# Impact of Folic Acid Food Fortification in South America

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**ECLAMC**

**15'**

Castilla-Budapest-2008-FAF-SAM.ppt

American Journal of Medical Genetics 123A:123–128 (2003)

**Step-1**

# Preliminary Data on Changes in Neural Tube Defect Prevalence Rates After Folic Acid Fortification in South America

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**Step-2**

American Journal of Medical Genetics 135A:120–125 (2005)

# Reduction of Birth Prevalence Rates of Neural Tube Defects After Folic Acid Fortification in Chile

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# ECLAMC NETWORK

In **2007**,

**86** hospitals

at **60** cities

of **9** countries

covering

**200.000** annual births

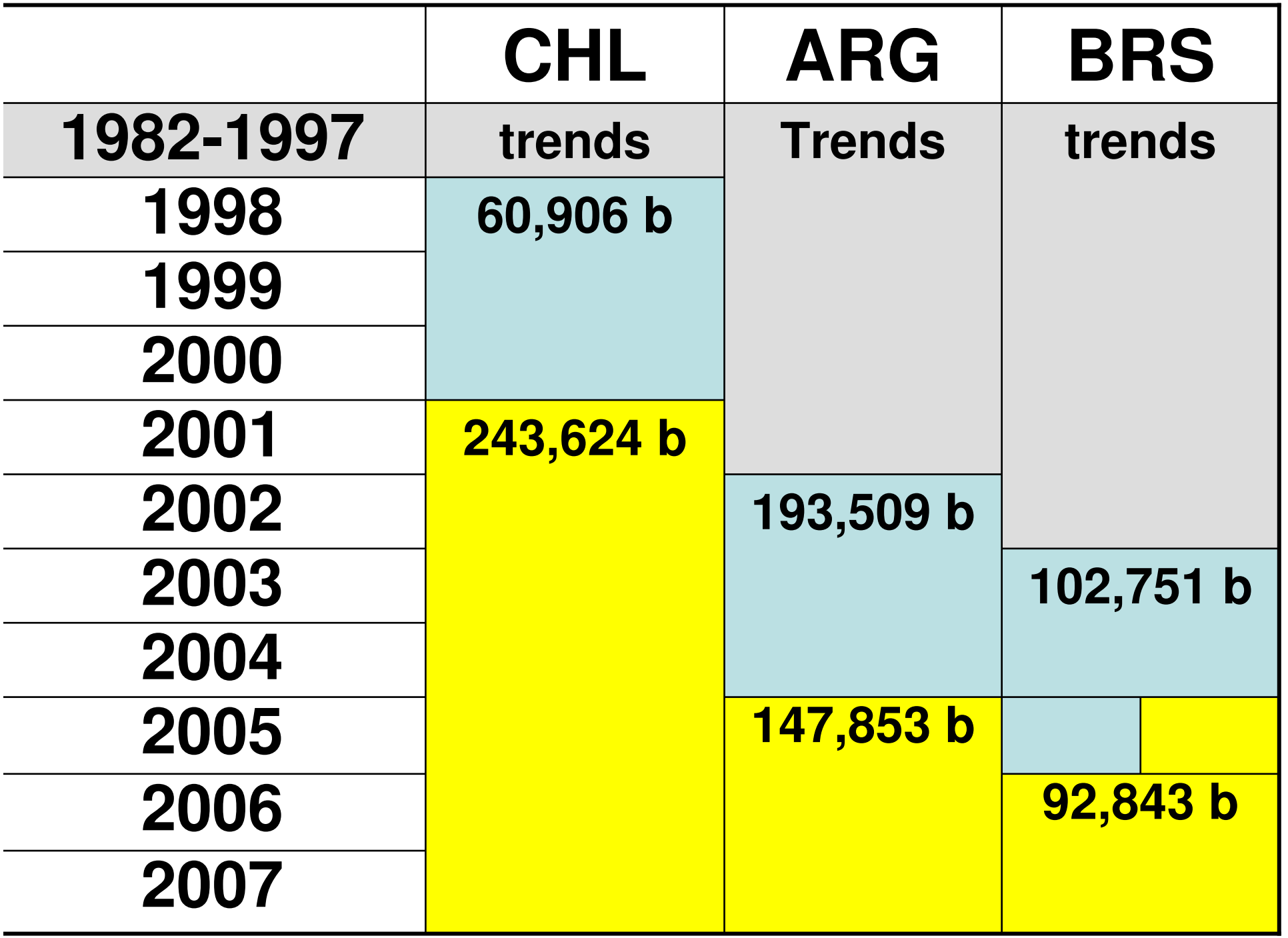
| | CHL | ARG | BRZ |
|---|---|---|---|
| Population Jul.2008 | 16 million | 42 million | 192 million |
| Births/yr | 244,000 | 685,000 | 3,000,000 |
| IMR | 10.1 | 17.6 | 33.1 |
| MR <5 yo | 14.5 | 24.5 | 45.9 |

| Cronogram | CHL | ARG | BRS |
|---|---|---|---|
| Legislation | Min.Act | Law 25.630 | Min.Act RDC 344 |
| Promulgated | 10-09-99 | 08-22-02 | 12-13-02 |
| Implemented | 01-01-00 | 11-13-03 | 06-13-04 |
| First Fortified Births | 01-01-01 | 11-13-04 ? | 06-13-05 ? |
| Flours | Wheat | Wheat | Wheat & Corn |

| | CHL | ARG | BRS |
|---|---|---|---|
| Folic Acid Concentration in Flour; mg/Kg | 2,2 | 2,2 | 1,5 |
| Estimated Daily Intake of Flour per Capita: g | 227 | 221 | ??? |
| Folic Acid Daily Dosis: µg | 499 | 486 | ??? |

# Materials

- **Study Period: 1982-2007**
- **Births : 3,347,559**
- **in 3 countries**
- **Malformed infants: 184,658**
- **64 selected anomaly types:**


