2 Global epidemiology and health burden of CFA

2.1 Global epidemiology

Cleft lip, with or without cleft palate (CL/P), and isolated cleft palate (CP) are serious birth defects which affect approximately 1 in every 600 newborn babies worldwide. This means that, assuming 15 000 children are born per hour worldwide (United States Bureau of the Census, 2001), a child is born with a cleft somewhere in the world approximately every 2½ minutes. From birth to maturity, children with orofacial clefts (OFC) undergo multidisciplinary surgical and non-surgical treatment with considerable disruption to their lives, and often with adverse psychological consequences to themselves and their families.

Over the years efforts have been made to record frequency of birth defects. Accurate data on the epidemiology are important not only for documenting the burden in relation to the planning of public health services, but also because they form the basis for research into the causes. The eventual objective, from both scientific and humanitarian viewpoints, must be to advance the knowledge and understanding of causative factors so as to be able to institute primary preventive measures. Among the barriers to achieving this objective are: (a) the heterogeneity of orofacial clefting; (b) the lack of standard criteria for the collection of data; and (c) in particular the lack of and/or failure to apply an internationally comparable classification for orofacial clefting.

The level of ascertainment differs between countries, depending on the method of cleft birth registration; the number of live births, terminations, stillbirths and syndromic individuals can considerably affect the validity of such data. The critical requirement is to precisely define the "population" in which malformations are measured. The main issue is whether one reports or estimates rates in all conceptuses, all births, or all live births. The word *births* is somewhat ambiguous because it usually includes stillbirths, a term which does not have a uniform definition.

2.1.1 Epidemiological data summary

Epidemiological data for orofacial clefts from the three different sources outlined above are presented in peer-reviewed publications. Tables 2 and 3 (WHO, 1998) show data from the peer-reviewed literature and that collected through the International Clearinghouse Birth Defects Monitoring System (ICBDMS) and European Registration of Congenital Anomalies (EUROCAT).

Birth prevalence studies on patients with CL/P and CP over the second half of the 20th century reveal that whilst there are ethnic and geographic differences, the "average" birth prevalence of orofacial clefting in the world's western populations is often quoted as 1:1000 total births for CL/P and 1:2000 total births for CP *(see Tables 2 and 3)*. The birth prevalence of CL/P is highest in Australia (Aborigines), Canada, the Far East, India, Scandinavia, parts of South America, and the USA, and lower in Southern Europe. In general populations of Asian origin have a higher incidence than Caucasian populations which, in turn, have a higher incidence than African populations. The birth prevalence of CL/P varies from 2.7:1000 in Native Americans to 2.1:1000 in Japan and to 0.4:1000 in Nigeria and 0.42:1000 in African Americans (Leck, 1972), with the geographical variation being less important than ethnic differences.

Cleft palate alone (CP) has a lower average birth prevalence and shows less variation in different racial groups. The prevalence of CP is highest in Australia, Finland, and Scotland (United Kingdom), and in general is higher in Asians than Caucasians or Africans (Melnick, 1992). Generally CL/P occurs more frequently in males whereas for CP the reverse is true. Significant racial differences in the birth prevalence of orofacial clefts exist. Two thirds of all cases of unilateral CL/P have left-sided defects regardless of gender, race and severity of defect (Fraser and Calnan, 1961).

Migrants studies show that African Americans have lower rates for both CP and CLP than Whites in the United States, and a study in Birmingham (United Kingdom) also showed that those originating from the Caribbean have low rates of orofacial clefting (Leck, 1969; Leck and Lancashire, 1995). Studies in North America also reveal similar rates among Japanese-Americans and Chinese-Americans compared to Caucasian-Americans (Croen et al, 1998); there is also evidence that the frequency of CL/P (but not CP) may be significantly lower among US-born Japanese and other Asians born in California and New York than among those born in Japan or Hawaii (Tyan, 1982). The worldwide variation in the frequency of orofacial clefts (OFC) is likely therefore to be influenced by the variable predisposing factors that exist, depending on ethnicity and geography. When comparing the data, however, it is important to consider issues which affect the figures, such as: (a) statistical variability of recorded rates; (b) live births versus stillbirths; and (c) associated malformations.

