

# Gastroschisis Meeting

London, March 1<sup>o</sup> , 2005

International Epidemiologic Collaborative  
Research in Gastroschisis

*Pierpaolo Mastroiacovo and Alessandra Lisi*

International Centre on Birth Defects (ICBD), Rome

International Clearinghouse for Birth Defects Research and Surveillance (ICBDSR)

# Outlines

- Problems of diagnosis – coding
- Prevalence and time trend worldwide
  - Review of specific published studies on the literature: prevalence and time trend
  - Review of unspecific available and/or published data from birth defects registries
    - Prevalence of gastroschisis in the most recent period
    - Time trends
- Risk factors
  - Review of the specific published studies
  - Unpublished data on drug exposure

# Problems on evaluating gastroschisis prevalence rates

- Case definition - Diagnosis
  - Abdominal wall defect not well described
  - Omphalocele not covered by membranes
  - Limb body wall complex
  - Pentalogy of Cantrell
  - Rare syndrome (e.g.:Fryns, chromosomal)
- Case registration
  - Livebirths and stillbirths
  - Termination of pregnancies (ToPs)
    - Not registered in some registries
    - If registered
      - started with delay
      - Undernotification may be wider

Rankin et al; 1999  
Prenat Diagn 1999; 19:662

Anterior abdominal defects  
= 296 (19 change  
diagnosis after review)

|                |     |
|----------------|-----|
| Gastroschisis  | 133 |
| Exomphalos     | 98  |
| Limb-body-wall | 30  |
| Others         | 23  |
| Unclassified   | 12  |

# Review of the published reports

| <b>Author, year</b>  | <b>Country</b>         | <b>Years</b> | <b>Rate</b> | <b>Trend</b>   |
|----------------------|------------------------|--------------|-------------|----------------|
| Baird, 1981          | Canada BC              | 1964-78      | 0.8         | No mention     |
| Lindham, 1981        | Sweden                 | 1965-76      | 0.4 --- 1.2 | Increasing     |
| Roeper, 1987         | US-California          | 1968-77      | 0.06 -- 0.9 | Increased      |
| Hemminki, 1982       | Finland                | 1970-79      | 0.8 -- 1.4  | Increased      |
| Martinez-Frias, 1984 | 78Spain                | 1976-81      | 0.4         | Increasing     |
| Bugge, 2000          | 80 Denmark             | 1970-89      | 1.3         | In-de-increase |
| Kazaura, 2004        | 82.5 Norway            | 1967-98      | 0.5 --- 2.9 | Increase       |
| Byron-Scott, 1998    | 84 Australia, S &W     | 1980-90      |             | No increase    |
| Reid, 2003           | 85 Australia Western   | 1980-01      | 1.0 --- 2.4 | Increase       |
| Calzolari, 1995      | 85 Europe Eurocat      | 1980-90      | 0.9         | No mention     |
| Suita, 2000          | 85 Japan – Hosp        | 1975-97      | 0.1 --- 0.5 | Increased      |
| Calzolari, 1993      | 86 Italy               | 1984-89      | 0.6         | No change      |
| Stone, 1998          | 86 Glasgow             | 1980-93      | 1.3         |                |
| Nichols, 1997        | 86.7 Australia Western | 1980-93      | 0.5 --- 3.2 | Increased      |
| Puffinbarger 1995    | US Oklahoma            |              | ????        | Increased      |

# Review of the published reports

| <b>1° author, year</b> | <b>Country</b>           | <b>Years</b> | <b>Rate</b> | <b>Time change</b> |
|------------------------|--------------------------|--------------|-------------|--------------------|
| Baerg, 2003            | 87.5 Canada-Saskatchewan | 1985-00      | 1.9 --- 4.1 | Increase           |
| Tan, 1996              | 90 England – Wales       | 1987-93      | 0.7 – 1.4   | Increased          |
| Dillon, 1997           | 90UK North Regions       | 1988-92      | 2.8         | No mention         |
| Penman, 1998           | 90 UK South-West         | 1987-95      | 1.6 --- 4.4 | Increased          |
| Rankin, 1999           | 91 UK-North              | 1986-96      | 1.5 --- 5.3 | Increased          |
| Forrester, 1999        | 91.5 US-Hawai            | 1986-97      | 3.0         | Increased          |
| Arnold, 2004           | 92 South Africa 2 Hosp   | 1981-01      | X 35        | Increase           |
| Zhu, 1996              | 92 China                 | 1990-94      | 1.6         | No mention         |
| Chalmers, 1997         | 92 Scotland              | 1989-95      | 1.9         | No mention         |
| Kilby, 1999            | 94 UK-West Midlands      | 1992-96      | 2.4         | No mention         |
| Laughon, 2003          | 98.5 US-North Caroline   | 1997-00      | 2.0 ---4.5  | Increase           |
| Salihu, 2003           | 95 US – New York         | 1992-99      |             | Increase           |
| Goldkrand, 2004        | 97 US – Georgia          | 1994-02      | 2.9 --- 6.0 |                    |

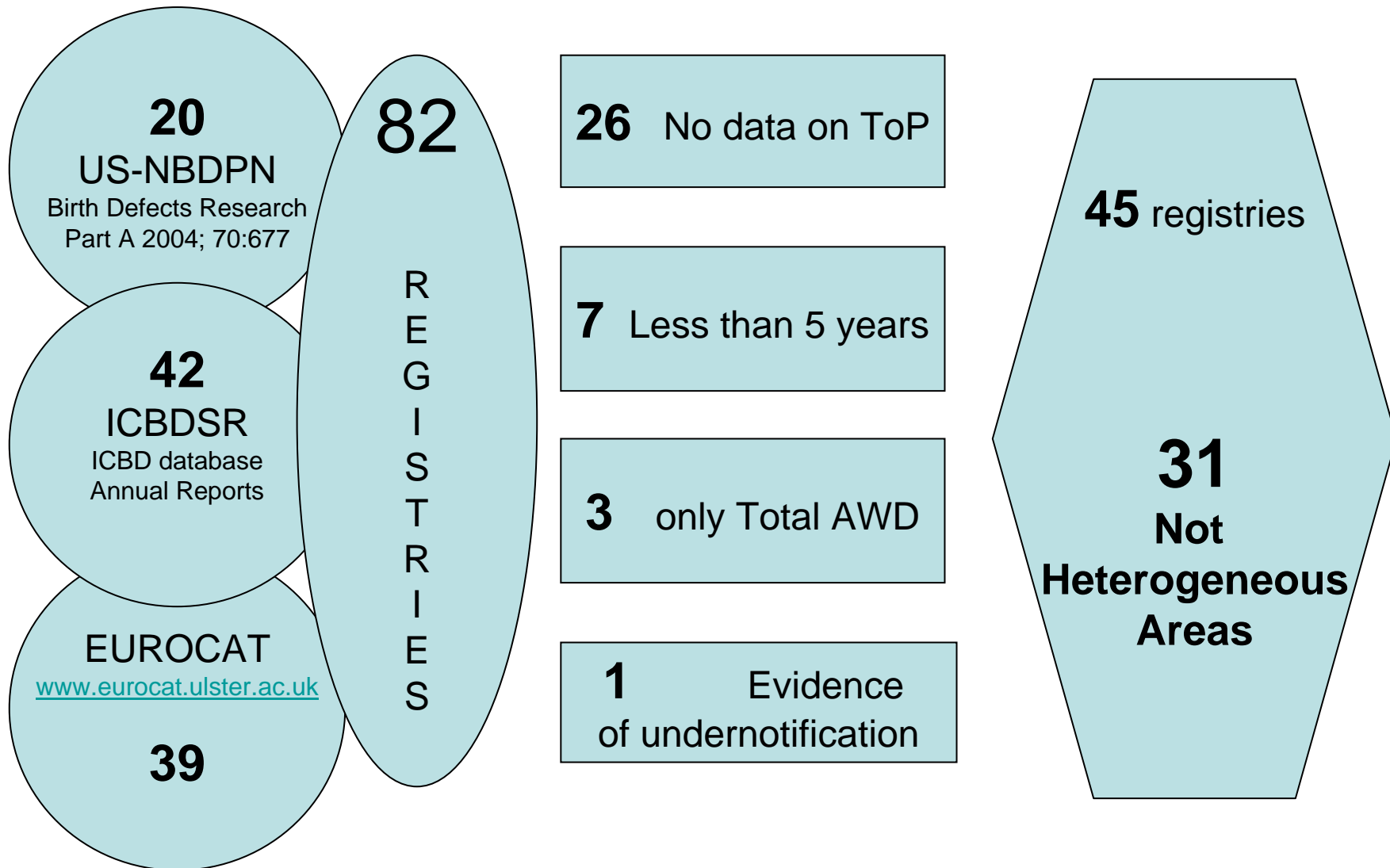
# Data from ICBDMS

# Prevalence of Gastroschisis

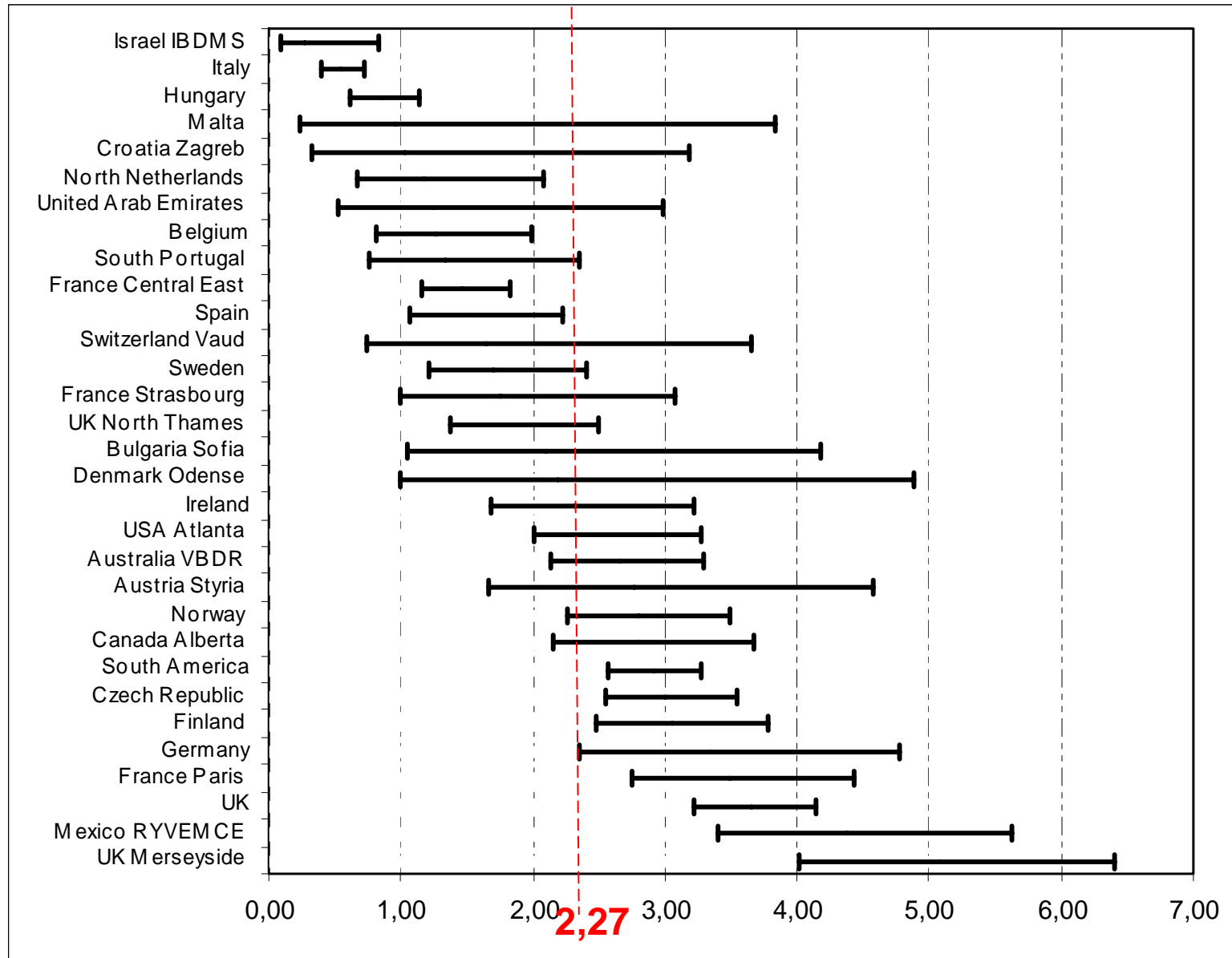
Recent data from three birth defects networks

