**

- **Surveillance, including periodic (quarterly and/or annual) exchange of data for monitoring purposes and for other surveillance activities:** Population-based and governmental systems would be more appropriate for this activity. A minimal core of exchanged data elements would be provided (*see para. 7.1.3 below*).
- **Registry and follow-up of cases, also specialized clinics with no denominators (e.g., Centrinho in Baurú):** Hospital-based systems, isolated clinics and other case repositories would be better adapted to this activity.
- **Research, including different levels of research (epidemiology, clinical dysmorphology, family studies, molecular analysis, etc.):** The feasibility of participating in this activity would depend on the specific project design, and for any particular research, the contribution of only some member systems would be expected.
- **Other activities, such as public health, community outreach, education and training, etc.,** could allow for the participation of all members, and membership could even extend to parent-patient associations, and other organizations dealing with CFA.

7.1.3 Core data elements

An agreed core or minimum dataset is an essential resource for surveillance/registration of a birth defect. This data must be available as a central and accessible resource, along with recommendations that may assist in those areas of the world that do not have such data available (*see Annex*).

BOX 20**Core data elements for CFA cases, case by case**

- identity number,
- birth date (month and year),
- place of birth (municipality),
- place of residence of mother during pregnancy (municipality),
- status (live birth, stillbirth or interrupted pregnancy),
- sex (male, female, intersex),
- twinning (no, yes/like-sexed, yes/unlike-sexed, yes/unknown sex),
- birth weight (grams),
- mother's age (years),
- parity (gravity or birth order).
- **For all births: aggregated monthly data (denominators).**

For monitoring purposes, the same information should be available for all examined births. A summary table recording the data collected could be used by each registry on a monthly basis, even if it is only submitted annually (*see Annex, Figure 6*).

7.1.4 A possible corporation

A Global Registry of Craniofacial Anomalies could be organized under the umbrella of the World Health Organization, using existing facilities. It could be housed in Rome by the ICBBD (International Centre for Birth Defects, which is the ICBBDMS headquarters) where it could profit from the following aspects of the ICBBD:

- global coverage,
- methodological flexibility,
- WHO-NGO status and inclusion of several WHO Collaborating Centres,
- recognized international expertise since 1974.

To hasten implementation of this new registry, the following four major networks that detect birth defects could be invited to provide data as initial members: ECLAMC, EUROCAT, ICBBDMS, NBDPN.

7.2 Proposal for the WHO/NIH Global Registry initiative

7.2.1 Create an international registry of oral clefts

Multiple sources will be used to collect cases:

- existing birth-defect registries,
- surgery clinics,
- parents' associations,
- any other possible source/s, to be identified country by country, area by area.

For each case a minimal data set of information will be collected: patient's identity (ID) and basic personal characteristics, type of cleft, possible associated anomalies. Where possible, or for selected sources only, more complete information will be collected, including family history, postnatal care and, perhaps, blood spots. Basic data will be used for simple descriptive epidemiology, but more sophisticated studies might be possible using more detailed data from a subset of participating registries.

A worldwide registry of oral clefts could almost be organized under the umbrella of WHO, through the use of existing facilities of the ICBBDMS. This registry could also be based in Rome, Italy at the ICBBD which is currently the ICBBDMS headquarters.

The ICBBD has the considerable advantages of:

- global coverage ,
- methodological flexibility,
- WHO-NGO status and inclusion of several WHO Collaborating Centres,
- recognized international expertise since 1974.

In the first instance, four major existing networks for detecting birth defects could be invited to provide data to the Global Registry at ICBBD as initial members for promptness of implementation, namely: ECLAMC, EUROCAT, ICBDDMS, NBDPN.

7.2.2 Create and maintain a directory of resources

A directory of resources would include a database on all possible information and resources on oral clefts around the world (published articles, books and other relevant documents; lists of institutions and researchers; funding bodies; treatment centres and other bodies concerned with CFA research). The following areas would be considered:

- **Genetics:** An update on research programmes, research teams and genetic clinics that at present aim to identify etiologic causes of non-syndromic OC through family-based studies and search for candidate genes.
- **Prevention:** Special attention would be given to reviewing evidence regarding the role of specific maternal nutritional factors and to making recommendations on the resources needed to implement international collaborative studies of cleft prevention with common core protocols.
- **Gene-environment interactions:** Descriptions of the state-of-the-science, would describe and highlight relevant research.
- **Treatment:** Identification of optimal clinical interventions for the management of oral clefts (evidence-based care), identification and dissemination of strategies to optimize the quality of care delivered, identification of strategies to increase the availability of care to all affected citizens in the world.

7.2.3 International Database on Craniofacial Anomalies

The International Database of Craniofacial Anomalies (IDCFA) is an initiative to help researchers all over the world to better understand the epidemiology of CFA and the epidemiology of health care related to persons with a CFA. It is a database with data being contributed by any collaborating organization in the world. Representatives of all the major

organizations contributing to the database serve on its Steering Committee: ECLAMC, EUROCAT, ICB, ICBMS, NBDPN, and WHO's Human Genetics Programme (WHO-HGN).

ICB is the coordinating office of the IDCFA (Coordinators: Pierpaolo Mastroiacovo and Elisabeth Robert-Gnansia), and most of the members of the above-mentioned member-programmes are contributing registries. Data are stored in an agreed-upon format, and the database is updated case by case every sixth month. The database is accessible through a password to collaborators who wish to consult or use it for a special study, after permission is obtained from the Steering Committee. Confidentiality and data protection are guaranteed by a complete set of data security rules, established for the use of any data in the frame of ICB.

8

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Annex

Table 1	Cleft lip with or without cleft palate
Table 2	Cleft palate without cleft lip
Table 3	ICBDMS synopsis of 28 monitoring systems, and prevalence rates and secular trends for oral clefts
Figure 1	Cleft lip with or without cleft palate (bar chart)
Figure 2	Cleft palate without cleft lip (bar chart)
Figure 3	Cleft lip with or without cleft palate (maps) a) The Americas b) Asia, Australia and Oceania, Africa, Middle East c) Europe
Figure 4	Cleft palate without cleft lip (maps) a) The Americas b) Asia, Australia and Oceania, Africa, Middle East c) Europe
Figure 5	Rates for cleft palate and cleft lip with or without cleft palate, 1980-1996
Figure 6	Monthly report form for examined births