Table 2: Cleft lip with or without cleft palate

	Live and stillbirths	Induced abortions	Total cases	Total births	Rates (per 10 000)	
Argentina	99	– (*)	99	73 942	13.4	↑
Australia – South Australia	–	–	19	19 801	9.6	
Australia – Victoria	26	47	73	65 182	11.2	
Belarus	–	–	–	–	–	
Belgium – Hainaut Namur	30	1	31	24 856	12.5	
Brazil	51	– (*)	51	36 689	13.9	
Chile	20	– (*)	20	22 276	9.0	
Czech Republic	113	–	113	107 153	10.5	
Denmark – Odense	17	0	17	12 054	14.1	
France – Bouches du Rhone	33	3	36	44 704	8.1	
France – Central East	74	4	78	100 074	7.8	↓
France – Paris	47	16	63	71 319	8.8	
France – Strasbourg	29	5	34	27 200	12.5	
Ireland – Dublin	31	– (*)	31	38 000	8.2	
Italy – Campania	38	2	40	43 325	9.2	
Italy – Emilia Romagna	25	–	25	25 924	9.6	
Italy – Toscana	42	1	43	48 991	8.8	
Japan	172	– (*)	172	113 702	15.1	↑
Mexico	81	– (*)	81	65 870	12.3	
Netherlands – North	52	6	58	38 670	15.0	↑
Norway	99	2	101	60 584	16.7	↑
Spain – Basque Country	114	2	16	31 248	5.1	↓
Switzerland	101	4	105	148 000	7.1	↓
United Kingdom – Belfast	10	1	11	49 482	2.2	↓
United Kingdom – Glasgow	19	1	20	22 570	8.9	
United Kingdom – North Thames	43	10	53	47 274	11.2	
USA – Atlanta	34	0	34	39 856	8.5	
USA – Hawaii	–	–	22	20 596	10.7	
Uruguay	17	– (*)	17	21 332	8.0	
Venezuela	21	– (*)	21	36 377	5.8	↓

Source: WHO (1998) World Atlas of Birth Defects (1st edition)

* Abortion for birth defect not permitted.

↑ = 99% significantly higher than the mean.

↓ = 99% significantly lower than the mean.

Table 3: Cleft palate without cleft lip

	Live and stillbirths	Induced abortions	Total cases	Total births	Rates (per 10 000)	
Argentina	43	– (*)	43	73 942	5.8	
Australia – South Australia	18	–	18	19 801	9.1	
Australia – Victoria	39	0	39	65 182	6.0	
Belarus	–	–	–	–	–	
Belgium – Hainaut Namur	15	2	17	24 856	6.8	
Brazil	19	– (*)	19	366 689	5.2	
Chile	13	– (*)	13	22 276	5.8	
Czech Republic	66	–	66	107 153	6.2	
Denmark – Odense	11	0	11	12 054	9.1	
France – Bouches du Rhone	23	5	28	44 704	6.3	
France – Central East	72	7	79	100 074	7.9	↑
France – Paris	36	14	50	71 319	7.0	
France – Strasbourg	21	2	23	27 200	8.5	
Ireland – Dublin	13	– (*)	13	38 000	3.4	
Italy – Campania	24	–	24	43 325	5.5	
Italy – Emilia Romagna	12	–	12	25 924	4.6	
Italy – Toscana	10	2	12	48 991	2.4	↓
Japan	52	– (*)	52	113 702	4.6	
Mexico	27	– (*)	27	65 870	4.1	
Netherlands – North	32	1	33	38 670	8.5	
Norway	26	0	26	60 584	4.3	
Spain – Basque Country	17	1	18	31 248	5.8	
Switzerland	63	3	66	148 000	4.5	
United Kingdom – Belfast	6	1	7	49 482	1.4	↓
United Kingdom – Glasgow	19	3	22	22 570	9.7	
United Kingdom – North Thames	20	2	22	47 274	4.7	
USA – Atlanta	12	1	13	39 856	3.3	
USA – Hawaii	12	–	12	20 596	5.8	
Uruguay	10	– (*)	10	21 332	4.7	
Venezuela	14	– (*)	14	36 377	3.8	
Total			**789**	**1 457 051**	**5.4**	

Source: WHO (1998) World Atlas of Birth Defects (1st edition)

* Abortion for birth defect not permitted.