CHL
ARG
BRS
1982-1997
trends
Trends
trends
1998
60,906 b
1999
2000
2001
243,624 b
2002
193,509 b
2003
102,751 b
2004
2005
147,853 b
2006
92,843 b
2007

# Analytic Strategy

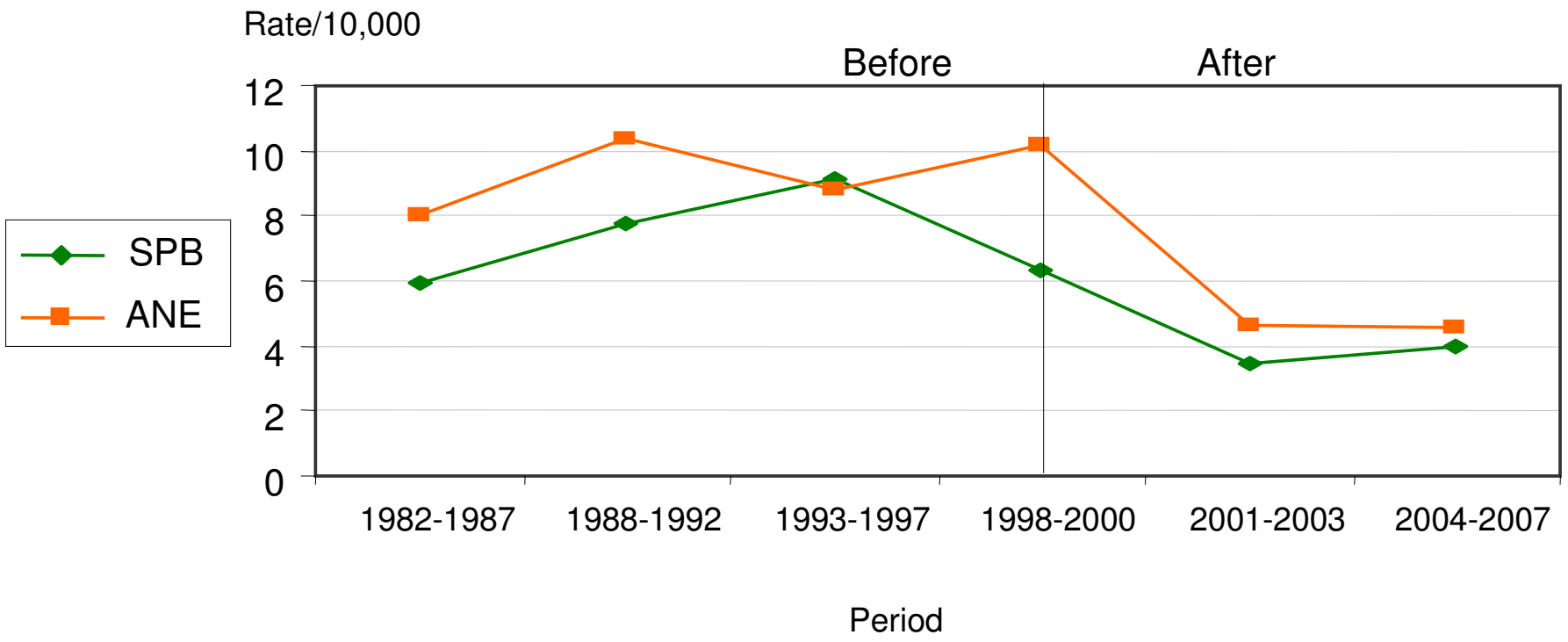
- Hospital-based data

- Changing secular trends

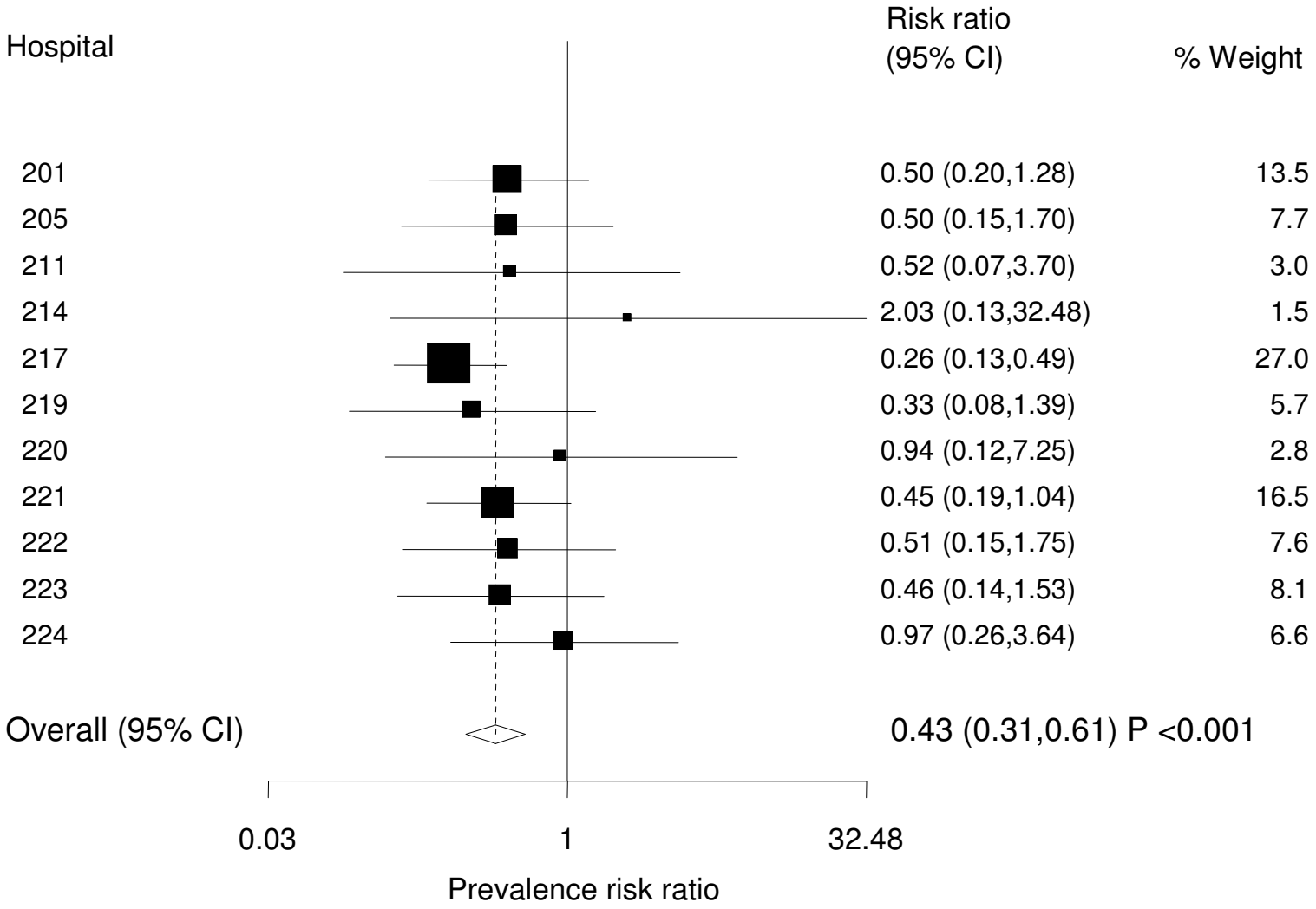
# Power and sample size to reduction detected depending on baseline malformation rate