Table 1: Cleft lip with or without cleft palate

Programme	Years		Cases	Births	Rate per 10 000	95% CI*		Trend
	from	to				lower	upper	
Bolivia	93	98	78	34 007	22.94	18.13	28.62	
Japan – JAOG	93	98	993	619 107	16.04	15.06	17.07	
Paraguay	93	98	24	16 108	14.90	9.53	22.17	
Germany – Saxony-Anhalt	93	98	71	50 947	13.94	10.88	17.58	
China – CBDMN	97	98	814	598 316	13.60	12.69	14.57	
Northern Netherlands	93	98	157	116 337	13.50	11.47	15.78	
Norway	93	98	483	360 906	13.38	12.22	14.63	
Denmark – Odense	93	98	46	35 285	13.04	9.54	17.39	
Mexico – RYVEMCE	93	98	369	294 380	12.53	11.29	13.88	
Argentina	93	98	509	412 862	12.33	11.28	13.45	
China – Beijing	97	98	325	267 071	12.17	8.25	15.73	
Brazil	93	98	263	220 452	11.93	10.53	13.46	
Canada – Alberta	95	98	178	151 200	11.77	10.11	13.63	
Belgium – Antwerp	93	98	83	76 426	10.86	4.63	18.53	↓
France – Strasbourg	93	98	84	79 393	10.58	8.44	13.10	
Scotland – Glasgow	93	98	69	66 729	10.34	8.04	13.08	
Ecuador	93	98	19	18 937	10.03	6.03	15.67	
Finland	93	98	372	371 826	10.00	9.01	11.07	
Chile	93	98	98	98 320	9.97	8.09	12.15	
Czech Republic	93	98	574	596 805	9.62	8.85	10.44	
Colombia	93	94	11	11 844	9.29	4.61	16.63	
United States – Atlanta	93	98	223	249 434	8.94	7.81	10.19	
Ireland – Dublin	93	98	101	113 719	8.88	7.23	10.79	
Australia	93	97	1 144	1 295 708	8.83	8.32	9.36	
Belgium – Hainaut	93	98	63	73 563	8.56	6.58	10.96	
Austria – Styria	93	98	62	73 918	8.39	6.43	10.75	
Malta	93	98	24	29 021	8.27	5.29	12.31	
England – Mersey	98	98	22	27 516	8.00	5.00	12.11	
Venezuela	93	98	70	89 441	7.83	6.10	9.89	
Southern Portugal	93	98	47	60 872	7.72	5.67	10.27	
Switzerland – Zurich	93	98	197	255 571	7.71	6.67	8.86	
Spain – Asturias	93	98	29	39 492	7.34	1.54	13.73	↓
France – Central East	93	98	440	609 089	7.22	6.56	7.93	

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Table 1: Cleft lip with or without cleft palate (*continued*)

Programme	Years		Cases	Births	Rate per 10 000	95% CI*		Trend
	from	to				lower	upper	
Hungary	93	98	457	650 371	7.03	4.76	9.62	
Uruguay	93	98	34	48 771	6.97	4.82	9.74	
France – Paris	93	98	152	220 330	6.90	5.85	8.09	
UK – North Thames West	97	98	65	94 949	6.85	5.28	8.72	
Italy – ISMAC	93	98	75	111 286	6.74	5.30	8.45	
Bulgaria – Sofia	96	97	12	18 230	6.58	3.38	11.51	
Italy – BDRCAM	93	98	180	276 108	6.52	5.60	7.54	
Croatia – Zagreb	93	97	20	31 719	6.31	3.84	9.74	
Italy – IMER	93	98	95	151 604	6.27	5.07	7.66	
Cuba	93	98	171	273 346	6.26	5.35	7.27	
England and Wales	93	98	2 430	3 934 009	6.18	5.93	6.43	
Italy – North East	93	98	179	316 862	5.65	4.85	6.54	
Spain – Basque Country	93	97	43	78 938	5.45	3.94	7.34	
United Arab Emirates	96	98	11	22 099	4.98	2.47	8.91	
Italy – Tuscany	93	98	73	148 120	4.93	3.86	6.20	
Spain – ECEMC	93	98	264	547 015	4.83	4.26	5.44	
Spain – El Valles	93	97	16	36 006	4.44	2.53	7.22	
Spain – Barcelona	93	98	30	73 501	4.08	2.75	5.83	
New Zealand	93	98	140	347 440	4.03	0.81	8.49	↑
Russia – Tomsk	93	98	9	24 160	3.73	1.69	7.08	
Canada – National	93	97	512	1 389 607	3.68	3.37	4.02	
South Africa – SABDSS	93	97	119	336 331	3.54	2.93	4.23	
Israel – IBDMS	93	98	35	103 924	3.37	2.34	4.68	

Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

* Bold characters do not represent the confidence interval (CI) but the range (for heterogenous prevalence only).

Table 2: Cleft palate without cleft lip*

Programme	Period		Cases	Births	Rate per 10 000	95% CI		Trend
	from	to				lower	upper	
Canada – British Columbia	93	98	695	274 542	25.31	19.34	30.41	↑
Finland	93	98	532	371 826	14.31	13.12	15.58	
Malta	93	98	41	29 021	14.13	10.13	19.16	
Canada – Alberta	95	98	122	151 200	8.07	6.70	9.63	
Scotland – Glasgow	93	98	53	66 729	7.94	5.95	10.39	
Ireland – Dublin	93	98	88	113 719	7.74	6.21	9.53	
France – Strasbourg	93	98	57	79 393	7.18	5.44	9.30	
Canada – National	93	97	975	1 389 607	7.02	6.58	7.47	
Paraguay	93	98	11	16 108	6.83	3.39	12.23	
Belgium – Hainaut	93	98	50	73 563	6.80	5.04	8.96	
Germany – Saxony-Anhalt	93	98	34	50 947	6.67	4.62	9.33	
Austria – Styria	93	98	49	73 918	6.63	4.90	8.76	
Australia	93	97	840	1 295 708	6.48	5.55	7.73	↑
New Zealand	93	98	224	347 440	6.45	4.15	9.55	↑
Czech Republic	93	98	378	596 805	6.33	5.71	7.01	
Croatia – Zagreb	93	97	20	31 719	6.31	3.84	9.74	
Denmark – Odense	93	98	22	35 285	6.23	3.90	9.44	
France – Central East	93	98	369	609 089	6.06	5.46	6.71	
Spain – Asturias	93	98	23	39 492	5.82	3.69	8.74	
Switzerland – Zurich	93	98	147	255 571	5.75	4.86	6.76	
Norway	93	98	200	360 906	5.54	4.80	6.36	
England – Mersey	98	98	15	27 516	5.45	3.04	9.00	
Southern – Portugal	93	98	33	60 872	5.42	3.73	7.61	
Spain – Basque Country	93	97	41	78 938	5.19	3.73	7.05	
Israel – IBDMS	93	98	53	103 924	5.10	3.82	6.67	
Northern Netherlands	93	98	59	116 337	5.07	3.01	9.33	↓
Belgium – Antwerp	93	98	38	76 426	4.97	0.00	9.30	↑
Italy – ISMAC	93	98	55	111 286	4.94	3.72	6.43	
Chile	93	98	48	98 320	4.88	3.60	6.47	
Italy – IMER	93	98	70	151 604	4.62	3.60	5.83	
Japan – JAOG	93	98	281	619 107	4.54	4.02	5.10	
France – Paris	93	98	100	220 330	4.54	3.69	5.52	
USA – Atlanta	93	98	113	249 434	4.53	3.73	5.45	