↑ = 99% significantly higher than the mean.

↓ = 99% significantly lower than the mean.

2.1.2. Variability of recorded rates

The precision of recorded rates depends on the recording of the total population birth rate (denominator data) and the recognition and recording of the number of affected births. Since the incidence and birth prevalence of OFC is low, the variability of the rate depends primarily on the level of ascertainment and number of abnormal births recorded. The standard error of the observed number x (Poisson distribution) is simply its square root ($\sqrt{}$) and the width of the 95% confidence limit for x is 1.96 $\sqrt{}$ x. The width of the confidence interval as a percentage of the observed number is a measure of the precision. Studies that have a statistical variability of more than 30%, however, need to be interpreted with caution.

There is apparent variation in the proportion of OFC cases with additional congenital anomalies and syndromes

Many of the studies described in developing countries are based on hospital rather than general population figures so will only be accurate in communities where it is likely that the vast majority of births have occurred in hospital. In the interests of recording reasonably accurate data, information from registries only is displayed above, and the figures for some studies in Africa, India and the Middle East are excluded.

2.1.3. Live births versus stillbirths

The proportion of serious malformations is higher in stillbirths than in live births so including stillbirths tends to raise the birth prevalence or incidence rates above those that only consider live births. Similarly, inclusion of data on earlier loss – miscarriages and abortions – will increase rates over data that analyse only live births and stillbirths.

Vanderas (1987) examined the problem of inclusion or exclusion of stillbirths as an issue in ascertainment of OFC in a number of international studies, some of which included live births, stillbirths and abortions in their evaluation of incidence rate. The OFC rates were 6.43 per 1000 stillbirths versus 2.16 per 1000 live births in Hay's study (1971) of Caucasians in the United States (Iowa); and 2.72 per 1000 stillbirths versus 0.91 per 1000 live births in the pooled data Lutz and Moore (Lutz et al., 1955) compiled on African Americans, Mexicans and Caucasians. It appears, therefore, that in stillbirths and abortions the risk of developing clefts is about three times more frequent than in live births; and clefts with associated malformations behave differently epidemiologically from clefts without associated malformations.

A further study in Hungary (Czeizel et al., 1984) reported that the proportion of cleft palate without cleft lip is about sevenfold greater in stillbirths (primary fetal deaths 28 weeks or older) than in live births (2.38 per 1000 versus 0.36 per 1000). Whereas for cleft lip (with or without cleft palate), the ratio is a little less than threefold (3.17 per 1000 versus

1.15 per 1000). As may be expected, this differential between live births and stillbirths is greater for those orofacial clefts that occur in individuals with additional malformations elsewhere, than in those with only cleft lip, cleft palate, or both.

Krause (1963) examined human embryos and fetuses and reported that the frequency of clefts with associated malformations was 11.61 per 1000, and fetuses with clefts but without associated malformations were 7.22 per 1000. Nishimura (1966), reported the frequency of cleft lip with or without cleft palate in 1213 voluntarily aborted human embryos in Japan to be 14.7 per 1000. In a later Japanese study on 5117 voluntarily aborted human embryos, Iizuka (1973), found that the incidence of cleft lip (CL) was 4.3 per 1000, cleft lip and palate (CLP) 8.1 per 1000 and isolated cleft palate (CP) 3.2 per 1000.

It is for this reason that the indiscriminate grouping of figures which include not only live births but also stillbirths and/or induced abortions will not be comparable to those which quote live births only. If fetal deaths or earlier losses are included in summary rates, this should be noted specifically and rates should be presented separately for live births and for embryonic and fetal deaths.