- Source
  - Available data from ICBDSR and published data from not overlapping EUROCAT or US-NBDPN registries
- Years
  - Last five years available, most 1998 – 2002
- Feto-neonatal prevalence
  - LB + SB + ToP or LB + SB in countries where ToP is not allowed

# Registries considered



# Feto-neonatal prevalence in 31 Areas



# How valid are these data ?

- They are crude rates, not standardized by maternal age
- Multiple sources
  - ...rarely proportion of each source is given
- Indirect evidence
  - unspecified abd wall def
    - ... not always reliable
  - isolated defects
    - ... processing
  - maternal age specific rates
    - ... processing
- Ad hoc studies
  - ... very very rare

# Feto-neonatal prevalence in 31 Areas

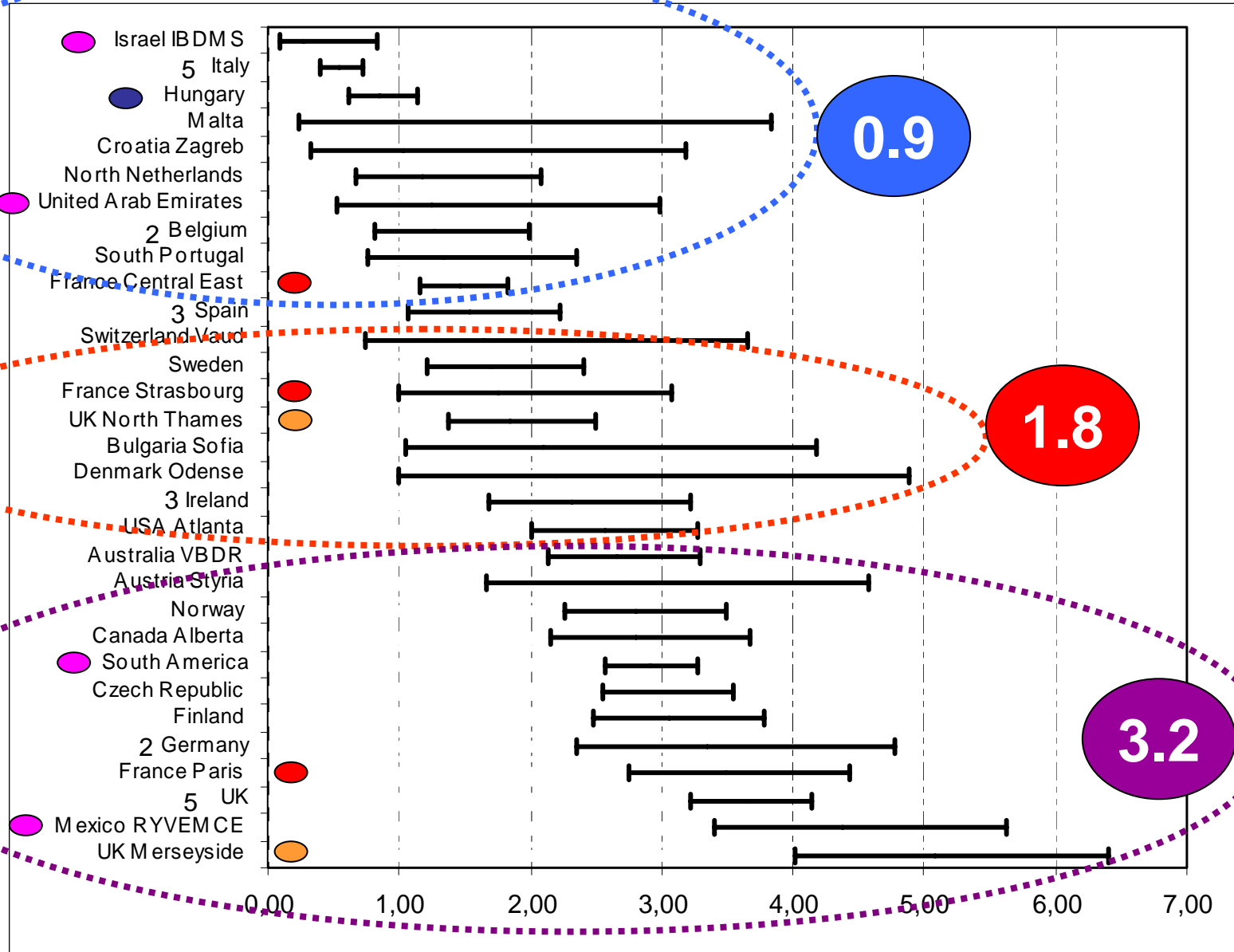
Hungary  
Only isolated

Heterogeneity in  
the same country

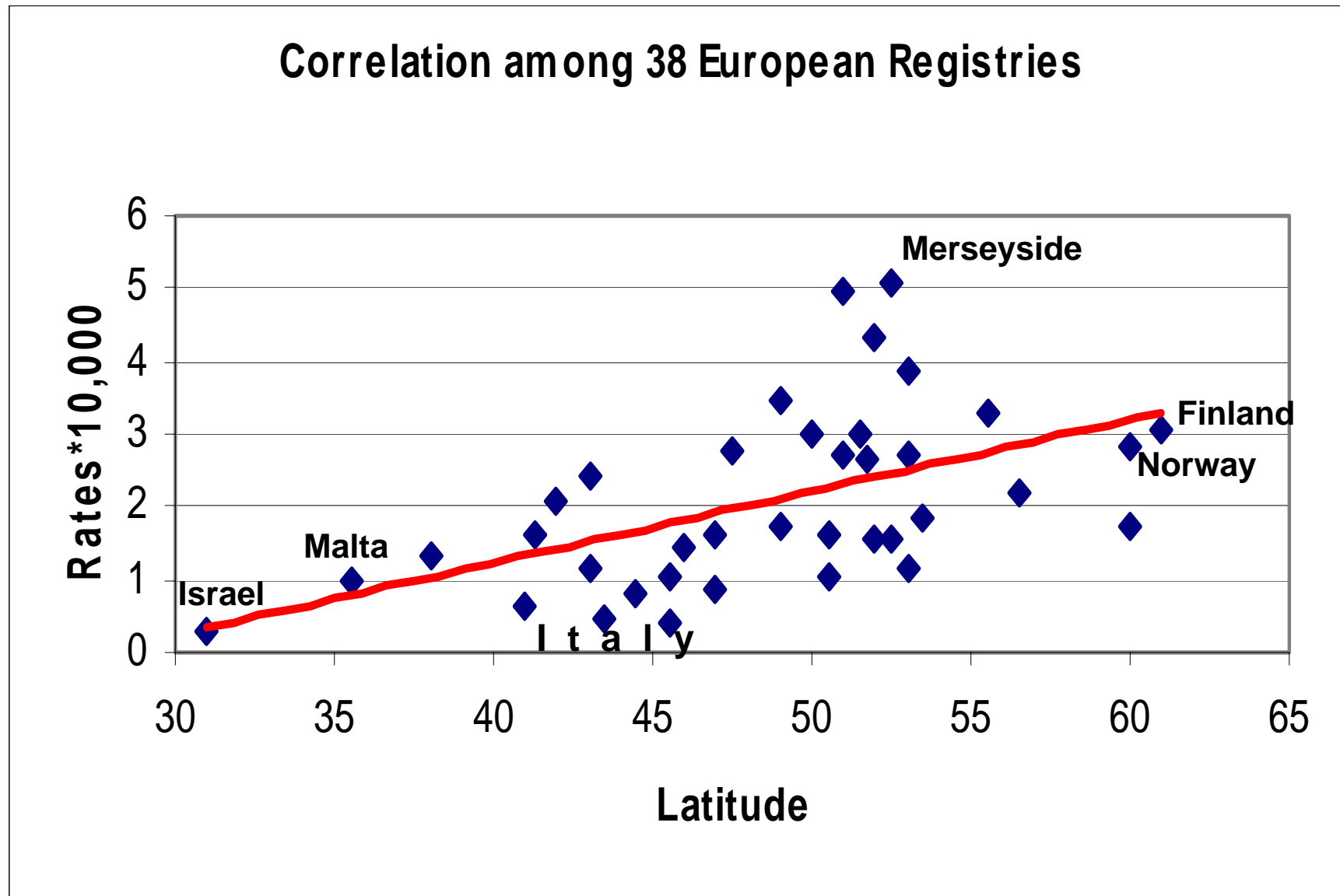
South America

Mexico

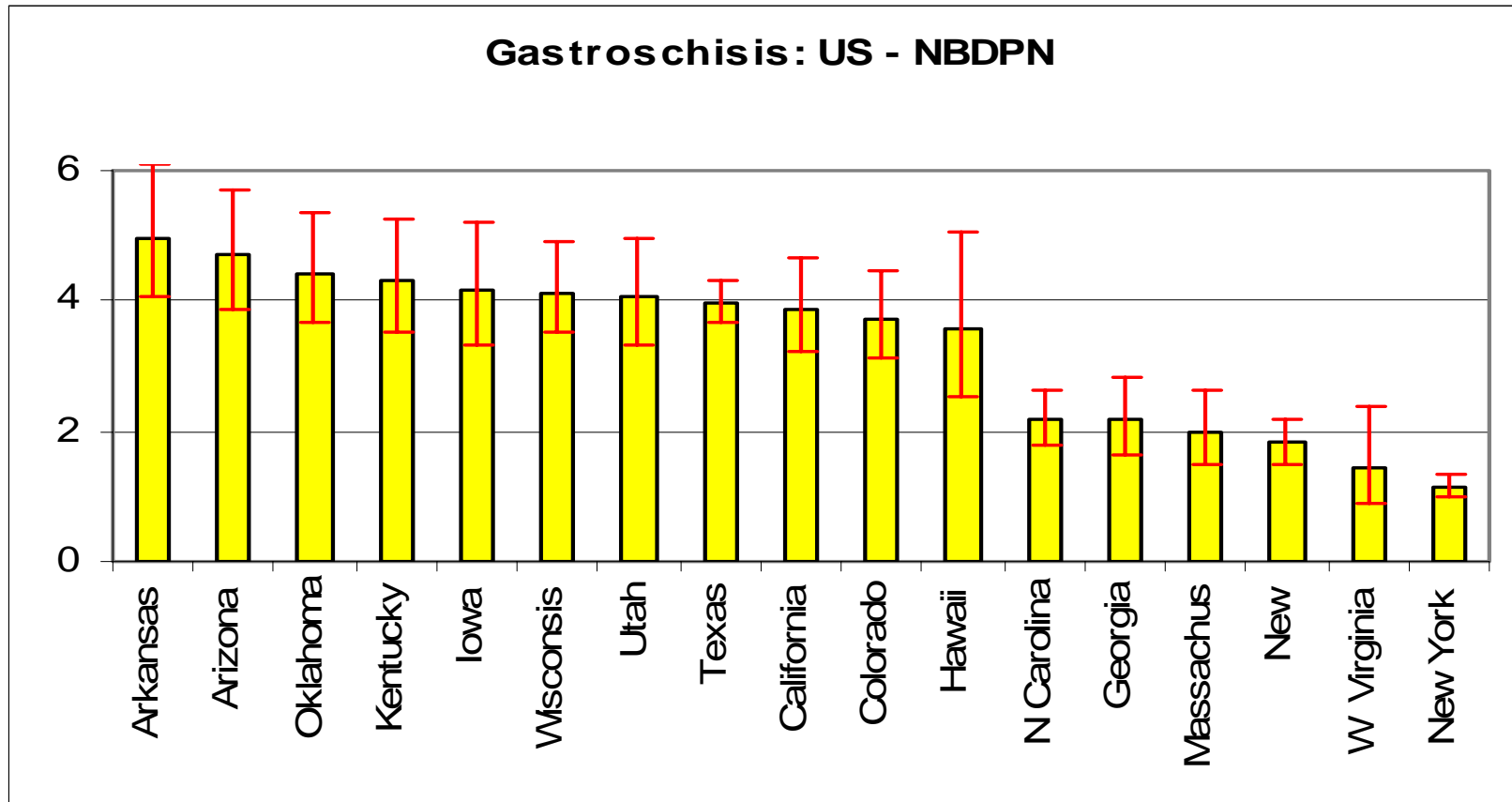
Hospital based



# Correlation with latitude in Europe



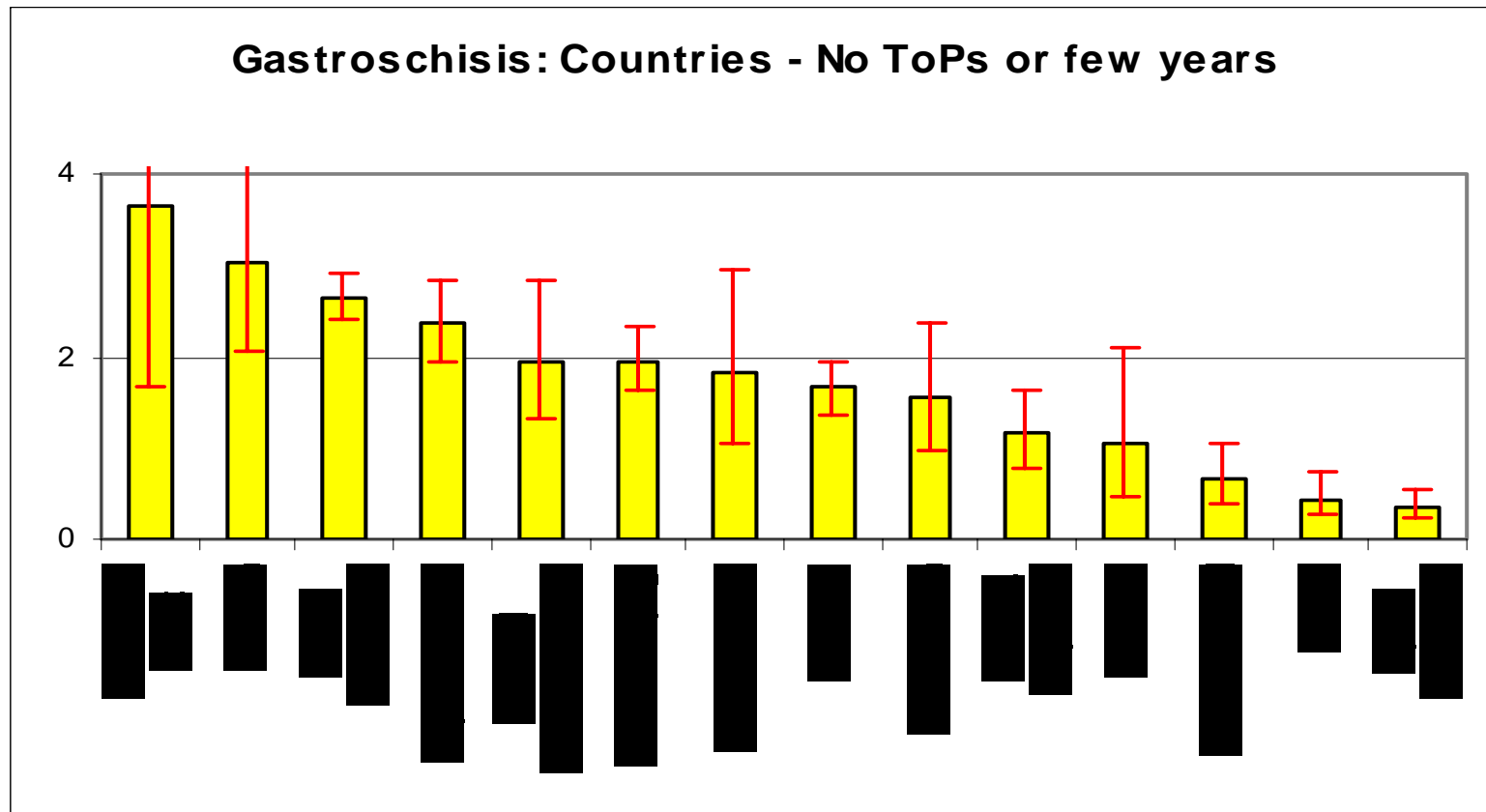
# More information



19 out of 32 state registries reporting (2 only few cases)

Two patterns (a) around 4/10.000 (b) around 2 or less