| Country | | Baseline rate | | | Sample size | |
|---|---|---|---|---|---|---|
| Chile | Reduction rate | 1/1000 | 1/2000 | 1/3000 | Pre-fortification | Post-fortification |
| | 20% | 0.315 | 0.176 | 0.119 | 69,677 | 243,624 |
| | 30% | 0.627 | 0.367 | 0.247 | | |
| | 40% | 0.875 | 0.606 | 0.431 | | |
| | 50% | 0.975 | 0.815 | 0.638 | | |
| Argentina | Reduction rate | 1/1000 | 1/2000 | 1/3000 | 193,509 | 147,853 |
| | 20% | 0.459 | 0.243 | 0.167 | | |
| | 30% | 0.828 | 0.516 | 0.356 | | |
| | 40% | 0.981 | 0.797 | 0.606 | | |
| | 50% | 0.999 | 0.954 | 0.832 | | |
| Brazil | Reduction rate | 1/1000 | 1/2000 | 1/3000 | 102,751 | 92,843 |
| | 20% | 0.285 | 0.151 | 0.106 | | |
| | 30% | 0.590 | 0.318 | 0.213 | | |
| | 40% | 0.859 | 0.549 | 0.378 | | |
| | 50% | 0.977 | 0.788 | 0.583 | | |