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Table 2: Cleft palate without cleft lip (*continued*)

Programme	Period		Cases	Births	Rate per 10000	95% CI*		Trend
	from	to				lower	upper	
Brazil	93	98	99	220 452	4.49	3.65	5.47	
Italy – BDRCAM	93	98	119	276 108	4.31	3.57	5.16	
Ecuador	93	98	8	18 937	4.22	1.80	8.34	
England – North Thames West	97	98	39	94 949	4.11	2.92	5.61	
Spain – ECEMC	93	98	224	547 015	4.09	3.58	4.67	
Italy – North East	93	98	125	316 862	3.94	3.28	4.70	
Argentina	93	98	154	412 862	3.73	2.37	5.82	↓
Uruguay	93	98	18	48 771	3.69	2.18	5.83	
Italy – Tuscany	93	98	50	148 120	3.38	2.50	4.45	
United Arab Emirates	96	98	7	22 099	3.17	1.26	6.54	
Mexico – RYVEMCE	93	98	90	294 380	3.06	2.46	3.76	
China – Beijing	97	98	81	267 071	3.03	1.96	4.01	
Spain – Barcelona	93	98	22	73 501	2.99	1.87	4.53	
England and Wales	93	98	1144	3 934 009	2.91	2.36	3.25	↓
Venezuela	93	98	26	89 441	2.91	1.90	4.26	
Russia – Tomsk	93	98	7	24 160	2.90	1.15	5.98	
Hungary	93	98	184	650 371	2.83	2.44	3.27	
Spain – El Valles	93	97	9	36 006	2.50	1.13	4.75	
China – CBDMN	97	98	141	598 316	2.36	1.98	2.78	
Bolivia	93	98	8	34 007	2.35	1.00	4.64	
Bulgaria – Sofia	96	97	4	18 230	2.19	0.57	5.64	
South Africa – SABDSS	93	97	65	336 331	1.93	1.49	2.46	
Colombia	93	94	2	11 844	1.69	0.16	6.16	
Cuba	93	98	37	273 346	1.35	0.95	1.87	

Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

* Bold characters do not represent the confidence interval but the range (for heterogeneous prevalence only).

Table 3: Synopsis of 28 monitoring systems: prevalence rates and secular trends for oral clefts

Monitoring programme	Coverage	Maximum age at diagnosis	Criteria defining stillbirths	Annual births (1998)	CL/P rate/ 10 000	CL/P trend	CP/ rate/ 10 000	CP trend
Australia	Population-based National	Hospital discharge	20 weeks or 400 g	250 000	9.29	#	7.34	↓
Canada – Alberta	Population-based Provincial	1 year	20 weeks or 500 g	40 000	8.93	#	9.19	↓
Canada – National	Population-based National	1 year	20 weeks	280 000	2.85	#	5.89	↓
China – Beijing	Population-based Four provinces	6 weeks	20 weeks	150 000	9.66	NA	1.90	NA
China – CBDMN	Hospital-based	7 days	28 weeks	260 000	14.22	NA	2.53	NA
Czech Republic	Population-based Bohemia & Moravia	Up to 15 years	500 grams	90 000	8.24	#	6.68	#
England and Wales	Population-based National	1995 onwards no limit	24 weeks	650 000	6.34	↓	2.94	↓
Finland	Population-based National	1 year	22 weeks or 500 g	57 000	8.31	↑	11.60	↑
France – Central-East	Population-based Regional	1 year	22 weeks	100 000	6.81	#	3.93	#
France – Paris	Population-based Regional	Hospital discharge	22 weeks	38 000	6.81	#	3.93	#
France – Strasbourg	Population-based Regional	1 year	26 weeks	13 000	13.74	#	3.62	#
Hungary	Population-based National	1 year	28 weeks	120 000	6.20	↓	3.05	↓
Ireland – Dublin	Population-based Regional	10 years	24 weeks or 500 g	20 000	8.41	#	4.95	#
Israel – IBDMs	Hospital-based Regional	Hospital discharge	28 weeks	20 000	6.47	#	3.23	#
Italy – BDRCam	Hospital-based Regional	7 days	180 days	50 000	7.81	#	4.43	#
Italy – IMER	Population-based Regional	7 days	180 days	28 000	5.83	#	0.42	#
Italy – ISMAC	Hospital-based Regional	1 year	180 days	57 000	NA	NA	NA	NA
Italy – North East	Population-based Regional	7 days	180 days	19 000	6.81	↓	3.86	↓
Italy – Tuscany	Population-based Regional	7 days	180 days	25 000	4.60	↓	5.37	#