2.1.4 Associated malformations

It is generally accepted that associated malformations occur more frequently in infants who have CP than in those who have CLP and even less still in those with isolated CL. For example, a 17-year study in North Eastern France reported the rate of associated malformations as 46.7% in CP, 36.8% in CLP and 13.6% in CL (Kallen et al., 1996). Cornel (1992) reported associated abnormalities in 23% of combined CL/P cases and in 52% of cases with isolated CP. Other studies that also found congenital anomalies to be much more commonly associated with CP than with CL/P were Ingalls et al., 1964; Drillien et al., 1966; Moller, 1972 and Emanuel et al., 1973. In the Finnish population, however, CL/P was as often associated with other malformations as was CP (Saxen et al., 1974). Familial background was also more often reported in association with CP than with CL/P in Finland; this is in contrast to that found by others, such as Fogh-Andersen (1942) in Denmark.

Some reports also sub-divide CL/P into unilateral and bilateral sub-groups when examining additional malformations and report an increase in additional malformations in the bilateral sub-group (e.g. Hagberg et al., 1997). When considering associated abnormalities some reports do not define what is meant by "associated abnormalities" while others give ambiguous descriptions, and Conway and Wagner (1966) record only the "10 most common" associated abnormalities listed on birth certificates over an 11-year period.

2.1.5 The prevalence of isolated cleft palate

There is considerable international variation in the frequency of OFCs

There is considerable heterogeneity in what is described as isolated cleft palate. Many figures for isolated cleft palate are provided without an adequate explanation of inclusion/exclusion criteria. For instance, the most common syndrome with isolated cleft palate as a feature is the Pierre Robin syndrome and its inclusion will therefore make a significant difference to the figures. This sub-group is also more susceptible to ascertainment bias as the prevalence of sub-mucous clefting within the general population is thought to be as common as overt isolated CP (Christensen and Fogh-Andersen, 1994). In a detailed study of isolated cleft palate in Denmark, these authors noted that there is a marked difference in sex ratios for non-syndromic overt CP including the hard palate, and non-syndromic overt CP of the soft palate only. This, combined with the tendency for hard palate and soft palate clefts not to occur within the same families, indicates that they may be two etiologically distinct sub-groups of cleft palate. Christensen and Fogh-Andersen (1994) therefore recommended that future studies on isolated cleft palate distinguish between hard palate, soft palate and sub-mucous hard palate in an attempt to disclose etiological heterogeneity within secondary palatal clefting.

The inclusion of the Pierre-Robin anomaly is also complicated by the fact that the diagnosis of Pierre-Robin is inconsistent; e.g. some clinicians insist that respiratory distress is an essential part of the anomaly while others make a diagnosis on the basis of glossoptosis and micrognathia with the cleft, whether or not there is respiratory distress.

Further complications in the consideration of isolated cleft palate are two recognized genetic phenomena:

(a) the association of CP with 22q11.2 deletion in the velo-cardio-facial syndrome (VCF); and

(b) X-linked clefting.

The incidence of VCF in many populations is unknown and diagnosis may be delayed, thus affecting the birth prevalence figures. X-linked clefting has been reported in some populations, such as the Icelandic population (Moore et al., 1987), but has not been investigated in many others. Also a study by Lowry and Rennick (1969), X-linked sub-mucous cleft palate that is part of an X-linked recessive trait; this might complicate the picture regarding cleft palate birth prevalence and sex ratio figures.

2.2 Recommendations for producing better descriptive statistics in OFC

2.2.1 Population-based versus hospital-based registries

In much of the older literature and in current work in less-developed countries, data are often available only on births delivered in hospital. Unless almost all births occur in hospital, such data may be biased. However, if hospital confinement is more available to women from the upper socioeconomic groups, hospital-derived rates may underestimate those for the community as a whole. Interpretation of hospital series, therefore, is not straightforward unless the proportion of births in the community delivered in hospital approaches 100%. Even so, when hospital records alone are searched, the number of cases expressed as a percentage of all known cases (found by using multiple sources of ascertainment) may be low, as indicated by the Hungarian figure of 52.5% based on hospital records only (Czeizel and Revesz, 1970).

