IDCFA
International Database of Craniofacial Anomalies

A world-wide initiative supported by
WHO – Human Genetics Programme
NIDCR – National Institute of Dental and Craniofacial Research

Coordinating Centre :
ICBD – International Centre on Birth Defects
Headquarter of the International Clearinghouse for Birth Defects Monitoring System

Coordinators :
Pierpaolo Mastroiacovo and Elisabeth Robert Gnansia

Advisor :
Eduardo E Castilla

www.icbd.org
The aim of the IDCFA

World-wide databases in the same basket
General philosophy

- Other cranio-facial defects and/or syndromes
- Syndromes with oral clefts
- Typical Oral Clefts
- Quality of health care services
- Quality of life
- Risk factors
- Classical descriptive epidemiology

ICBD
www.icbd.org
Long terms aims of the IDCFA

• To evaluate:
  – the incidence and prevalence of the various CFA in some populations around the world
  – the main risk factors
  – the main characteristics (e.g.: clinical, genetic, psycho-social) of persons with a CFA
  – the needs of persons with a CFA and of their families in the various populations
  – the answers of the health care services and social organizations to the patients’ and their families’ needs in the various countries
Long terms aims of the IDCFA

Areas who needs major attention, efforts and impulses

Person’s needs

- Health care services
- Quality of life
- Prevention and risk factors
- Clinical and genetic studies
- Incidence and prevalence
Main Sources of IDCFA

- Surgical Departments
- Clinical Genetic Services
- Birth Defects Registries
- Support Associations
- Special Projects
  - MADRE
  - MMI
- ECLAMC
- Eurocat
- US NBDPN
- ICBDMS
- MADRE
- MMI
- Special Projects
- Support Associations
- Surgical Departments
- Clinical Genetic Services
Each database provides specific information, it is based on:

- case
- by
- case

and is periodically updated or established.

IICCBBDD

www.icbd.org
Some organizational aspects of IDCFA

• Each database will be anonymous at the central level
  – Key code available only to the local organizations

• All databases will be located within the WHO – Human Genetics Programme

• Aggregated data will be available on tables, figures and maps through the web site

• The access to case by case data of any database will be possible for any researcher according to specific rules developed by the IDCFA Steering Committee
The first step

Typical Oral Cleft Perinatal Database

Source: Birth Defects Registries

Simple Descriptive Epidemiology

www.icbd.org
Definitions

Cleft palate (749.0) Q35

A visible congenital malformation characterized by a closure defect of the hard palate and/or soft palate behind the foramen incisivum without cleft lip.

Exclude: submucous cleft palate, occult cleft palate, cleft uvula.
In some database cleft palate includes Pierre Robin Sequence
Cleft palate, ambition!

- Hard: wide U shaped, narrow V shaped
- Soft: wide U shaped, narrow V shaped

Pierre Robin Sequence

www.icbd.org
Working definition

Pierre Robin Sequence
(756.03) Q87.08
A congenital malformation characterized by a closure defect of the palate behind the foramen incisivum without cleft lip associated to (a significant) micrognathia (small mandible) with or without a clinically relevant glossoptosis (retroposition of tongue) or respiratory distress.
This is not a multiple malformations condition but a sequence. This means that may be isolated or associated to unrelated defects or part of a known syndrome.
In some database this condition has a distinct code and it is differentiated from usual cleft palates.

The critical point is “a significant” small mandible
Definitions

Cleft lip (749.1) Q36
A congenital malformation characterized by partial or complete clefting of the upper lip.
Exclude: median cleft lip part of Holoprosencephaly Sequence; rare and oblique facial clefts
Definitions

Cleft lip and palate (749.2) Q37
A congenital malformation characterized by partial or complete clefting of the upper lip with clefting of the alveolar ridge and/or the hard palate.
Exclude: any oral cleft part of the Holoprosencephaly Sequence; rare and oblique facial clefts
**Definitions**

**Isolated cases**
Any case with only one major defect registered. In this Database with only a oro-facial cleft.

**Cases with associated defects, multimalformed infant**
Any case with a major defect registered other than the orofacial cleft.