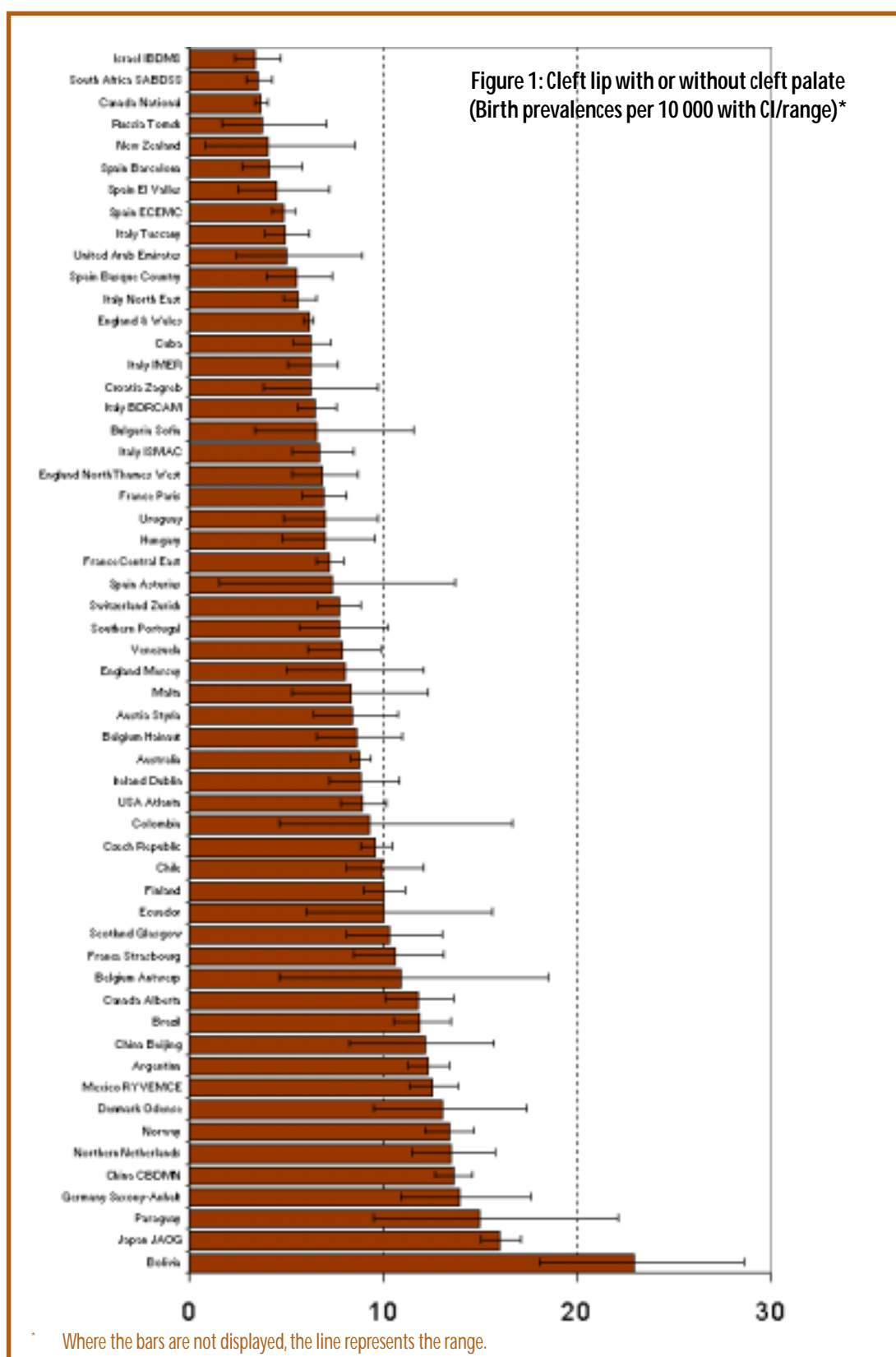
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Table 3: Synopsis of 28 monitoring systems: prevalence rates and secular trends for oral clefts (*continued*)

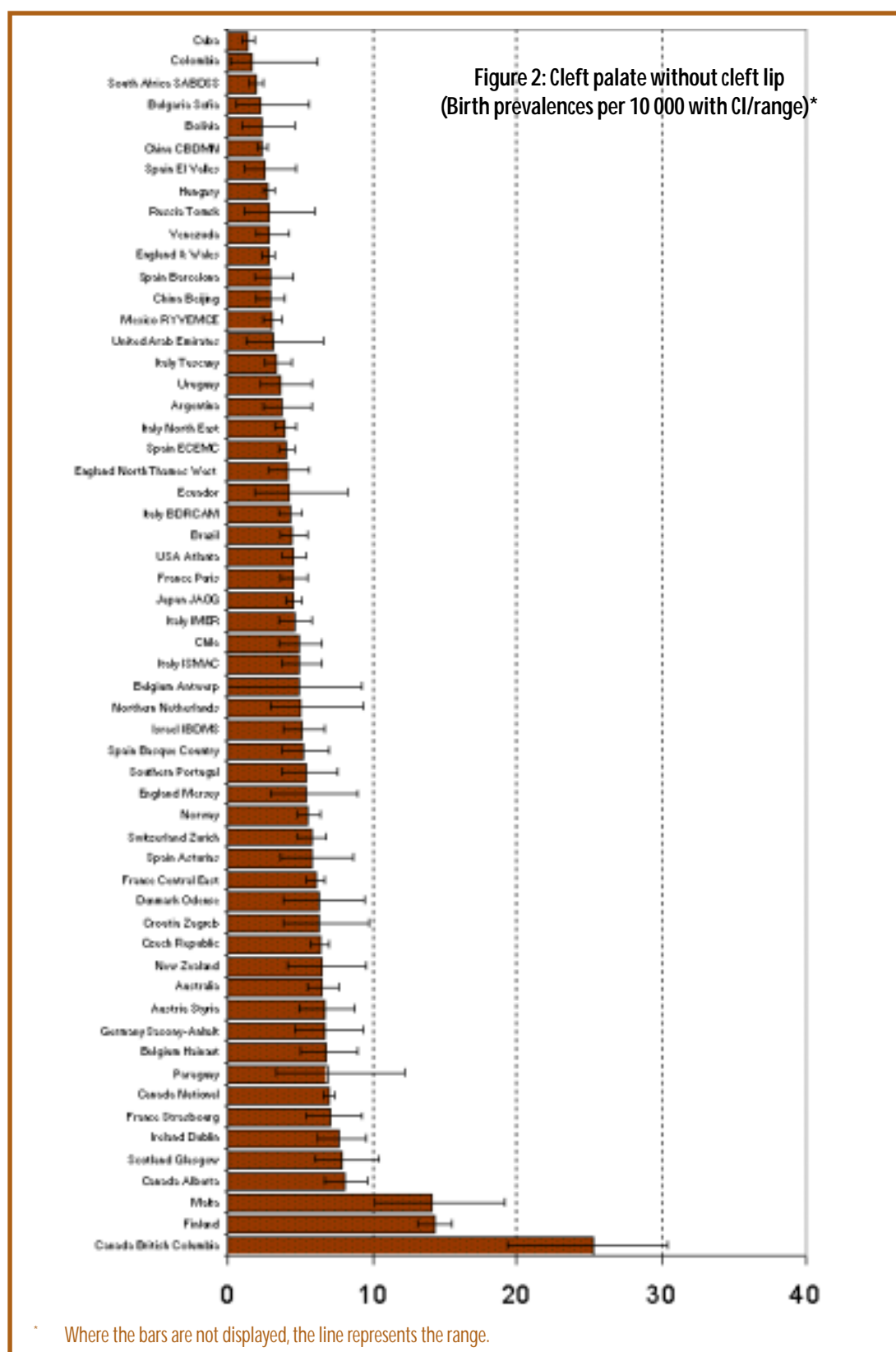
Monitoring programme	Coverage	Maximum age at diagnosis	Criteria defining stillbirths	Annual births (1998)	CL/P rate/ 10 000	CL/P trendrate/ 10 000	CP/ trend	CP trend
Japan – JAOG	Hospital-based National	7 days	22 weeks	100 000	17.15	h	4.12	i
Malta	Hospital-based National	1 year	24 weeks	5 000	13.83	#	25.35	#
Mexico – RYVEMCE	Hospital-based National	72 hours	20 weeks or 500 g	40 000	12.91	#	2.40	#
New Zealand	Population-based National	1 year	20 weeks or 400 g	56 000	6.46	↓	10.29	#
Northern Netherlands	Population-based National	No limit	24 weeks	7 500	13.39	#	7.44	#
Norway	Population-based National	Hospital discharge	16 weeks	60 000	10.55	↑	5.86	#
South Africa – SABDSS	Hospital-based	Hospital discharge	not recorded	75 000	3.05	#	3.05	#
South America – ECLAMC	Hospital-based Multinational	3 days	500 g	150 000	14.83	↑	4.34	↑
Spain – ECEMC	Hospital-based National	3 days	24 weeks or 500 g	100 000	4.12	↓	4.12	#
Sweden	Population-based National	28 days	22 weeks	100 000	17.29	NA	6.33	NA
United Arab Emirates	Hospital-based National	7 days	23 weeks	8 000	6.43	NA	7.72	NA
USA – Atlanta	Population-based Regional	1 year	20 weeks or 500 g	47 000	8.00	↓	6.74	#
USA – California	Population-based Regional	1 year	20 weeks	56 000	NA	NA	NA	NA