# More information



# Time trend analysis in 35 registries

- Only if :
  - Feto-neonatal prevalence available
  - At least 7 years
  - At least 10 total cases
- Analysis by type of register
  - Population based (32)
  - Hospital based (3)
- ... and by
  - Birth prevalence, longer period
  - Feto-neonatal prevalence, shorter period

# Time trend analysis in 35 registries

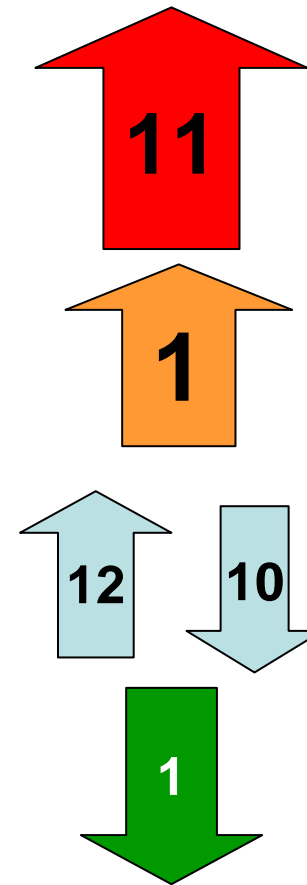
where feto-neonatal prevalence may be analyzed  
with at least 7 years and 10 total cases

- Analysis
  - Chi square for trend ( $p < 0.05$ )
  - Mantel-Haenszel Rate Ratio by year (RR<sub>y</sub>)  
with CI 95% (lower > 1)
  - Rate Ratio (RR-5y) = last 5 years rate / first  
5 years rate with CI

# Time trend analysis in 35 registries where feto-neonatal prevalence may be analyzed with at least 7 years and 10 total cases

- Results

- Evidence of a statistically significant increasing trend in birth prevalence and feto-neonatal prevalence
- Evidence of a statistically significant increasing trend in the last years only
- No evidence of statistically significant time trend
- Evidence of statistically significant decreasing trend in 1



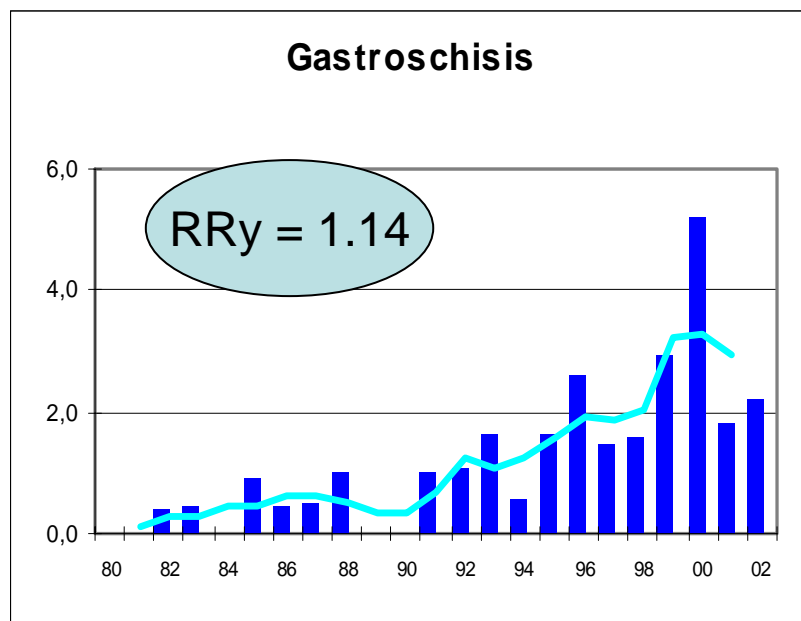
# Next slides :