**Syndromes**
Any case with appropriate field filled by a name of recognized pattern of multiple malformations

An algorithm is applied and a review is performed centrally, to define more uniformly cases with **major** associated malformations, the so called: **multi-malformed infants (MMI)**.

See Guidelines for MMI used at ICBD since 2001
Typical Oral Cleft Perinatal Database
Information for each case

• All information available in a participating register
  OR
  • Suggested set of data
    OR
    • Minimum dataset

www.icbd.org
Suggested and minimum information dataset

- Subject code
- Date of birth (at least month and year)
- Place of birth, Area of residence codes
- Sex, BW, GA, singleton/twin
- Maternal age, gravidity and parity
- Family history of birth defects
- Living status at registration
- Diagnosis
  - ICD IX or ICD X Code
    - Verbatim description
    - Photographs, Rx, drawings, clinical evaluation, diagnosis of syndrome if appropriate (when and where)

(§) All codes are hidden centrally, key available only locally

In yellow the minimum data set

www.icbd.org
How data arrives at ICBD

Any format, in Excel, is accepted. Just code’s keys needed
What ICBD does before sending “final” data to WHO

- General check of all data
- Create the appropriate variables needed (e.g.: date of birth by yy/mm/dd; specific field for OFC; country code; gravidity)
- Code the final diagnosis:
  - Isolated
  - Multimalformed infants, coded by number of associated unrelated malformations
  - Cases with syndromes, coded with OMIM
- Request of information when needed
- Interact with local registries
Request information

When?

- Median cleft lip (holoprosencephaly ? Syndrome ?)
- Bilateral cleft lip (only lip ?!)
- Cleft lip / palate in:
  - chromosomal syndromes (holoprosencephaly ?)
  - so called “amniotic band syndrome”
- Pierre Robin with cleft lip
- Any syndrome:
  - with a too generic name (eg.: first arch syndrome)
  - without a commonly available lab confirmation: please what is the evidence?
Interaction with source database

From May 1st, 2004

- Sending back the final database and asking comments and agreement

- Asking comments to the ongoing results
Typical Oral Cleft Database

Recent data

Europe – EU15

Europe – Others

South America

Other Countries

520,000 Exp Births/Year

330,000 Exp Births/Year

250,000 Exp Births/Year

210,000 Exp Births/Year

17 Reg

8 Reg

9 Areas

7 Reg
1,300,000 births per year are expected. Probably more, since some registries have expressed the desire to participate.
# Case by case information available

<table>
<thead>
<tr>
<th>Information</th>
<th># of Reg</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full minimum data set</td>
<td>41</td>
<td>... but 3, do not report GA</td>
</tr>
<tr>
<td>Maternal age</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Parity (SB + LB)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Gravidity (ToP+Sab+SB+LV)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Maternal occupation</td>
<td>18</td>
<td>Not always spec before / during</td>
</tr>
<tr>
<td>Maternal education</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Drugs in pregnancy</td>
<td>19</td>
<td>Not always perfect (trimester; specific type)</td>
</tr>
<tr>
<td>Smoking, alcohol</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Prenatal diagnosis, CVS</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>
Case by case information available

<table>
<thead>
<tr>
<th>Information</th>
<th># of Reg</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father age</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Father occupation</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Father education</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Consanguineity</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>
| Nuclear family malformations               | 25       | …. but, 2 report only sibs
                                                    |           | Often not specified                              |
| Blood’s group Proband+Mother+Father        | 10       |                                                    |
| **Verbatim, full description**            | **1 !**  |                                                    |
## Routine tables or maps