Source: WHO, 2003

- # Secular trend, stable
- ↓ Secular trend, decreasing
- ↑ Secular trend, increasing
- NA Data not available.

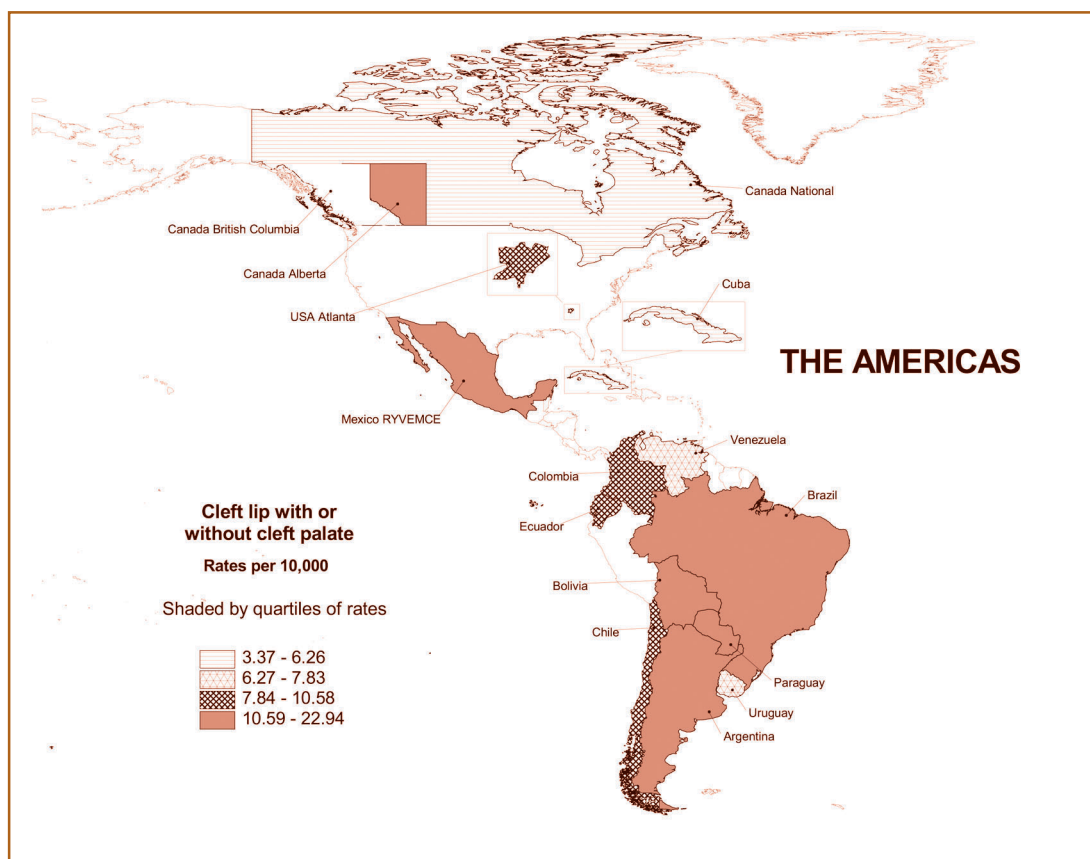


Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.