## 11 + 1 Registries with an increasing trends

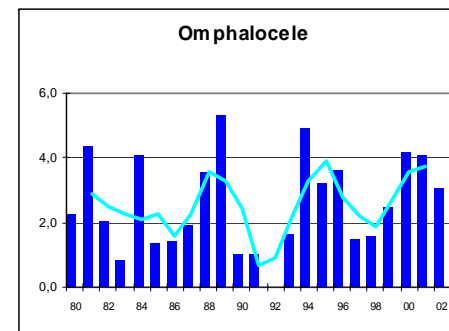
- Validity of time trend is higher if ...
  - Omphalocele does not decrease in parallel
  - Oesophageal atresia – arbitrary marker of a stable defect – does not increase in parallel
- Problems
  - Gastroschisis probably not well diagnosed and registered in the early years of some registries
  - ToPs have been registered with some delay and are underreported in some registries
  - Maternal age standardized rate should be evaluated

# Registries with an increasing time trend

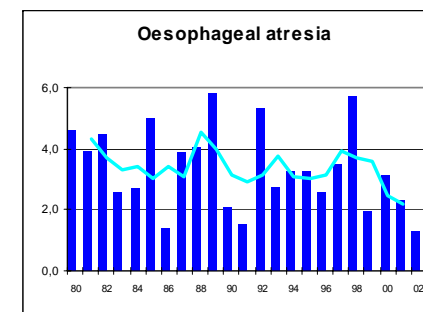
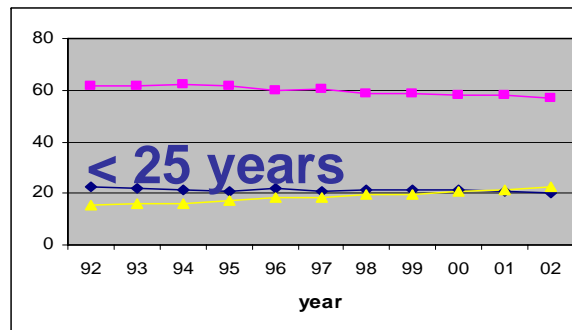
## Ireland, Dublin (20,000 births / year)



Births ToPs



Population maternal age distribution

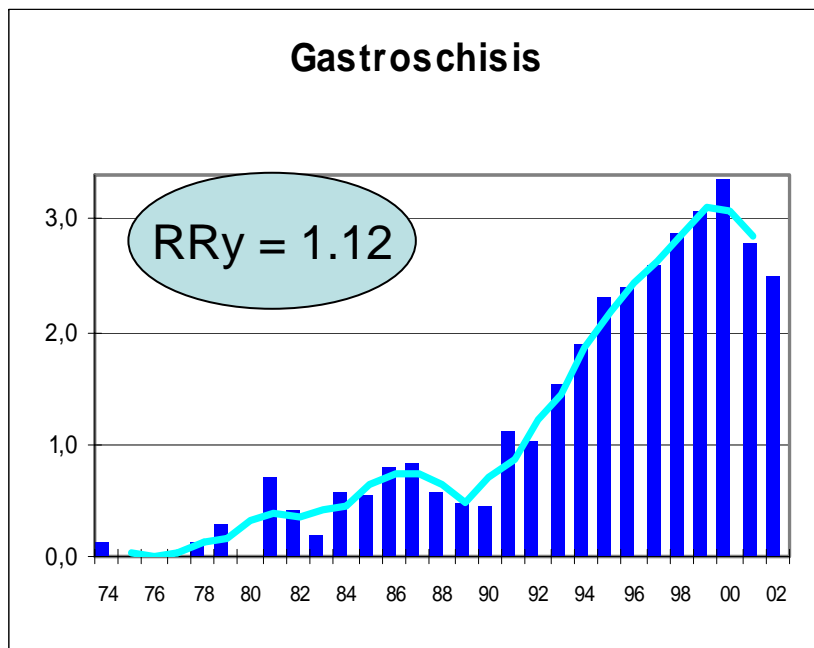


| 80-84 | 98-02 | RR-5y (CI 95%)   | Starting    | Peak       |
|-------|-------|------------------|-------------|------------|
| 0.16  | 2.71  | 17.3 (4.8-107.7) | Early 90ies | 5.2 – 2000 |

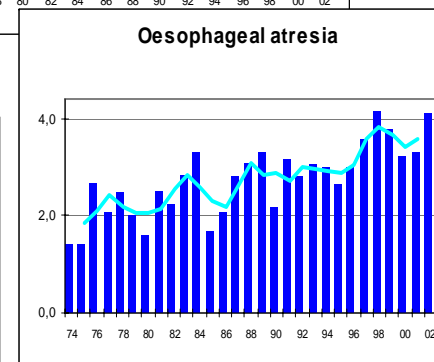
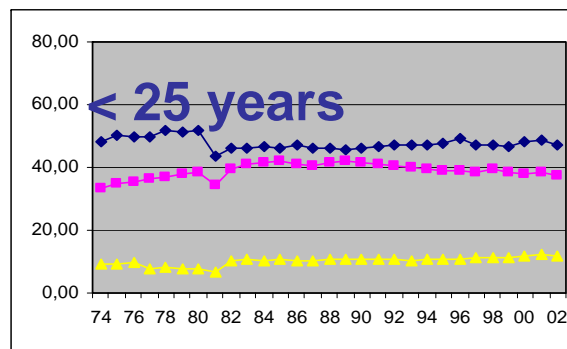
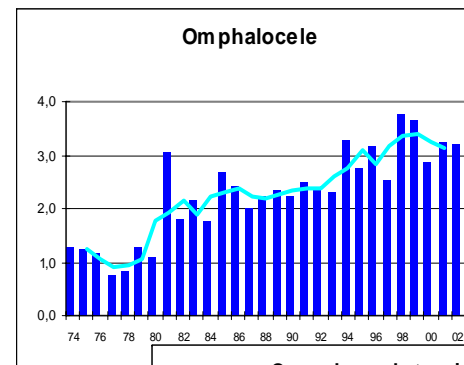
RR-5y = last 5 years rate / first 5 years rate

# Registries with an increasing time trend

## South America (up to 220,000 births / year)



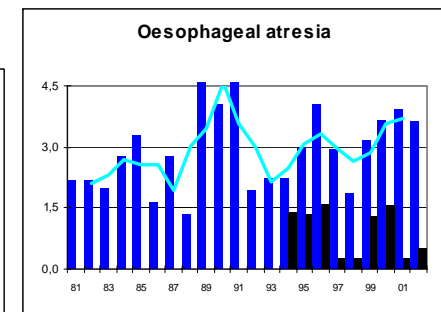
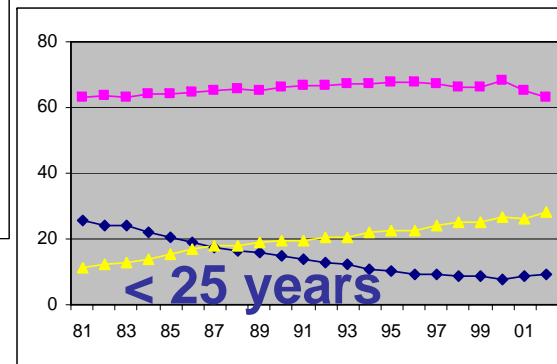
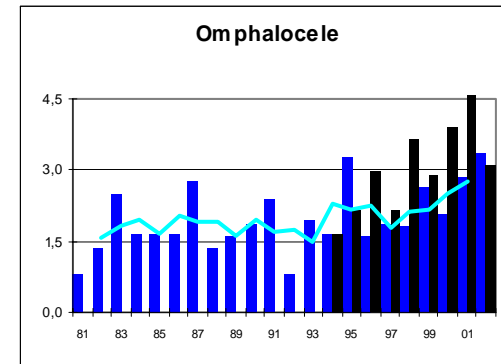
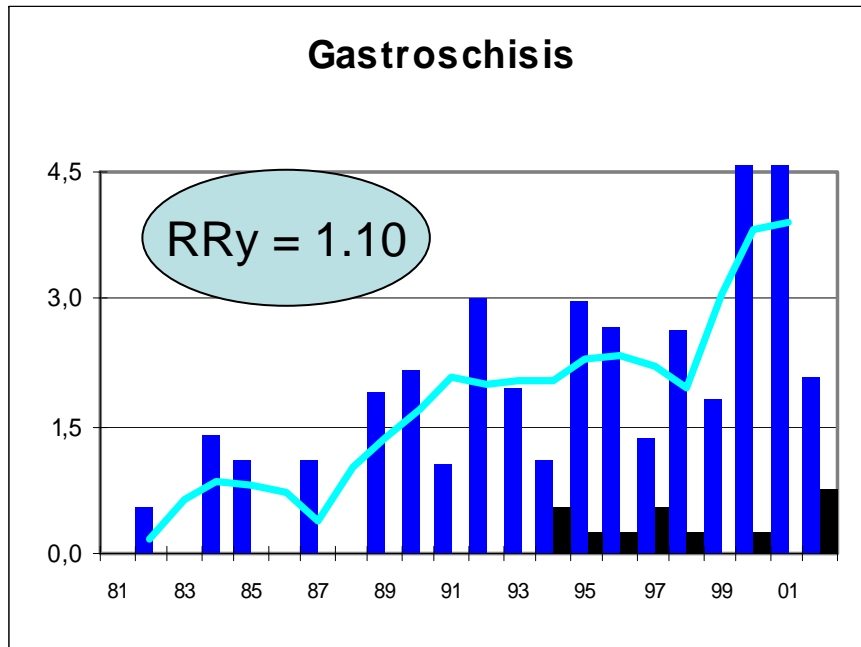
Unspecified  
= 10 -20%



| 74-78 | 98-02 | RR          | Starting      | Peak       |
|-------|-------|-------------|---------------|------------|
| 0.05  | 2.90  | 55 (16-329) | 70ies + 90ies | 3.2 – 2000 |