<table>
<thead>
<tr>
<th>Variable X (e.g. sex ratio)</th>
<th>CL</th>
<th>CLP</th>
<th>CL/P</th>
<th>CP</th>
<th>PR</th>
<th>CP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registers (41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reg Grouped x 4 (or more)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gran Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rates; Rate Ratios; Range of Values; Heterogeneity Test, Confidence Intervals
### Number of Typical Oral Clefts

<table>
<thead>
<tr>
<th>Registries Set</th>
<th>Period sent</th>
<th># of Reg.</th>
<th># of Cases</th>
<th>Total Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe 15</td>
<td>2001 (1)</td>
<td>17</td>
<td>681</td>
<td>401 586</td>
</tr>
<tr>
<td>Europe Others</td>
<td>2001-2002</td>
<td>8</td>
<td>505</td>
<td>329 908</td>
</tr>
<tr>
<td>South America</td>
<td>2001</td>
<td>9</td>
<td>367</td>
<td>207 423</td>
</tr>
<tr>
<td>Other Countries</td>
<td>2001-2002</td>
<td>7</td>
<td>649</td>
<td>325 358</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>41</strong></td>
<td><strong>2 272</strong></td>
<td><strong>1 263 980</strong></td>
<td></td>
</tr>
</tbody>
</table>

(1) France Paris only 2002-1; Germany Saxony Anhalt also 2002 2003-1
Male sex proportion

Total cases

Cleft lip +/− palate

Cleft palate

"Not yet" heterogeneity for
• cleft lip vs cleft lip palate
• isolated vs MMI
• among registries or group of them

M:F = 1.56

M:F = 0.75
# Rates of Oral Clefts by Group of Registries

<table>
<thead>
<tr>
<th>Group of Registries</th>
<th>CL</th>
<th>CLP</th>
<th>Total CL +/- P</th>
<th>CP</th>
<th>Pierre Robin</th>
<th>Tot CP</th>
<th>Total Oral Clefts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe 15</td>
<td>3.3</td>
<td>6.1</td>
<td>9.4</td>
<td>3.7</td>
<td>0.9</td>
<td>4.6</td>
<td>14.0</td>
</tr>
<tr>
<td>Europe Others</td>
<td>3.3</td>
<td>6.4</td>
<td>9.7</td>
<td>5.1</td>
<td>0.5</td>
<td>5.6</td>
<td>15.3</td>
</tr>
<tr>
<td>South America</td>
<td>2.9</td>
<td>9.4</td>
<td>12.3</td>
<td>5.4 *</td>
<td>0.1 *</td>
<td>5.4</td>
<td>17.7</td>
</tr>
<tr>
<td>Other Countries</td>
<td>5.1</td>
<td>10.6</td>
<td>15.7</td>
<td>3.7</td>
<td>0.6</td>
<td>4.3</td>
<td>20.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3.7</td>
<td>8</td>
<td><strong>11.8</strong></td>
<td>4.4</td>
<td>0.5</td>
<td><strong>4.9</strong></td>
<td><strong>16.7</strong></td>
</tr>
</tbody>
</table>

* Not yet reviewed centrally

**Rates per 10 000 births**
Variations in oral clefts rates seems to be due mainly to CLP rates variations.
Highest and lowest rates

Northern Europe = 17.3

Southern Europe = 8.7
Highest and lowest rates

18.7 (n=170)

11.1 (n=25)
Highest and lowest rates

South America

Total cases

9 Areas

27.6 (19)

14.7 (17)

Equador

Chile

Uruguay

Argentina

Perú

Brasil

Bolivia

Colombia

Venezuela

Guyana

Francesa

Total cases

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Highest and lowest rates
Rate Ratios of Oral Clefts by Group of Registries