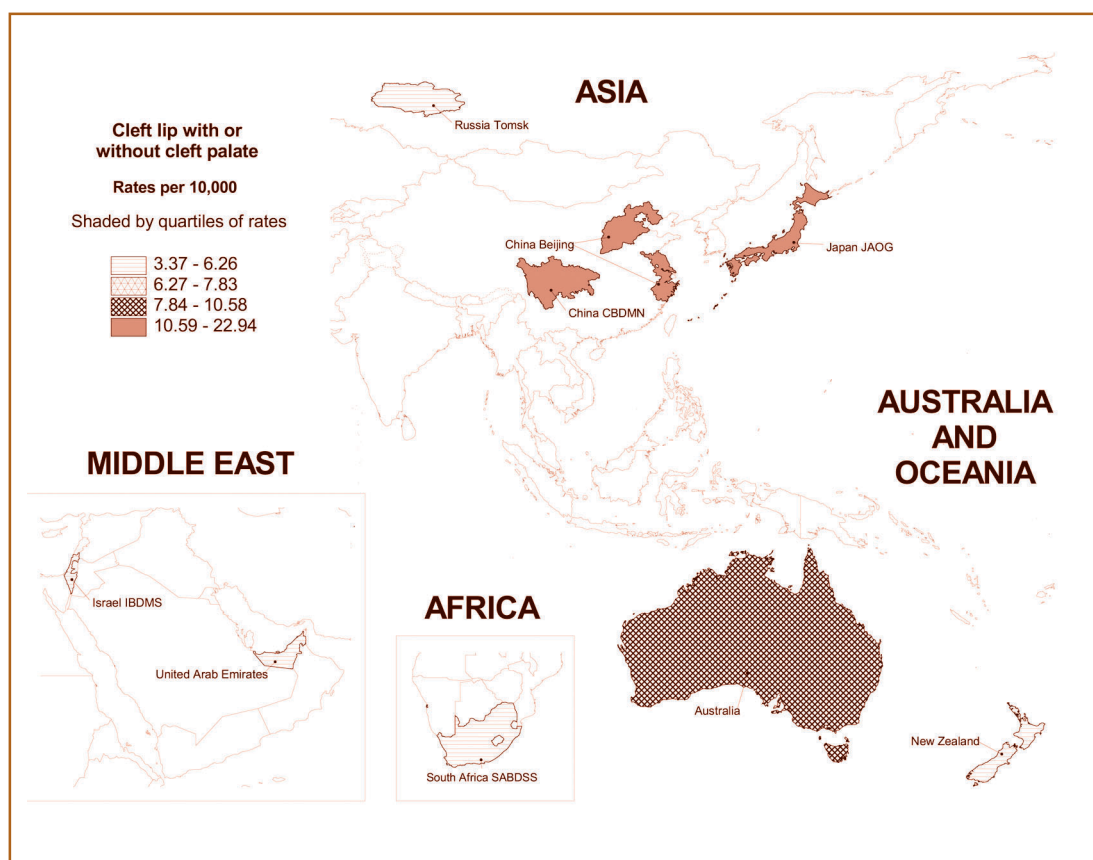
Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

**Figure 3a: Cleft lip with or without cleft palate
The Americas**



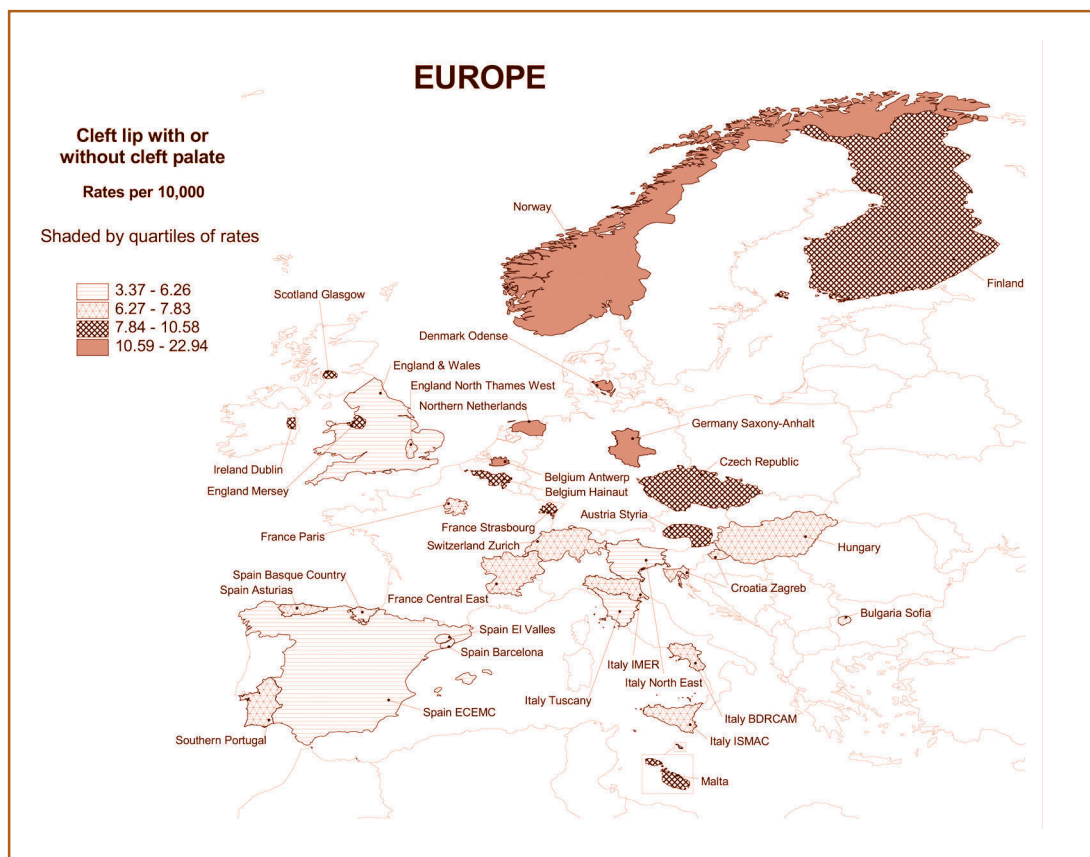
Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

**Figure 3b: Cleft lip with or without cleft palate
Asia, Middle East, Australia & Oceania, Africa**



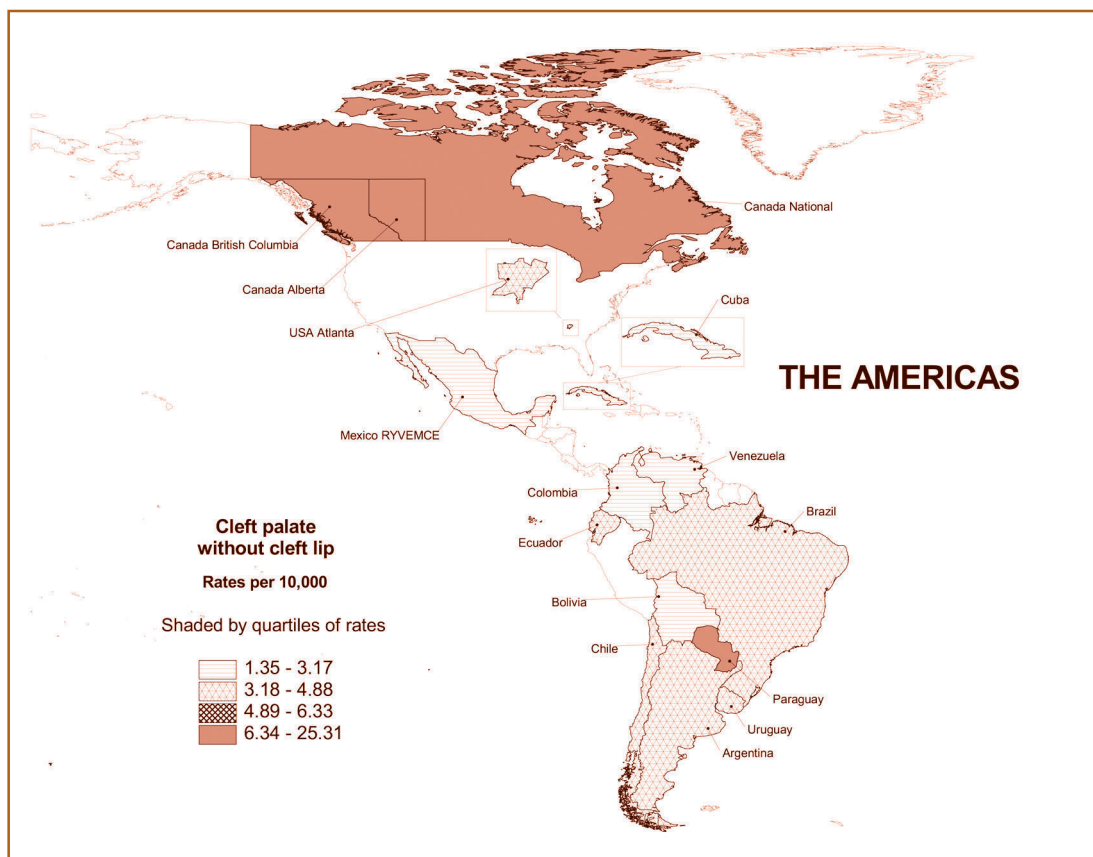
Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