# Registries with an increasing time trend

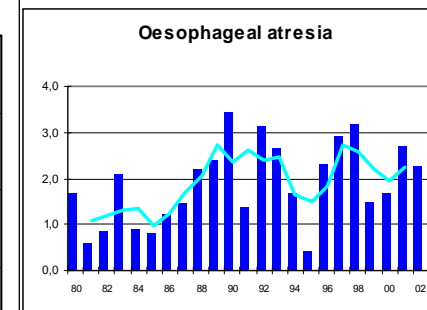
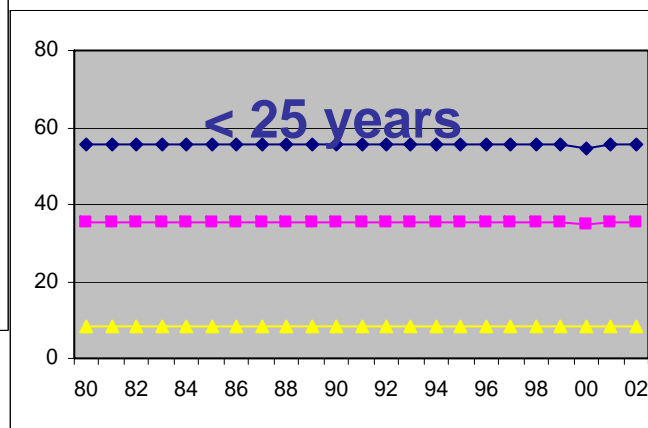
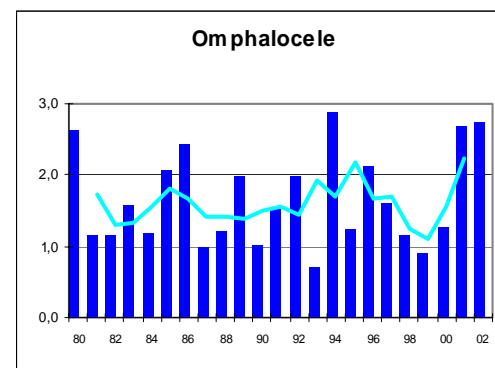
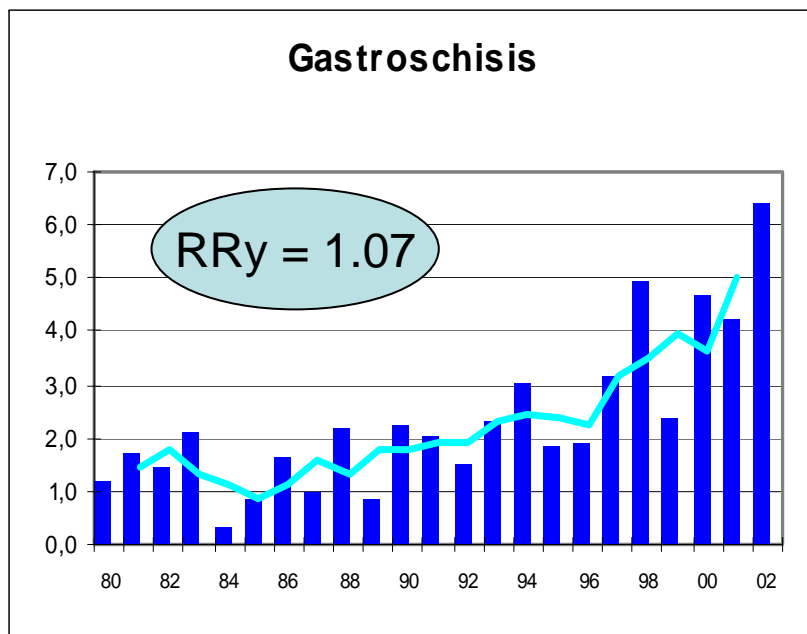
## France, Paris (37,000 births / year)



| 81-85 | 98-02 | RR             | Starting   | Peak       |
|-------|-------|----------------|------------|------------|
| 0.6   | 3.5   | 5.8 (3.2-11.5) | Late 80ies | 4.7 – 2000 |

# Registries with an increasing time trend

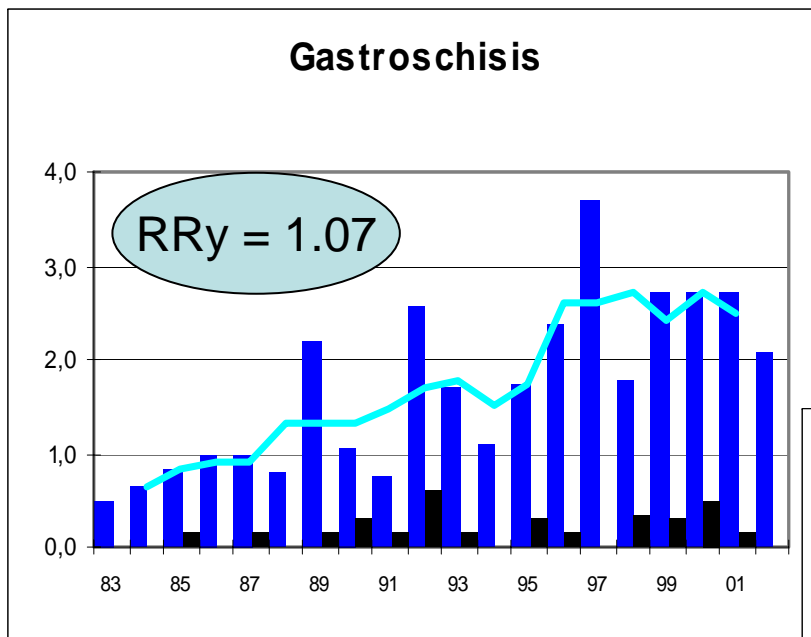
## Mexico (30 → 60 → 22.000)



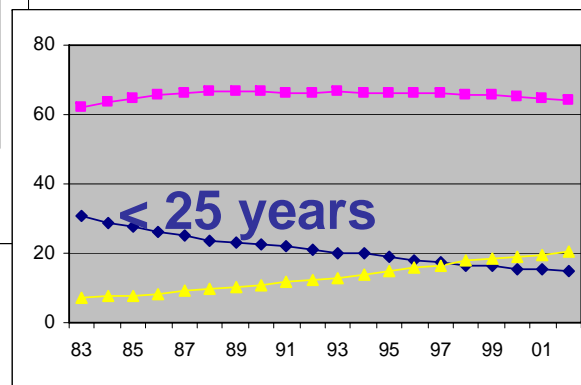
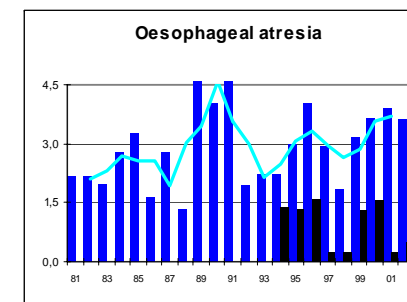
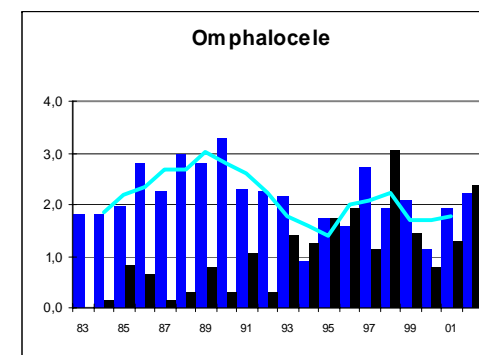
| 80-84 | 98-02 | RR            | Starting | Peak       |
|-------|-------|---------------|----------|------------|
| 1.4   | 4.4   | 3.2 (2.0-5.1) | 90ies    | 6.4 – 2002 |

# Registries with an increasing time trend

## Australia Victoria (63,000 births / year)



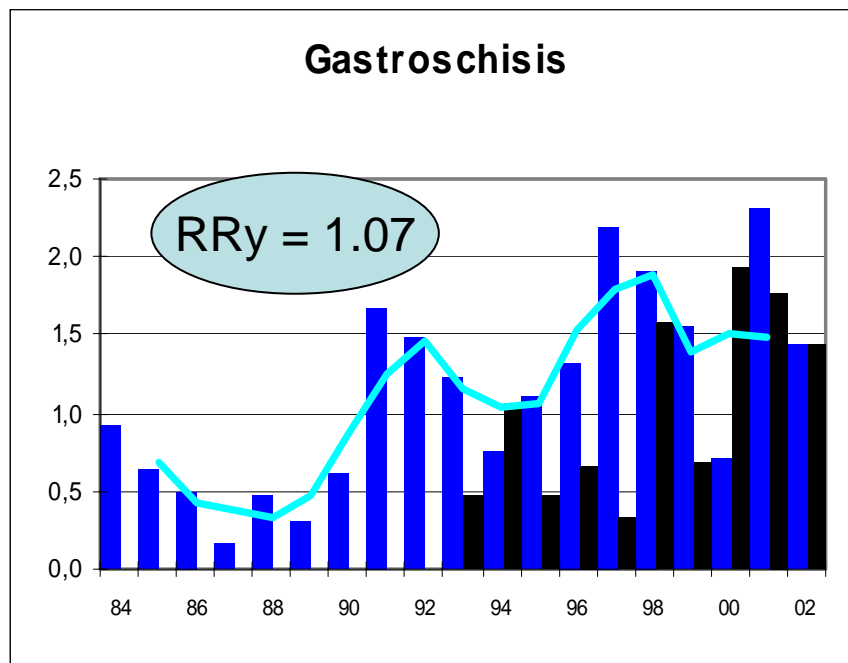
Unspecified  
25-35 %



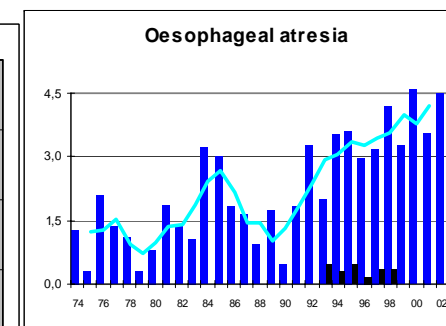
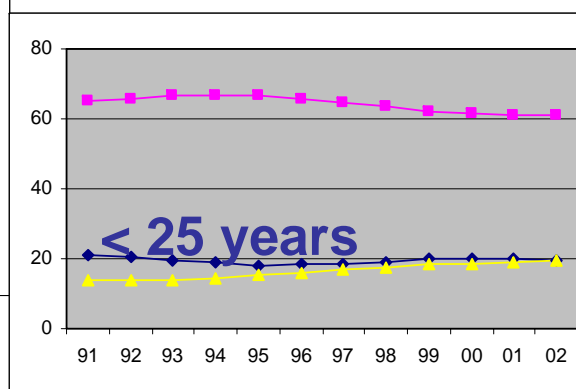
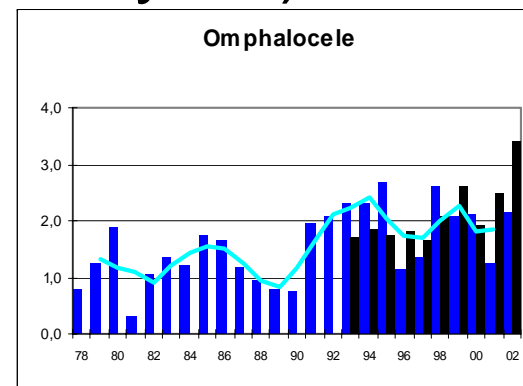
| 83-87 | 98-02 | RR            | Starting    | Peak       |
|-------|-------|---------------|-------------|------------|
| 0.9   | 2.7   | 3.1 (2.0-4.9) | Early 80ies | 3.8 – 1997 |