While complete ascertainment is almost impossible to achieve, we can come close to it by pooling data from several overlapping sources. The quality of a population-based perinatal register will depend on how many sources are used and how thorough the ascertainment process is; also, cleft registers or hospital-based registers tend to be a subset, excluding stillbirths, early deaths, minor anomalies not requiring surgery, patients who move away, miscoding, etc. As well as being less complete, a hospital-based registry will tend to have fewer cases with associated abnormalities because of stillbirths and perinatal deaths (not requiring admission) and because another feature may be more important than the cleft.

2.2.2 Multiple sources of ascertainment

Multiple sources of ascertainment from population-based samples should be used for incidence statistics, and complete censuses or representative samples should be employed for prevalence statistics. These constitute the best approaches available for preparing accurate estimates of rates, because no single data source has sufficient reliability (Czeizel and Tusnadi, 1971).

In preparing incidence data to support genetic and other etiological studies, all aborted fetuses and stillbirths should either be included or appropriate adjustments made. Whether terminations and fetal deaths are included, the inclusion criteria, and the methods used should be clarified. Similarly, the effects of differential prenatal and postnatal death rates on the apparent sex ratios for clefts should be documented. All degrees of cleft expression should be diagnosed to prevent under-ascertainment.

2.2.3 Cleft-type and associated malformations

All epidemiological and genetic data should be presented by specific cleft type whenever possible (Fogh-Andersen, 1942; Fraser, 1970). Each cleft type should be subdivided by the presence or absence of associated congenital malformations (Emanuel et al., 1973). Where possible, syndromic cleft cases should be separated from nonsyndromic ones; and the classification used and how this was done should be explained, for example, by a dysmorphologist. Birth prevalence statistics for clefts will further benefit risk-factor studies if they are tallied separately for familial and sporadic cases (Melnick et al., 1980; Bixler, 1981) in which the genetic and environmental risk factors may differ, and then for syndromic versus nonsyndromic status within these categories. Since the major cleft phenotypes are actually heterogeneous entities, disaggregating them for statistical purposes may aid the investigation of unitary disease categories.

Grouping by ethnic origin is not entirely objective

2.2.4 Ethnic grouping

Where possible, data within countries should be presented by ethnic group, although it must be recognized that grouping by ethnic origin is not entirely objective. Also, in light of some emerging evidence, it may be useful to have a record of socioeconomic status. Ideally, datasets containing core information agreed by consensus should be collected while, for studies in suspected high-risk population subgroups, additional information should be collected, such as specific parental genotypes or phenotypes, older parents, medicated mothers, mothers with certain chronic diseases, and parents with unique dietary or other environmental exposures.

BOX A

Recommendations for producing better descriptive statistics in OFC and epidemiology

Orofacial clefting (OFC) is a heterogeneous group of defects with a considerable range of severity; therefore, there will inevitably be variability in ascertainment rates, and multiple sources of ascertainment should be used where possible. Studies also vary in the criteria used for differentiating syndromic from non-syndromic clefts. Many of the earlier publications were less discriminating on the differences in frequency between CP and CL/P, often quoting a combined figure. Many more recent papers do differentiate and some even subdivide CL and CLP. The validity of inter-centre comparisons is dependent on the comparison of similar groups of patients, and standardized classifications are necessary. Molecular diagnoses will increasingly assist with the differentiation and classification *(see Section 5.2)*

2.3 Conclusions

The overall conclusions to be drawn from the data presented in this chapter are as follows:

- There is ample evidence of the distinctly different nature of CL/P and CP, and emerging evidence of distinct differences in subgroups within these overall conditions.
- There is a great deal of geographical variation, more apparent for CL/P than CP.
- There is apparent variation in the proportion of OFC cases with additional congenital anomalies and syndromes.
- There is no consistent evidence of time trends, nor is there consistent variation by socioeconomic status or seasonality, but these aspects have not been adequately studied. There is a need to investigate such parameters within, as well as between, different populations.
- There is considerable international variation in the frequency of OFCs, but validity and comparability of data are adversely affected by numerous factors, among which are: source population of births considered (hospital versus population), time period, method of ascertainment, inclusion/exclusion criteria and sampling fluctuation.
- There are many parts of the world for which we have little or no information on the frequency of OFCs, in particular parts of Africa, Central Asia, Eastern Europe, India and the Middle East. This needs to be addressed urgently.