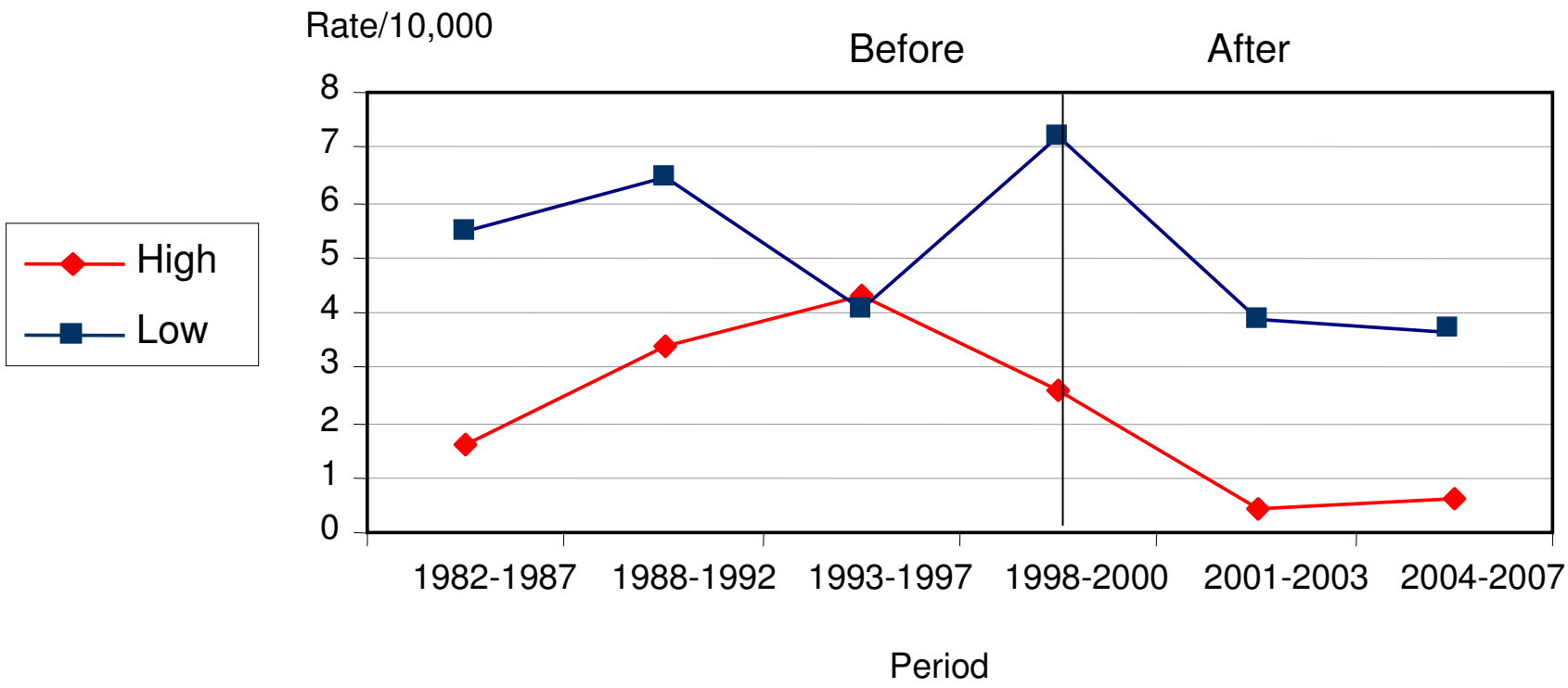
# CHL. Spina Bifida and Anencephaly



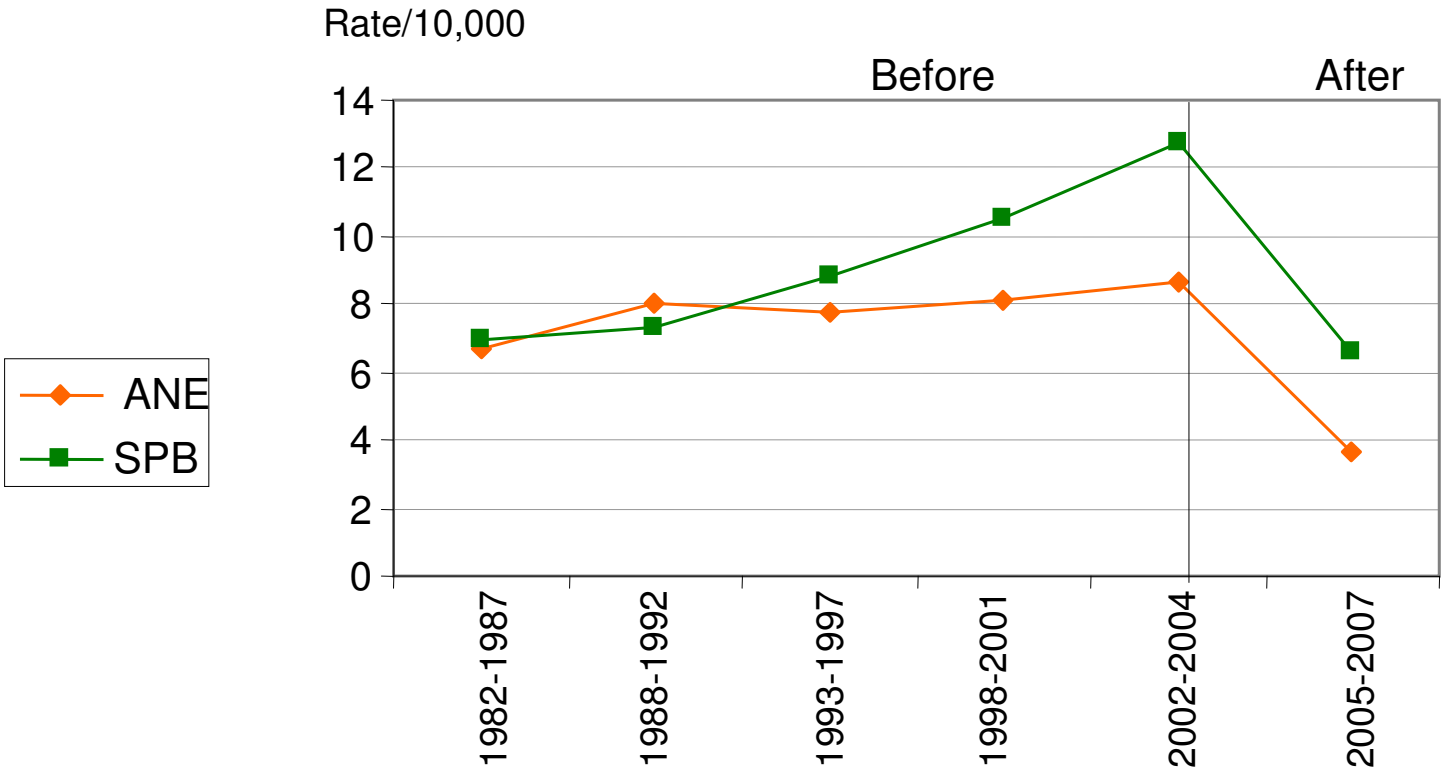
# CHL. Spina Bifida



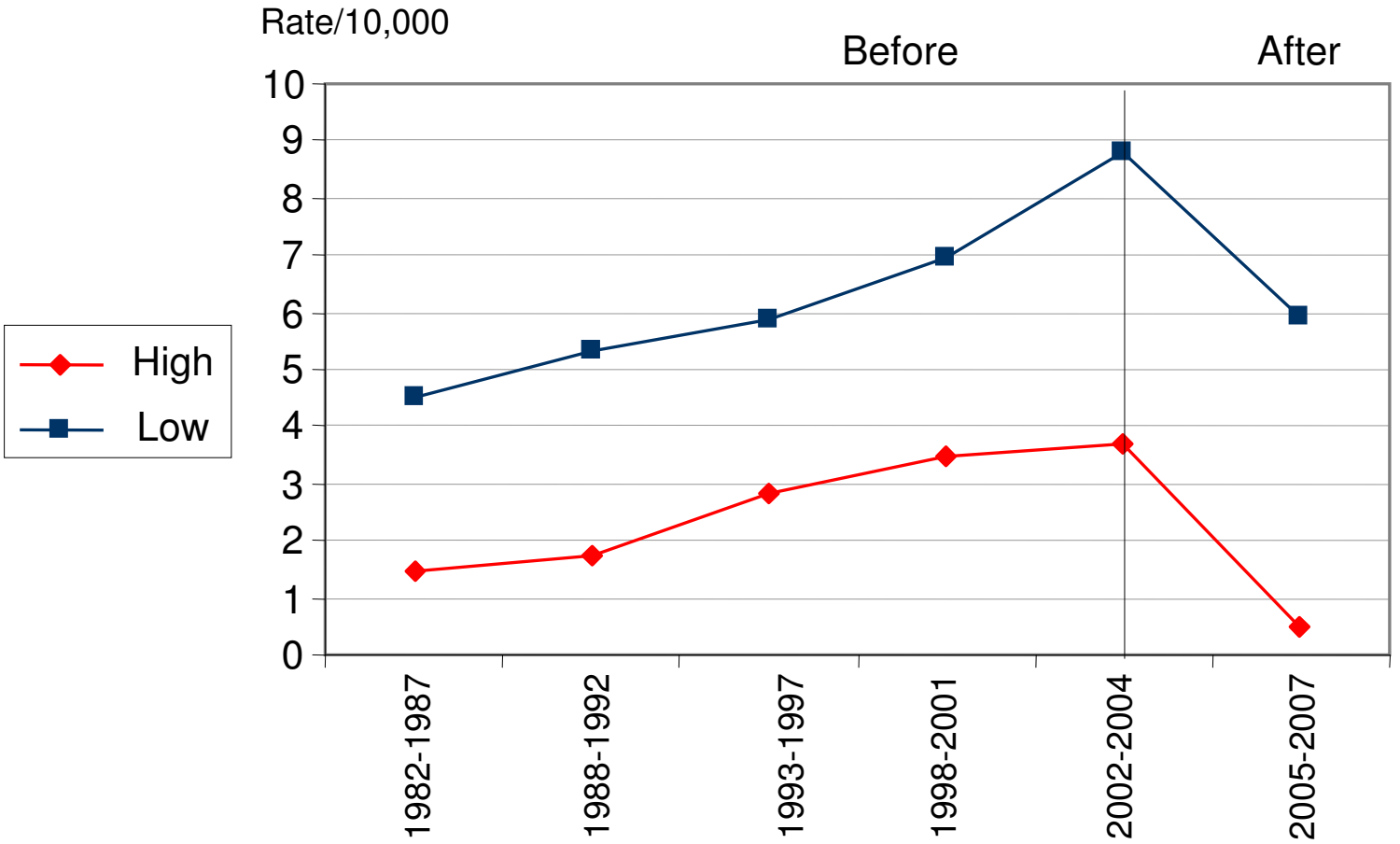
# CHL. Spina Bifida: High and Low



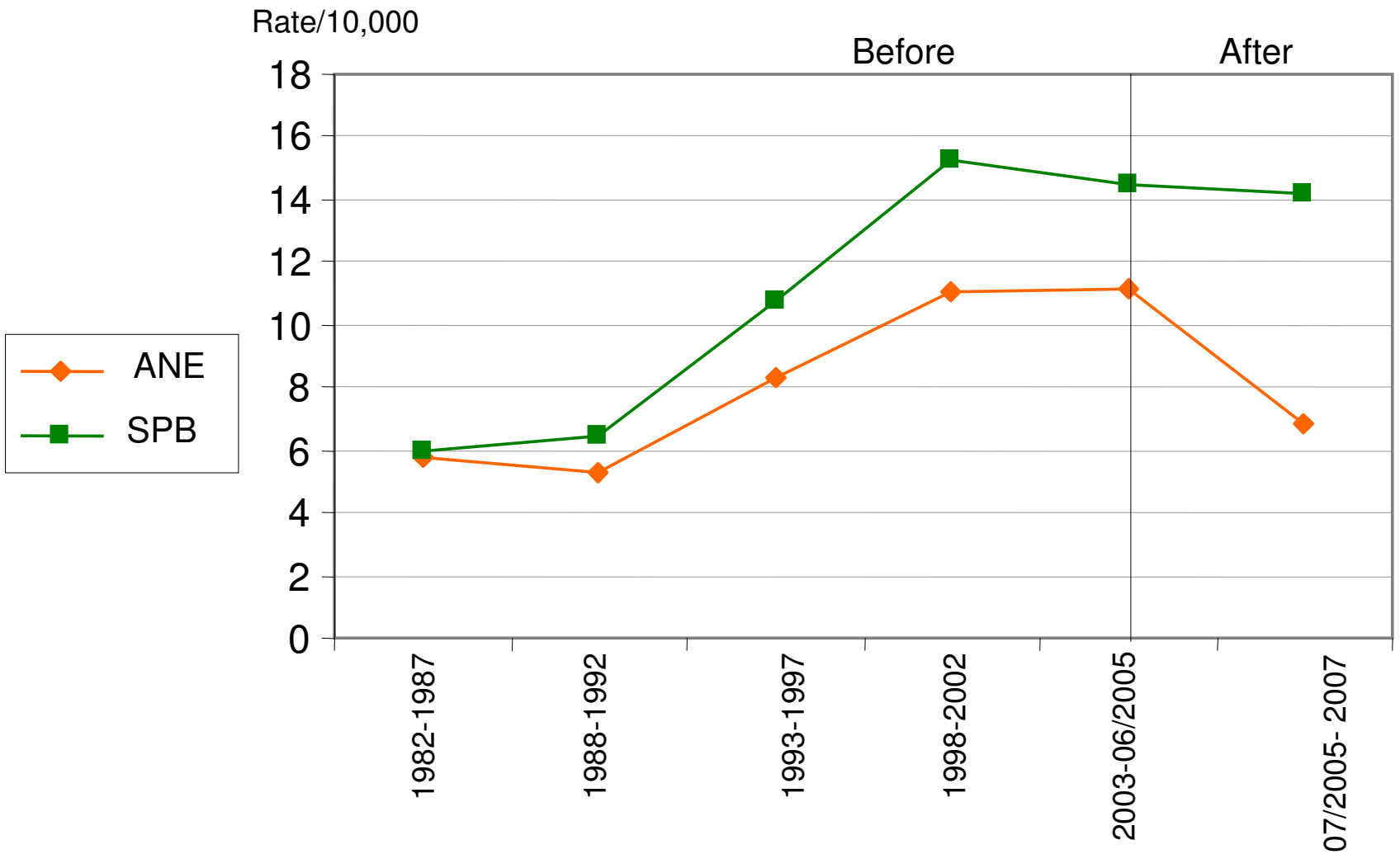
# ARG. Spina Bifida and Anencephaly



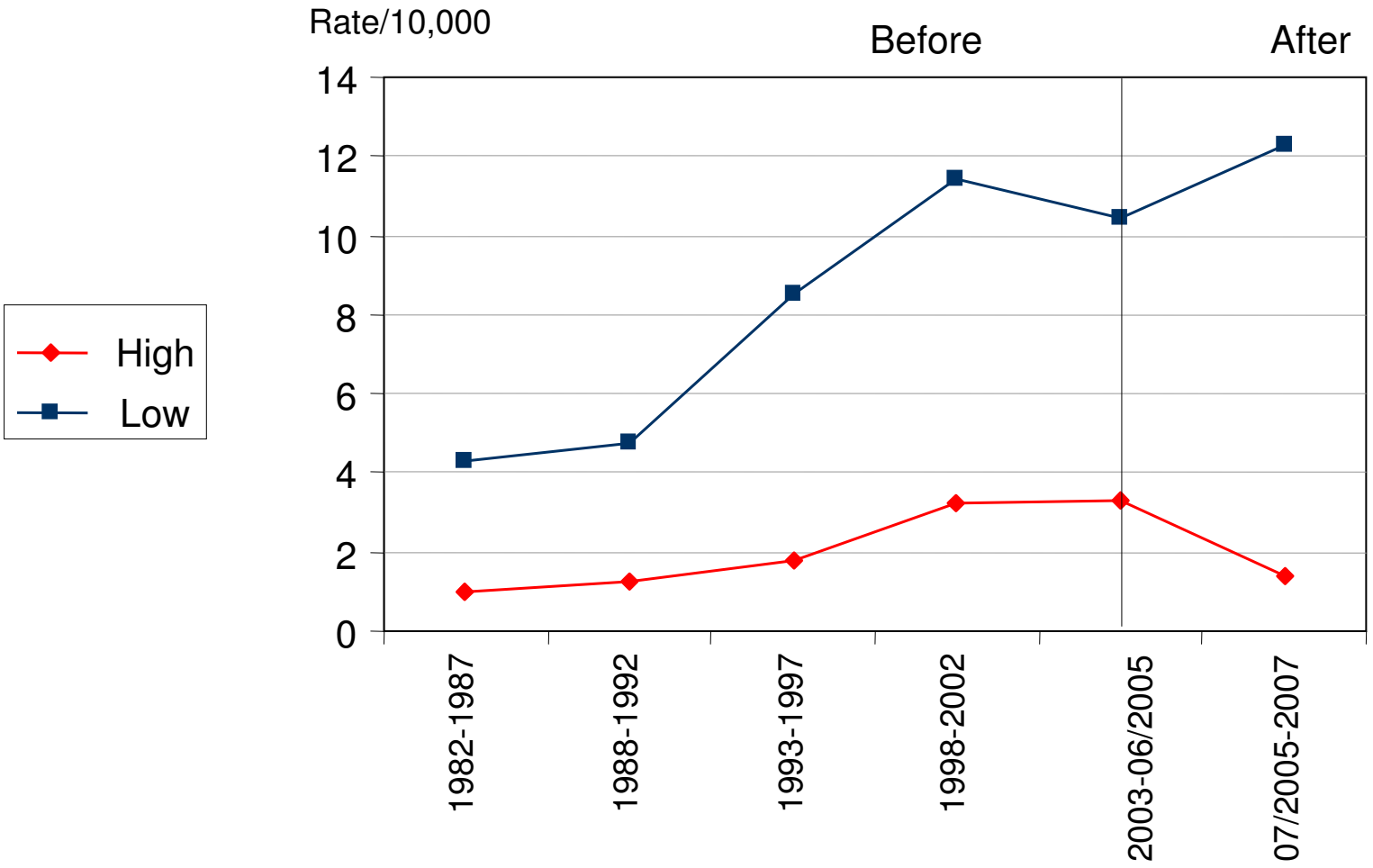
# ARG. Spina Bifida: High and Low



# BRZ. Spina Bifida and Anencephaly



# BRZ. Spina Bifida: High and Low



# Anomalies proven to be folate dependent

| | | Pre-fortification | Post-fortification | | Adjusted by hospital | | |
|---|---|---|---|---|---|---|---|