<table>
<thead>
<tr>
<th>Grouped Registries</th>
<th>CL</th>
<th>CLP</th>
<th>Tot CP</th>
<th>Ratio</th>
<th>Total Oral Clefts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe 15</td>
<td>3.3</td>
<td>6.1</td>
<td>4.6</td>
<td>1 : 1.9 : 1.4</td>
<td>14.0</td>
</tr>
<tr>
<td>Europe Others</td>
<td>3.3</td>
<td>6.3</td>
<td>5.7</td>
<td>1 : 1.9 : 1.7</td>
<td>15.3</td>
</tr>
<tr>
<td>South America</td>
<td>2.9</td>
<td>9.4</td>
<td>5.5</td>
<td>1 : 3.2 : 1.9</td>
<td>17.7</td>
</tr>
<tr>
<td>Other Countries</td>
<td>5.1</td>
<td>11.0</td>
<td>4.3</td>
<td>1 : 2.2 : 0.8</td>
<td>20.0</td>
</tr>
<tr>
<td>Total</td>
<td>3.7</td>
<td>8</td>
<td>4.9</td>
<td>1 : 2.2 : 1.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Published</td>
<td></td>
<td></td>
<td></td>
<td>1 : 2 : 1</td>
<td></td>
</tr>
</tbody>
</table>
Higher rates of CL+/- P are associated to higher CLP : CL ratios = more severe types of primary palate defects

South Africa

Mexico

$r = 0.35; p = 0.036$
Proportion of specific types

Only registries with less than 20% of unknown

<table>
<thead>
<tr>
<th>Registries Set</th>
<th>C P hard</th>
<th>CL bilateral</th>
<th>CLP bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Reg</td>
<td>Cases</td>
</tr>
<tr>
<td>Europe 15</td>
<td>23</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Europe Others</td>
<td>66</td>
<td>6</td>
<td>149</td>
</tr>
<tr>
<td>Other Countries</td>
<td>100</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

South America not yet coded
### Proportion of specific types

Only registries with less than 20% of unknown

<table>
<thead>
<tr>
<th>Registries Set</th>
<th>C P hard</th>
<th>CL bilateral</th>
<th>CLP bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Reg</td>
<td>Cases</td>
</tr>
<tr>
<td>Europe 15</td>
<td>23</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Europe Others</td>
<td>66</td>
<td>6</td>
<td>149</td>
</tr>
<tr>
<td>Other Countries</td>
<td>100</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

South America not yet coded

Legittima suspicione

Total cases
Proportion (%) of isolated cases

<table>
<thead>
<tr>
<th>Registries Set</th>
<th>CL</th>
<th>CLP</th>
<th>Tot +/- P</th>
<th>CP</th>
<th>Pierre Robin</th>
<th>Tot CP</th>
<th>Total Oral Clefts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Countries</td>
<td>77.0</td>
<td>71.5</td>
<td>73.2</td>
<td>68.1</td>
<td>50.0</td>
<td>65.7</td>
<td>71.6</td>
</tr>
<tr>
<td>Europe 15</td>
<td>80.2</td>
<td>67.2</td>
<td>71.7</td>
<td>74.1</td>
<td>66.7</td>
<td>72.6</td>
<td>72.0</td>
</tr>
<tr>
<td>Europe Others</td>
<td>90.8</td>
<td>85.2</td>
<td>87.1</td>
<td>79.5</td>
<td>81.3</td>
<td>79.7</td>
<td>84.4</td>
</tr>
</tbody>
</table>

South America not yet coded

Other European countries has lower ascertainment of associated defects?

Legittima suspicione
Small for gestational age
Weight < 10° centile for gestational age from Canadian data (1994-96).