# Registries with an increasing time trend

## Finland (65 --- 55,000 births / year)



Unspecified  
1-3 %

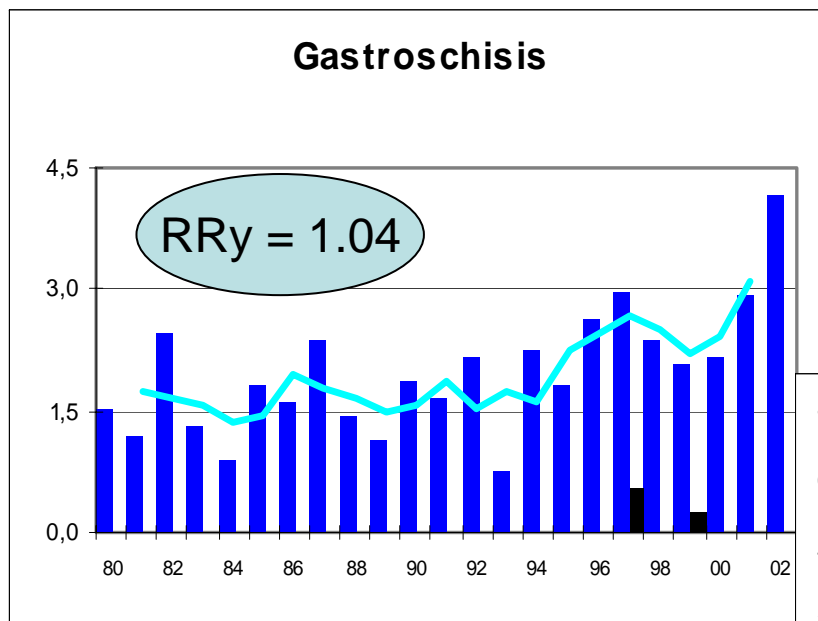


Feto – neonatal prevalence

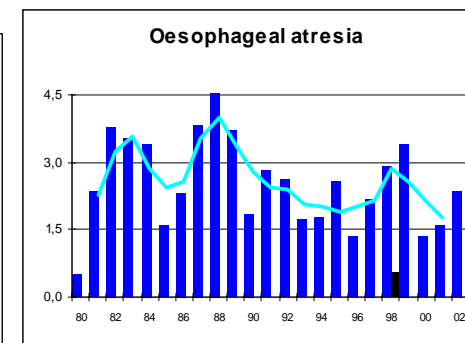
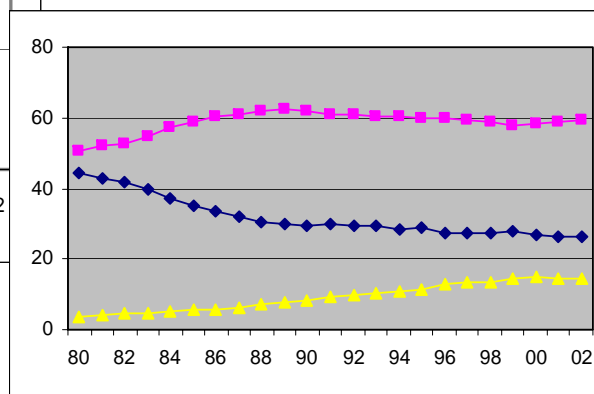
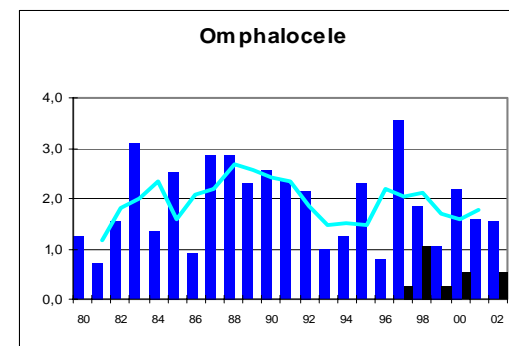
| 84-88 | 98-02 | RR             | Starting    | Peak       |
|-------|-------|----------------|-------------|------------|
| 0.5   | 3.1   | 5.8 (3.5-10.0) | Early 90ies | 4.0 – 2001 |

# Registries with an increasing time trend

## Canada Alberta (44 --- 37,000 births / year)



Unspecified  
10-20 %

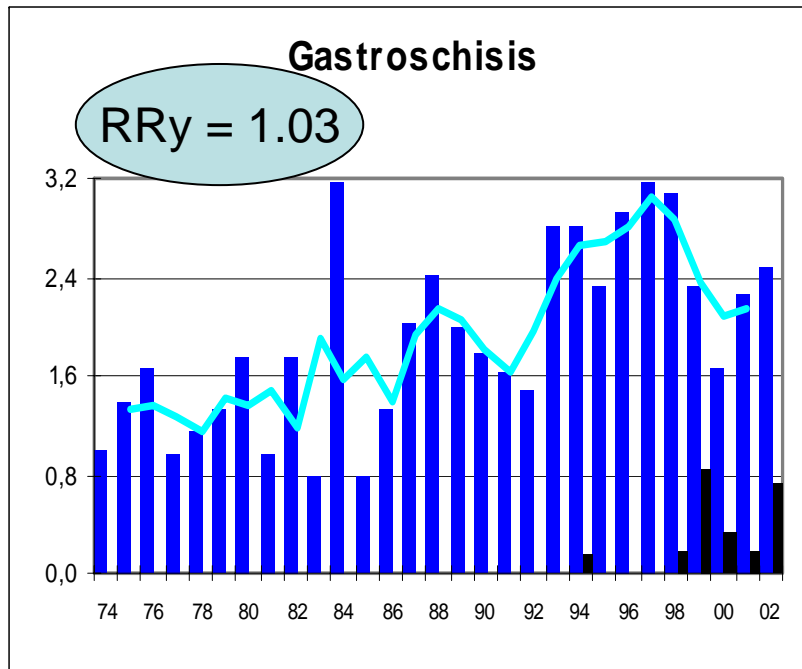


Feto – neonatal prevalence

| 80-84 | 98-02 | RR  | Starting     | Peak       |
|-------|-------|-----|--------------|------------|
| 1.5   | 2.8   | 1.8 | Before 80ies | 4.2 - 2002 |

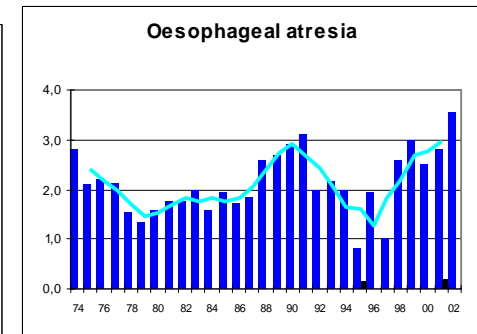
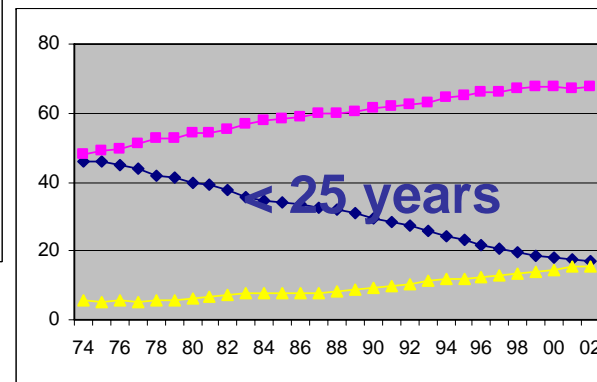
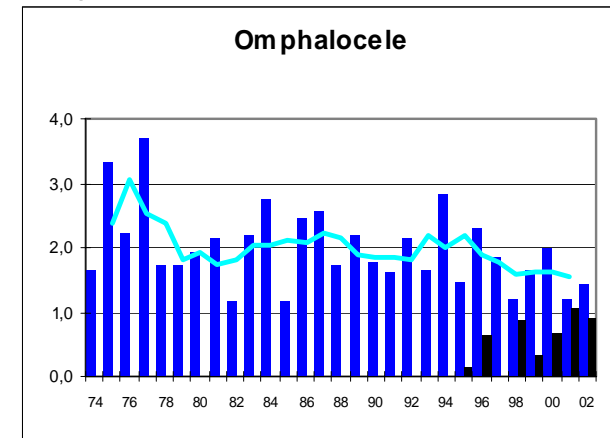
# Registries with an increasing time trend

## Norway (55.000 births / year)



Feto – neonatal prevalence

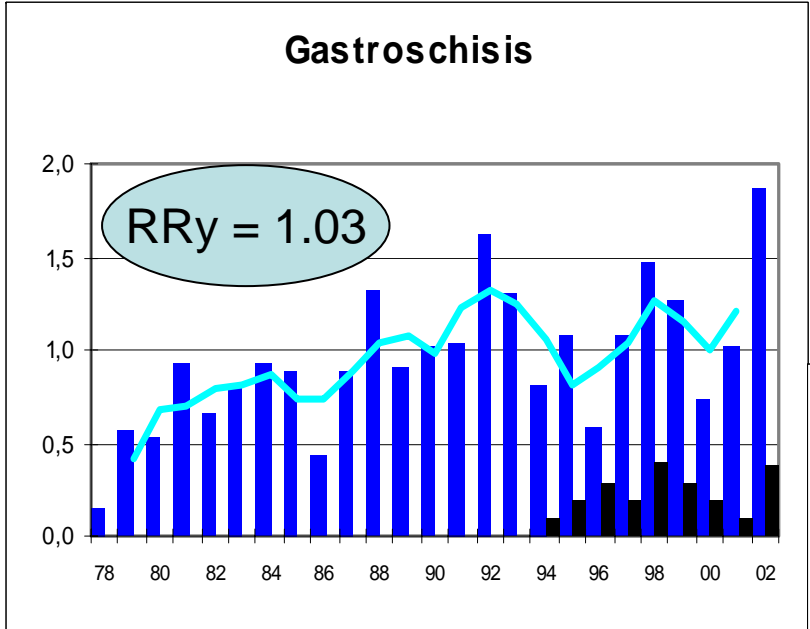
Unspecified  
= 0 ???



