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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

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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

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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.

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.

There can be no single ideal model that has universal applicability for a registry ...

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).