Figure 3c: Cleft lip with or without cleft palate
Europe



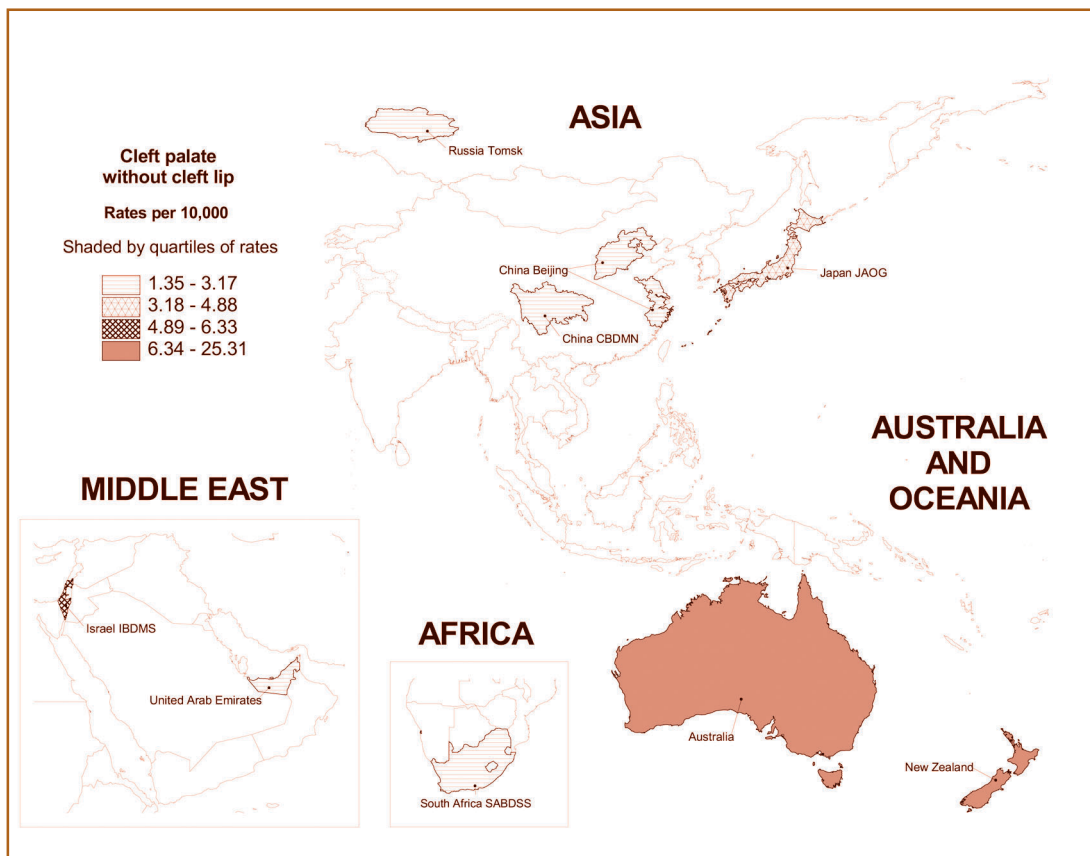
Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

Figure 4a: Cleft palate without cleft lip
The Americas



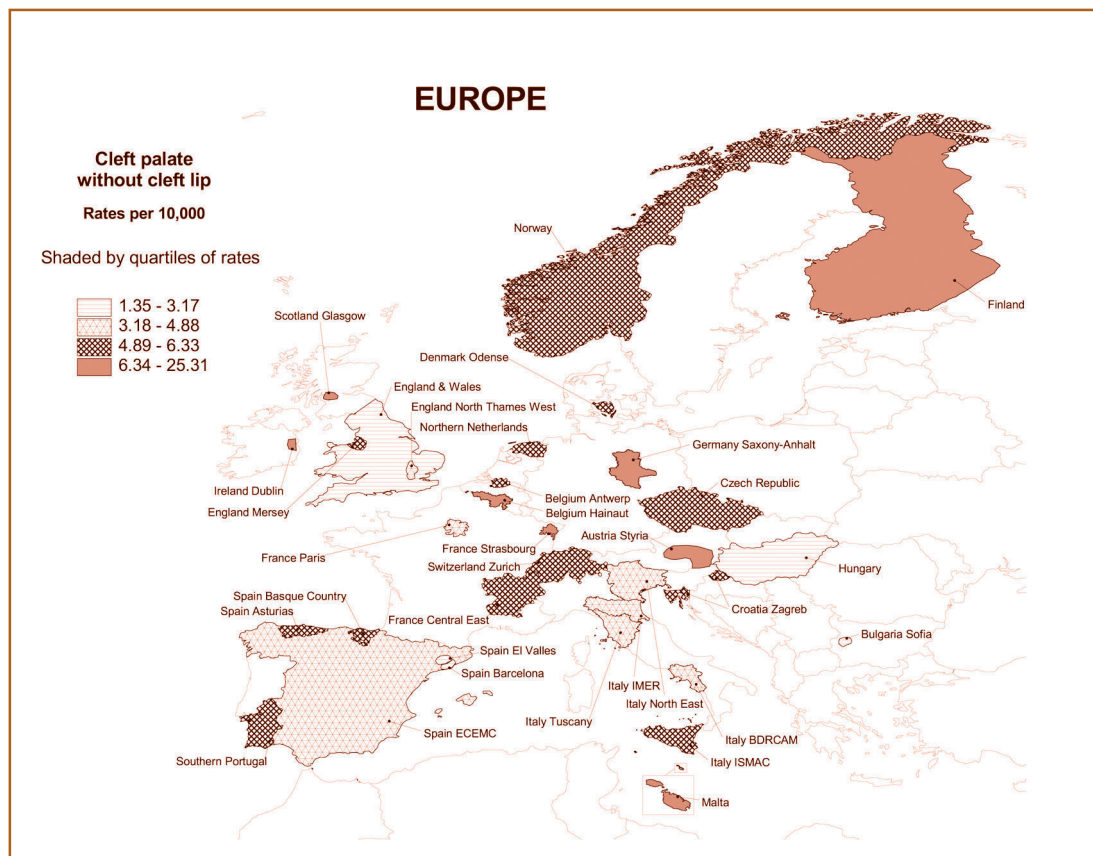
Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