| Malformation | Country | Rate/10,000 | Rate/10,000 | PRR | PRR | 95% CI | p |
| Anencephaly | CHL | 6.31 | 3.65 | 0.58 | 0.54 | 0.36-0.83 | 0.004 |
| | ARG | 8.63 | 3.65 | 0.42 | 0.59 | 0.42-0.82 | 0.002 |
| | BRS | 11.19 | 6.89 | 0.62 | 0.57 | 0.37-0.87 | 0.010 |
| Spina Bifida | CHL | 10.19 | 4.60 | 0.45 | 0.43 | 0.31-0.60 | <0.001 |
| | ARG | 12.71 | 6.63 | 0.52 | 0.59 | 0.46-0.76 | <0.001 |
| | BRS | 11.19 | 6.89 | 0.62 | 0.57 | 0.37-0.87 | 0.010 |
| Spina Bifida high | CHL | 2.58 | 0.49 | 0.19 | 0.17 | 0.07-0.42 | <0.001 |
| | ARG | 3.72 | 0.47 | 0.13 | 0.27 | 0.14-0.53 | <0.001 |
| | BRS | 3.31 | 1.40 | 0.42 | 0.49 | 0.26-0.96 | 0.036 |
| Spina bifida low | CHL | 7.18 | 3.78 | 0.53 | 0.55 | 0.37-0.81 | 0.002 |
| | ARG | 8.79 | 5.95 | 0.68 | 0.75 | 0.57-0.99 | 0.044 |
| | BRS | 10.41 | 12.28 | 1.18 | 1.12 | 0.62-2.02 | 0.703 |
| Spina bifida isolated | CHL | 7.32 | 2.38 | 0.33 | 0.30 | 0.19-0.46 | <0.001 |
| | ARG | 8.16 | 3.31 | 0.41 | 0.43 | 0.30-0.63 | <0.001 |
| | BRS | 8.47 | 6.79 | 0.80 | 0.60 | 0.31-1.14 | 0.119 |
| Spina bifida associated | CHL | 2.87 | 2.22 | 0.77 | 0.62 | 0.37-1.10 | 0.106 |
| | ARG | 4.55 | 3.31 | 0.73 | 0.83 | 0.55-1.23 | 0.349 |
| | BRS | 6.03 | 7.43 | 1.23 | 1.11 | 0.63-1.95 | 0.710 |
| Cephalocele | CHL | 3.30 | 1.81 | 0.55 | 0.47 | 0.27-0.83 | 0.009 |