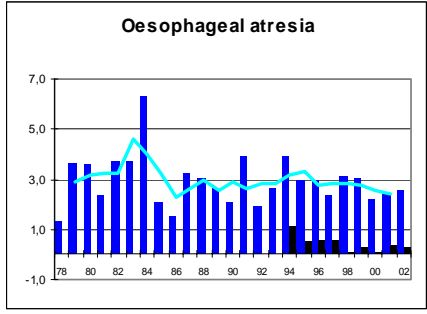
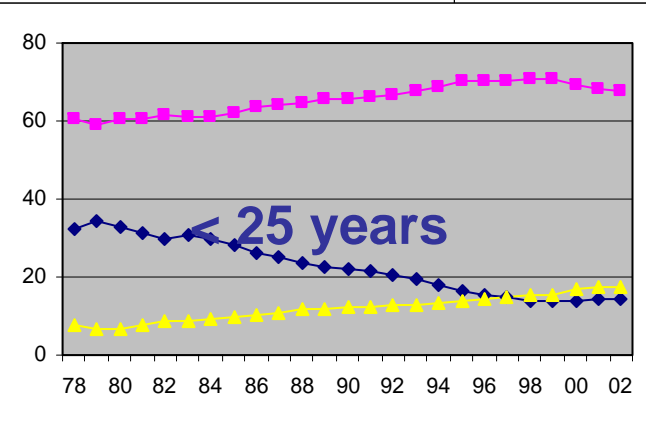
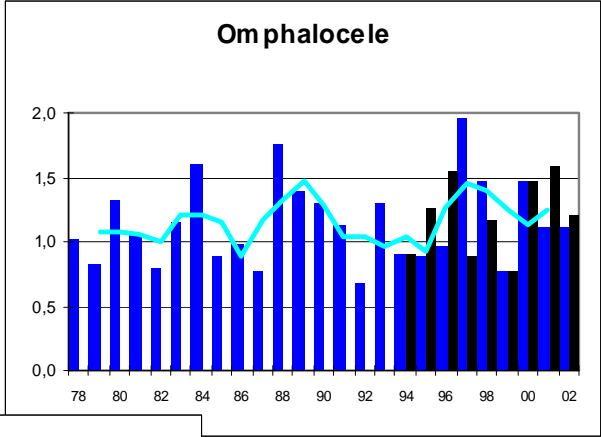
| 74-78 | 98-02 | RR            | Starting    | Peak       |
|-------|-------|---------------|-------------|------------|
| 1.2   | 2.8   | 2.4 (1.6-3.6) | Early 70ies | 3.2 – 1984 |

# Registries with an increasing time trend

## France Central East (100.000 births / year)



Unspecified  
= 0 ???

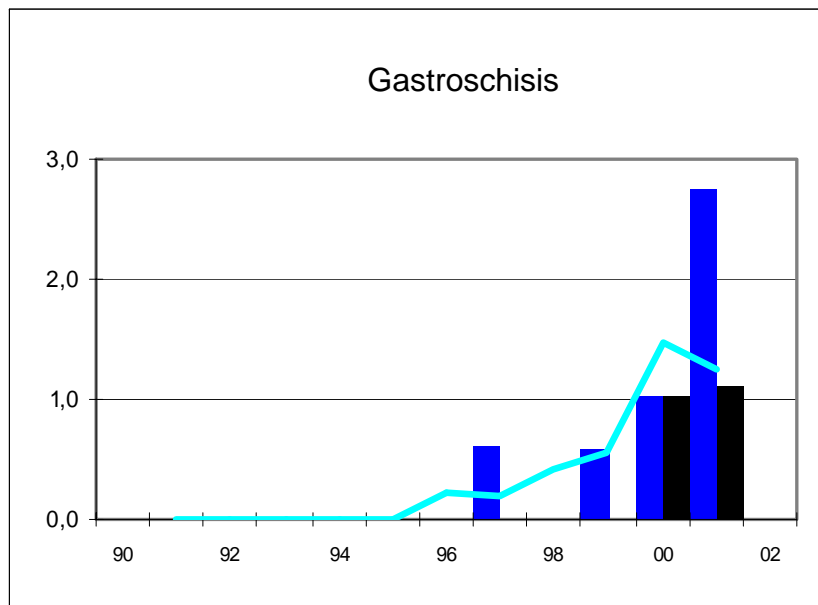


Feto – neonatal prevalence

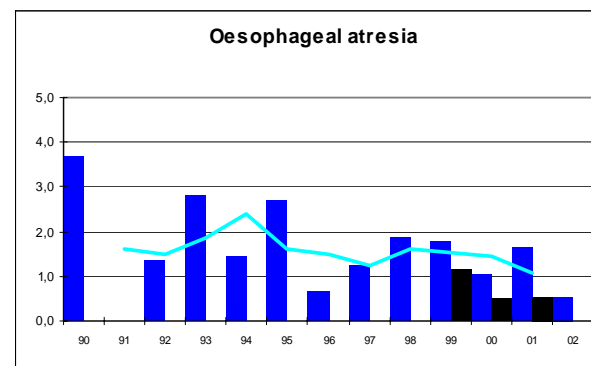
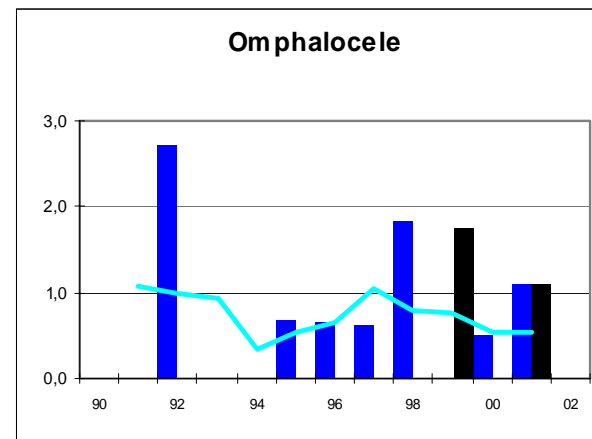
| 78-82 | 98-02 | RR            | Starting    | Peak       |
|-------|-------|---------------|-------------|------------|
| 0.6   | 1.5   | 2.5 (1.6-4.1) | Early 70ies | 2.2 – 2002 |

# Registries with an increasing time trend

## Portugal South (??????? births / year)



Unspecified  
= ???

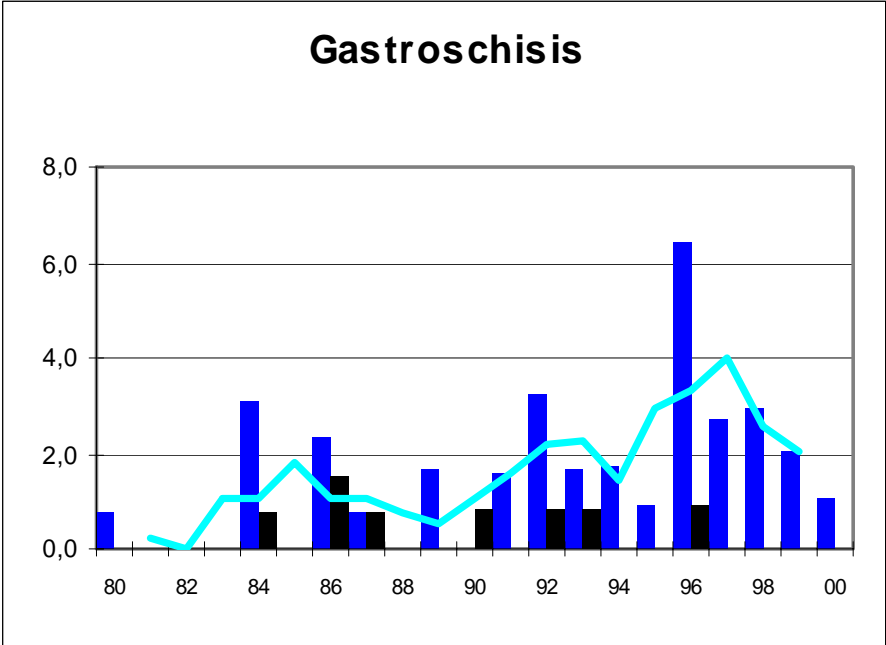


Feto – neonatal prevalence

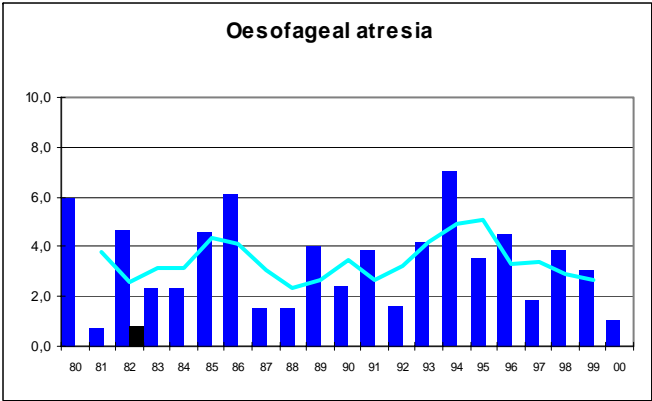
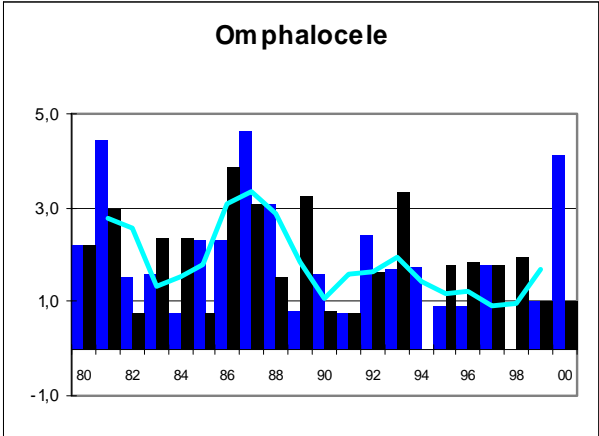
| 90-95 | 98-02 | RR   | Starting   | Peak       |
|-------|-------|------|------------|------------|
| 0     | 1.33  | Inf. | Late 90ies | 2.7 – 2001 |

# Registries with an increasing time trend

## UK Glasgow (??????? births / year)



specified  
??