<table>
<thead>
<tr>
<th>Region</th>
<th>CL</th>
<th>CLP</th>
<th>CP</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>(n)</td>
<td>%</td>
<td>(n)</td>
</tr>
<tr>
<td>Europe 15</td>
<td>10.3</td>
<td>(68)</td>
<td>14.3</td>
<td>(112)</td>
</tr>
<tr>
<td>Eu-Others</td>
<td>12.2</td>
<td>(41)</td>
<td>26.2</td>
<td>(84)</td>
</tr>
<tr>
<td>S America (1)</td>
<td>28.6</td>
<td>(56)</td>
<td>20.0</td>
<td>(125)</td>
</tr>
<tr>
<td>Others</td>
<td>21.2</td>
<td>(125)</td>
<td>27.6</td>
<td>(234)</td>
</tr>
</tbody>
</table>

Suggestion: compare between columns, not between rows
## Registered syndromes

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Number</th>
<th>Prevalence of...... with oral clefts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q91.4-7</td>
<td>Trisomy 13</td>
<td>58</td>
<td>1 : 20.000</td>
</tr>
<tr>
<td>Q91.0-3</td>
<td>Trisomy 18</td>
<td>38</td>
<td>1 : 64.000</td>
</tr>
<tr>
<td>Q90.0-9</td>
<td>Trisomy 21</td>
<td>7</td>
<td>1 : 165.000</td>
</tr>
<tr>
<td>Q899A</td>
<td>Amniotic band</td>
<td>6</td>
<td>1 : 193.000</td>
</tr>
<tr>
<td>Q93.3</td>
<td>4p –</td>
<td>5</td>
<td>1 : 231.000</td>
</tr>
<tr>
<td>119300</td>
<td>Van der Woude</td>
<td>5</td>
<td>1 : 231.000</td>
</tr>
<tr>
<td>Q899V</td>
<td>VATER</td>
<td>4</td>
<td>1 : 290.000</td>
</tr>
<tr>
<td>164210</td>
<td>Hemifacial Microsoma</td>
<td>4</td>
<td>1 : 290.000</td>
</tr>
<tr>
<td>129900</td>
<td>E E C</td>
<td>3</td>
<td>1 : 386.000</td>
</tr>
</tbody>
</table>
## Registered syndromes

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Number</th>
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<tr>
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<td>4p –</td>
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<td>Van der Woude</td>
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</tr>
<tr>
<td>Q899V</td>
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<td>4</td>
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</tr>
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<td>164210</td>
<td>Hemifacial Microsomia</td>
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<tr>
<td>129900</td>
<td>E E C</td>
<td>3</td>
<td>1 : 386.000</td>
</tr>
</tbody>
</table>

Exp 35 cases

[www.icbd.org](http://www.icbd.org)
Quality of data may be improved.

Registries’s coordinator and local doctors should be ready to collaborate to improve the quality of data.
The second step

A specific syndrome database

Source: Support Organization

Case Finding and Simple Epi
Craniofacial Anomalies Database → Case Finding and Simple Epi

Source: Surgical Dpts

The third step
Requested information

- Date of form compilation
- Participating Hospital–Doctor
- New/old patient – new/old follow up
- Patient’s identity code
- Date of birth (mm/yy)
- Place of birth (Nation, region)
- Residence (Nation, region)
- Sex

- Date of diagnosis (mm/yy)
- Place of diagnosis
- Evidence of diagnosis
- Full and detailed description
- Copy of relevant medical record
- Consultation diary
- Informed consent and agreement to be furtherly contacted
Requested Information

• Selected clinical data
  – Month and year of
    • CFA
      – Discovery (6)
      – Diagnosis confirmed
    • Syndrome
      – Suspected
      – Diagnosis confirmed

• **Selected data on surgical treatment of CFA**
  – Surgery procedure(s) : yes/not
    • Place (specify hospital name and city)
    • Type of surgery
    • Month and year
    • Outcome
Requested Information

• Father and Mother
  – working activity at present (*)
  – years of school attended (*)
  – affected or operated upon of any congenital anomaly (if yes specify)

• Siblings
  – Total number of sibs (include aborted fetuses after prenatal diagnosis of any congenital anomaly; specify sex and birthweight)
  – Affected sibs by any congenital anomaly (if yes specify)

(*) The common best indicator of socio-economic status
The fourth step

MADRE
All cases with CL/P plus random controls (1:5)

World-wide databases in the same basket

MMI
All cases with CL/P

www.icbd.org