PRR: Prevalence Rate ratio

# Anomalies shown to decrease with folates at least once

| | | Pre-fortification | Post-fortification | | Adjusted by hospital | | |
|---|---|---|---|---|---|---|---|
| Malformation | Country | Rate/10,000 | Rate/10,000 | PRR | PRR | 95% CI | p |
| Omphalocele | CHL | 2.73 | 2.71 | 0.99 | 0.95 | 0.56-1.62 | 0.856 |
| | ARG | 3.46 | 3.72 | 1.08 | 1.34 | 0.92-1.96 | 0.782 |
| | BRS | 5.94 | 6.25 | 1.05 | 1.00 | 0.62-1.61 | 0.994 |
| CHD-Conotruncal | CHL | 0.29 | 0.16 | 0.55 | 0.58 | 0.16-2.14 | 0.415 |
| | ARG | 0.41 | 0.14 | 0.34 | 0.92 | 0.25-3.41 | 0.898 |
| | BRS | 0.19 | 0.32 | 1.68 | 1.36 | 0.26-7.07 | 0.713 |
| CHD | CHL | 51.67 | 61.69 | 1.19 | 1.19 | 0.89-1.57 | 0.236 |
| | ARG | 36.79 | 36.59 | 0.99 | 0.92 | 0.76-1.11 | 0.386 |
| | BRS | 45.45 | 47.50 | 1.05 | 0.94 | 0.75-1.18 | 0.616 |
| Cleft palate only | CHL | 4.02 | 6.32 | 1.57 | 1.22 | 0.73-2.06 | 0.441 |
| | ARG | 4.08 | 5.28 | 1.29 | 1.43 | 1.04-1.48 | 0.027 |
| | BRS | 5.94 | 4.20 | 0.71 | 0.68 | 0.46-1.04 | 0.077 |
| Cleft lip with/without palate | CHL | 11.91 | 11.58 | 0.97 | 0.97 | 0.74-1.27 | 0.819 |
| | ARG | 13.75 | 10.82 | 0.79 | 0.79 | 0.61-1.03 | 0.081 |
| | BRS | 11.09 | 13.03 | 1.17 | 1.20 | 0.91-1.57 | 0.196 |
| Cleft lip without cleft palate | CHL | 2.73 | 2.30 | 0.84 | 0.81 | 0.46-1.43 | 0.462 |
| | ARG | 2.95 | 2.57 | 0.87 | 0.97 | 0.63-1.51 | 0.906 |
| | BRS | 3.50 | 3.77 | 1.08 | 1.15 | 0.70-1.89 | 0.573 |
| Cleft lip with cleft palate | CHL | 9.19 | 9.28 | 1.01 | 0.99 | 0.72-1.33 | 0.929 |
| | ARG | 10.80 | 8.25 | 0.76 | 0.81 | 0.62-1.07 | 0.129 |
| | BRZ | 7.59 | 9.26 | 1.22 | 1.21 | 0.87-1.69 | 0.245 |

PRR: Prevalence Rate ratio

# Anomalies shown to decrease with folates at least once

| | | Pre-fortification | Post-fortification | | Adjusted by hospital | | |
|---|---|---|---|---|---|---|---|
| Malformation | Country | Rate/10,000 | Rate/10,000 | PRR | PRR | 95% CI | p |
| Down syndrome | CHL | 23.11 | 25.37 | 1.10 | 1.09 | 0.91-1.32 | 0.326 |
| | ARG | 19.07 | 18.46 | 0.97 | 1.01 | 0.86-1.20 | 0.859 |
| | BRS | 19.85 | 15.83 | 0.80 | 0.81 | 0.65-1.02 | 0.069 |
| Down syndrome ≤ 19 | CHL | 14.59 | 8.65 | 0.59 | 0.55 | 0.29-1.03 | 0.064 |
| | ARG | 5.91 | 10.80 | 1.83 | 2.00 | 1.10-3.64 | 0.023 |
| | BRS | 8.85 | 6.58 | 0.74 | 0.85 | 0.38-1.84 | 0.666 |
| Down syndrome ≥ 35 | CHL | 83.61 | 110.02 | 1.32 | 1.33 | 1.03-1.73 | 0.027 |
| | ARG | 85.49 | 84.42 | 0.99 | 1.05 | 0.82-1.34 | 0.705 |
| | BRS | 92.25 | 77.23 | 0.84 | 0.88 | 0.64-1.20 | 0.420 |
| Stillbirths (%) | CHL | 0.75 | 0.71 | 0.95 | 0.92 | 0.81-1.04 | 0.198 |
| | ARG | 1.16 | 1.10 | 0.95 | 0.92 | 0.83-1.03 | 0.142 |
| | BRS | 1.39 | 1.30 | 0.94 | 0.91 | 0.78-1.05 | 0.202 |
| Low birth weight (%) | CHL | 7.71 | 7.72 | 1.00 | 1.01 | 0.94-1.11 | 0.675 |
| | ARG | 11.39 | 10.77 | 0.95 | 0.93 | 0.89-0.96 | <0.001 |
| | BRS | 13.9 | 13.6 | 0.98 | 0.96 | 0.91-1.01 | 0.124 |