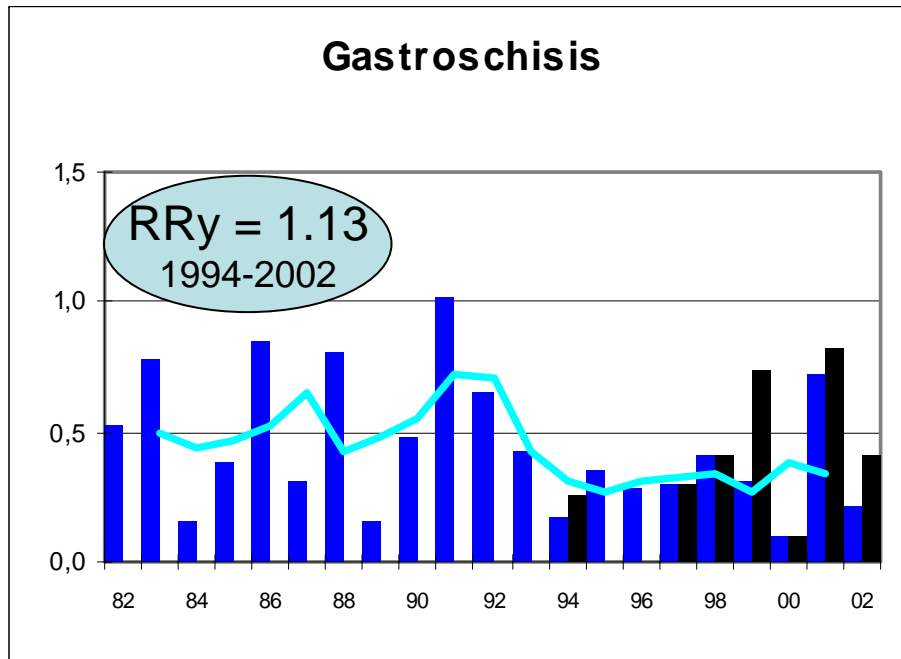


Feto – neonatal prevalence

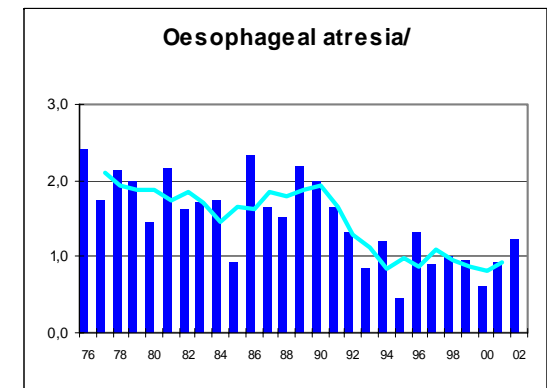
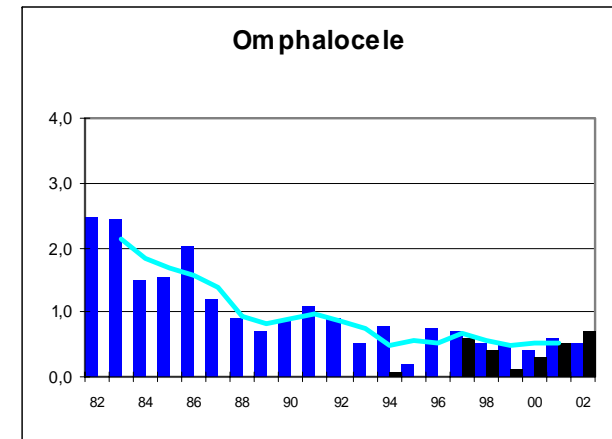
|  | 98-02 | RR  | Starting      | Peak  |            |
|--|-------|-----|---------------|-------|------------|
|  | 0.8   | 3.3 | 3.6 (1.5-9.9) | 80ies | 6.4 - 1996 |

# Registries with an increasing time trend

## Hungary (??????? births / year)



nspecified  
???



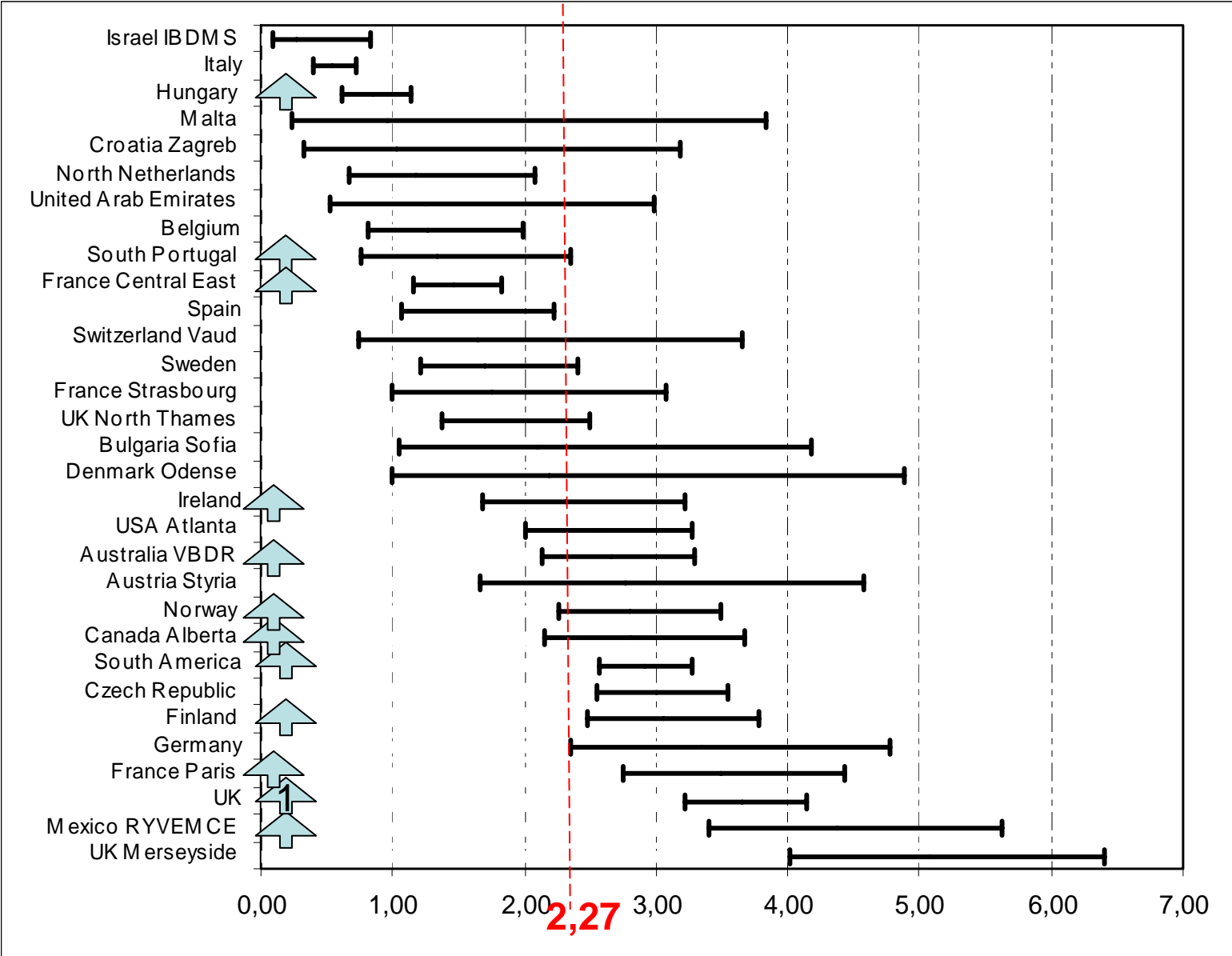
Feto – neonatal prevalence

| 82-86 | 98-02 | RR-5y (CI 95%) | Starting | Peak       |
|-------|-------|----------------|----------|------------|
| 0.5   | 0.8   | 1.6 (1.0-2.5)  | 90ies    | 1.5 – 2001 |



Ungheria

# Feto-neonatal prevalence in 31 Areas



# Italy North East

# 14 Registries with no evidence of an increasing time trend

| Register               | Rate (Last 5 y) | Years | N       | Comments                  |
|------------------------|-----------------|-------|---------|---------------------------|
| Israel – IBDMS         | 0?????          | 25    | 11 + 2  | 1988-2002 very few cases  |
| Italy – Tuscany        | 0.46            | 11    | 4 + 7   | Concordant in the country |
| Italy – Campania       | 0.61            | 12    | 18 + 12 | Concordant in the country |
| Italy – Sicily         |                 |       |         |                           |
| Italy – Emilia Romagna | 0.78            | 25    | 41 + 2  | Concordant in the country |
| Croatia – Zagreb       | 1.02            | 20    | 19 + 1  |                           |
| Netherlands – North    | 1.18            | 22    | 23 + 6  |                           |
| Spain – Basque         | 1.16            | 13    | 7 + 14  | Concordant in the country |
| Spain – Barcelona      | 1.60            | 11    | 10 + 6  | Concordant in the country |
| Spain – Asturias       | 2.16            | 13    | 7 + 6   | Concordant in the country |
| Belgium – Antwerpen    | 1.02            | 13    | 9 + 3   | Concordant in the country |
| Belgium – Hainaut      | 1.63            | 23    | 26 + 15 | Concordant in the country |

# Conclusions on prevalence

# Registries with no evidence of an increasing time trend

| Register                | Rate<br>(Last 5 y) | Years       | N       | Comments              |
|-------------------------|--------------------|-------------|---------|-----------------------|
| Switzerland – Vaud      | 1.64               | 14          | 10 + 7  |                       |
| France – Strasbourg     | 1.75               | 20          | 50 + 8  | Discordant in country |
| Denmark – Odense        | 2.20               | 15          | 15 + 3  |                       |
| US – Atlanta            | 2.56               | 29          | 220 + 9 |                       |
| UK – North Thames       | 1.85               | 12          | 86 + 18 |                       |
| UK – Wessex             | 2.71               | 9           | 59 + 5  |                       |
| UK – Oxford             | 2.63               | 12          | 14 + 1  |                       |
| Austria – Styria        | 2.76               | 17          | 60 + 12 |                       |
| Czech Republic          | 3.01               | 9 anni soli | vedi    |                       |
| Germany – Saxony Anhalt | 3.01               | 16          | 35 + 11 |                       |
| Germany – Mainz         | 4.98               | 13          | 20 + 1  |                       |

# Risk factors

# Analysis of drug exposures

- MADRE Database
  - All registered malformed cases (births and ToPs) with 1 or more drug(s) exposure(s) during the first trimester of pregnancy
  - From and idea of Bengt Kallen
  - Currently analyzed by ICBG and Elisabeth Robert Gnansia.
  - Participating registries =
  - Number of malformed–exposed cases stored =15 342
  - Coding of drugs = ATC codes
  - Coding of defects = dedicated codes
- Use of the MADRE Database
  - Frequency of malformed cases exposed to a specific drug
  - Rotating case – control design to test or generate hypothesis
- Analysis for gastroschisis cases
  - Classification of 104 gastroschisis in “isolated” (74+7) and “associated to unrelated – major defects” (23)
  - 81 isolated cases analyzed

# Frequency of drugs associated to gastroschisis

| ATC Class  | N  | Class with more than 5 cases   |
|------------|----|--|
| 3 – digits | 36 | A03-Antispasmodics = 19<br>N02-Analgesics = 12<br>G03-Sex hormones = 7<br>J01-Antibacterials = 12<br>N05-Psycholeptics = 10<br>B03-Antianemics = 6 |
| 4 - digits | 53 | N02B-Analgesics = 11<br>A03A-Antispasmodics = 8  |
| 5 - digits | 65 | N02BE-Anilides = 7<br>N05BA-Benzodiazepines = 6  |

N = Total class with 1 or more exposure

M01 = ..... 1 esposto

# Association between drugs and isolated gastroschisis

| ATC   | Drugs           | N  | OR   | CI 95%     |
|-------|-----------------|----|------|------------|
| N05BA | Benzodiazepines | 5  | 2.66 | 1.09-6.51  |
| R03CC | Beta-2 agonists | 3  | 3.88 | 1.27-11.85 |
| A03   | Antispasmodics  | 17 | 1.71 | 1.01-2.90  |

# Proportion of ToPs

Ale .... Mi fai per favore il grafico per le 31 aree

**MMI**

# Sex ratio and twins

- Sex ratio ----- Alessandra dati originali, copiare titolo pdf
- Twins vedi paper pdf