Figure 4b: Cleft palate without cleft lip
Asia, Middle East, Australia & Oceania, Africa



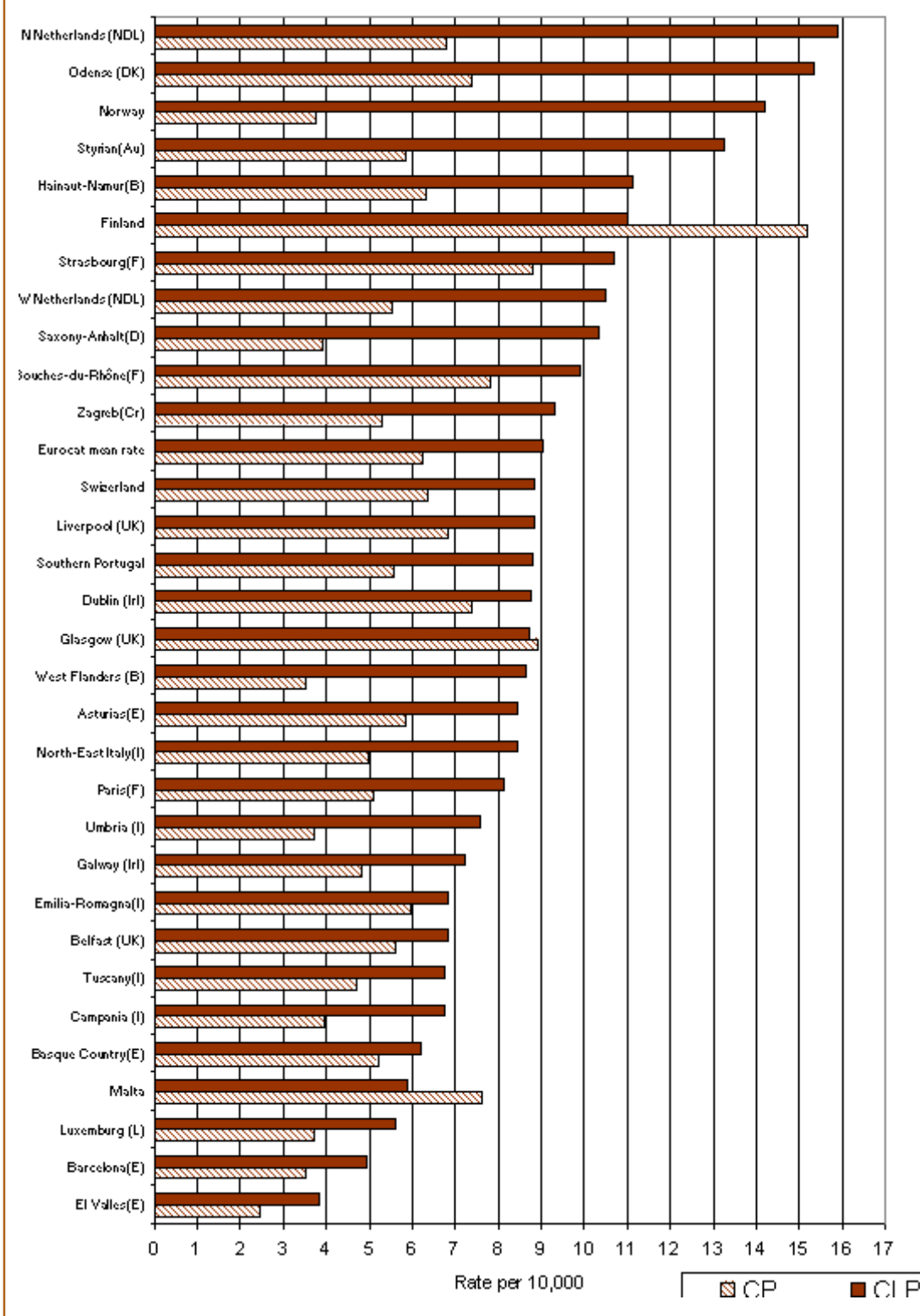
Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

**Figure 4c: Cleft palate without cleft lip
Europe**



Source: World Atlas of Birth Defects, 2nd edition, World Health Organization, Geneva, Switzerland, 2003.

Figure 5: Rates for cleft palate and cleft lip with or without cleft palate, 1980-1996



Source: Bianchi F (2001) EUROCATOC: A collaborative study on oral clefts in EUROCAT registries during the period 1980-1996. Preliminary analysis

Figure 6: Monthly report form for examined births

Registry: _____ Month: _____ Year: _____

Sex		Live births	Stillbirths
Male			
Female			
Intersex			
Not specified			
Total			

Weight		Live births	Stillbirths
< 500	////////		
500-1000			
1001- 1500			
1501- 2000			
2001- 2500			
2501- 3000			
3001- 3500			
3501- 4000			
4001- 4500			
4501- 5000			
5001 +			
Not specified			
Total			

G r a v i d i t y		Live births	Stillbirths
1			
2			
3			
4			
5			
6			
7			
8			
9			
10 or more			
Not specified			
Total			

Cases reported		Live births	Stillbirths
Autopsies			

M o t h e r ' s a g e		Live births	Stillbirths
< 14			
15-19			
20-24			
25-29			
30-34			
35-39			
40-44			
45 +			
Not specified			
Total			

B i r t h p l a c e		Live births	Stillbirths
1			
2			
3			
4			
5			
6			
7			

Source: ICBOMS, 2000