PRR: Prevalence Rate ratio

# Anomalies shown to increase with folates at least once

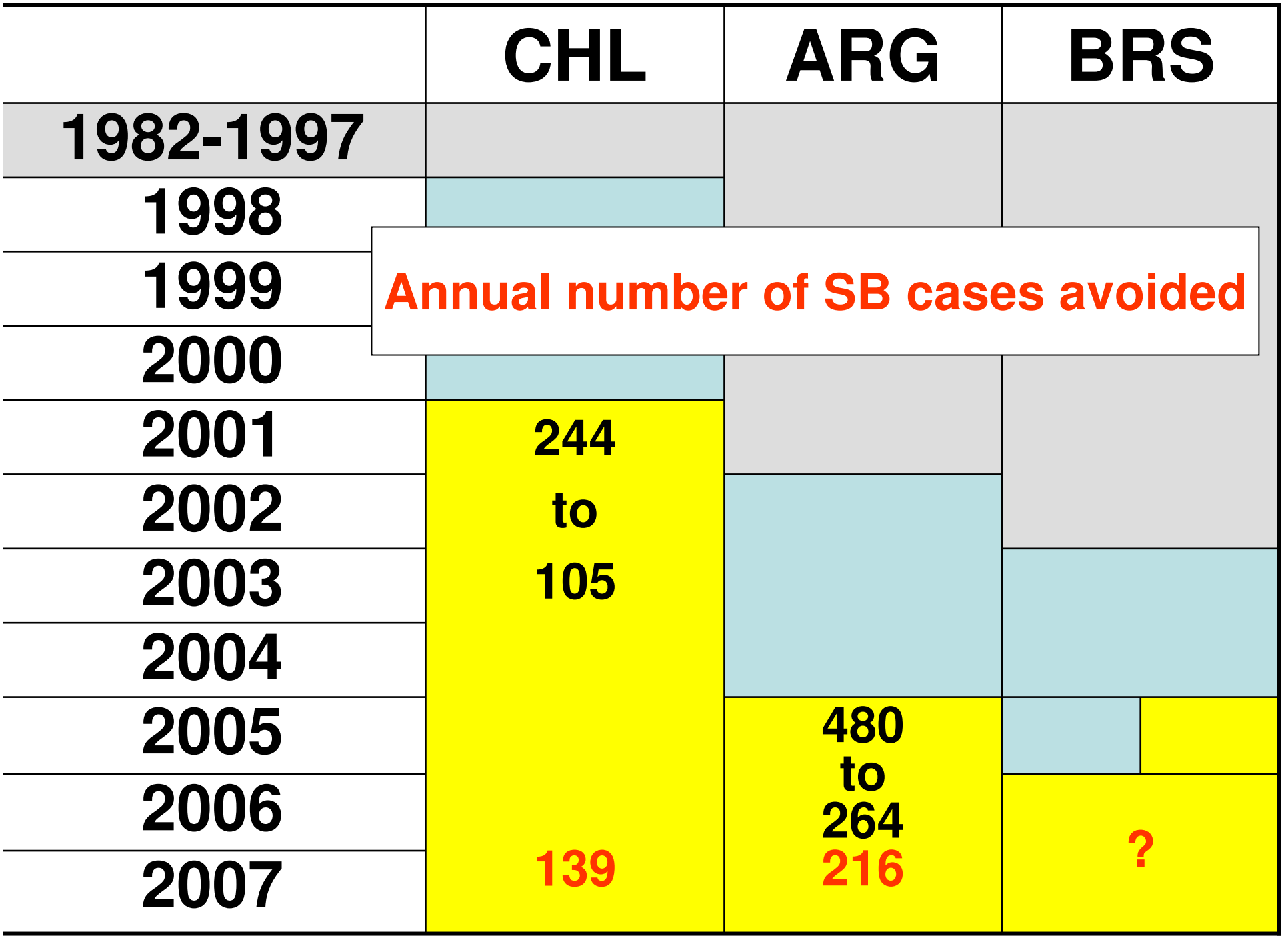
| | | Pre-fortification | Post-fortification | | Adjusted by hospital | | |
|---|---|---|---|---|---|---|---|
| Malformation | Country | Rate/10,000 | Rate/10,000 | PRR | PRR | 95% CI | p |
| Twinning (%) | CHL | 0.87 | 0.98 | 1.13 | 1.12 | 1.00-1.26 | 0.043 |
| | ARG | 1.10 | 1.14 | 1.04 | 1.00 | 0.91-1.09 | 0.997 |
| | BRS | 1.24 | 1.33 | 1.07 | 1.02 | 0.93-1.13 | 0.610 |
| Polydactyly-Postaxial | CHL | 12.34 | 12.77 | 1.03 | 0.92 | 0.71-1.21 | 0.575 |
| | ARG | 1.10 | 1.14 | 1.04 | 1.00 | 0.91-1.09 | 0.997 |
| | BRS | 1.24 | 1.33 | 1.07 | 1.02 | 0.93-1.13 | 0.610 |
| Polydactyly-Preaxial | CHL | 4.45 | 4.39 | 0.99 | 0.91 | 0.60-1.39 | 0.671 |
| | ARG | 0.72 | 0.88 | 1.22 | 1.06 | 0.50-1.22 | 0.881 |
| | BRS | 0.39 | 0.65 | 1.67 | 1.27 | 0.40-4.08 | 0.685 |

PRR: Prevalence Rate ratio

# Conclusions

## all based on $p < 0.001$

- FAF reduced the BPR of SB and AN in CHL and ARG, not in BRZ.
- Larger reduction for SB (57%) and CEPH (53%), than for AN (46%)
- Larger reduction for H-SB (83 %) than for L-SB (45 %)
- No other changes for another 61 CA types.


CHL
ARG
BRS
1982-1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
Annual number of SB cases avoided
244
to
105
480
to
264
139
216
?

# Step-4

## ....next year