Eurocat

European Surveillance of Congenital Anomalies

Supported by the EU-Commission Public Health Directorate Programme of Community Action on Rare Diseases
WHO Collaborating Centre for the Epidemiologic Surveillance of Congenital Anomalies

Special Report:

Special Report:

An Assessment and Analysis of Surveillance Data on Hypospadias in Europe

2003

(Uploaded to EUROCAT's website December 2003)

EUROCAT Central Registry
University of Ulster
Newtownabbey, Co Antrim
Northern Ireland, BT37 0QB

Tel: +44 28 90366639
Fax: +44 28 90368341
Email: eurocat@ulster.ac.uk
Web: www.eurocat.ulster.ac.uk

Table of Contents

Contributors to this Report

The EUROCAT Working Group on the Surveillance of Hypospadias (in alphabetical order):

Marie Claude Addor (Vaud, Switzerland)
Elisa Calzolari (Emilia Romagna, Italy)
Catherine de Vigan (Paris, France)
Hermien de Walle (Northern Netherlands)
Helen Dolk (EUROCAT Central Registry, London/ Belfast UK)
Ester Garne (Odense, Denmark)
Maria Loane (EUROCAT Central Registry, Belfast UK)
Sixto Garcia Minaur (Basque Country, Spain)
Anna Pierini (Tuscany, Italy)
John Scott (Northern & Yorkshire Regional Health Authority)
David Stone (Glasgow, UK)
Romano Tenconi (North East Italy)
Martine Vrijheid (EUROCAT Central Registry, London UK)
Awi Wiesel (Mainz, Germany)

In collaboration with the National Congenital Anomaly System (England and Wales):

Bev Botting (The National Congenital Anomaly System ,Office for National Statistics, London UK)
Nigel Physick (The National Congenital Anomaly System ,Office for National Statistics, London UK)

Further EUROCAT data and questionnaire completion:

Barisic, Ingeborg (Children's Hospital Zagreb); Bianca, Sebastiano (ISMAC Registry, Sicily); Edwards, Grace (Merseyside & Cheshire Congenial Anomaly Survey); Gatt, Miriam (Malta Congenital Anomalies Registry); Gener, Blanca (RACAV); Gillerot, Yves (Institut de Morphologie Pathologique, Belgium); Haeusler, Martin (Styrian Malformation Registry); Irgens, Lorentz (Medical Birth Registry of Norway); Lillis, David (University College Hospital, Galway); McDonnell, Bob (Eastern Health Board, Ireland); Mosquera-Tenreiro, Carmen (Asturias, Spain); Nelen, Vera (Provinciaal Instituut voor Hygiene); Ritvannen Annukka (STAKES, Finland); Salvador, Joaquin (Barcelona Birth Defects Registry, Spain); Scarano, Gioacchino (Registro Campano Difetti Congeniti, Italy); Steinbicker, Volker (Malformation Monitoring Saxony-Anhalt); Stoll, Claude (Service de Genetique Medicale (Strasbourg); Tucker, Dave (Congenital Anomaly Register & Information Services, Wales).

Acknowledgements

We thank Mr Vic Boston (Belfast), Mr A E MacKinnon (Sheffield), Mr P Malone (Southampton), Morten Bischoff-Mikkelsen (Denmark) and the paediatric surgeons across Europe who provided data for this survey. We thank the British Association of Paediatric Surgeons for supporting the study.

We thank Michael Rosato for his help in extracting EUROCAT data. We thank Barbara Norton for secretarial and administrative assistance.

The analysis of the EUROCAT database and production of this Report was funded by EU-Commission Public Health Directorate Programme of Community Action on Rare Diseases.

This report is based on part of a study which was supported by Joint DH/HSE/DETR Male Reproductive Health Research Programme Project No. 121/6763.

Scientific Papers and Reports, and Sources of Further Information

A summary paper based on the material in this Report is available:

> Dolk H, Vrijheid M, Scott J et al, "Towards the Effective Surveillance of Hypospadias", *Environmental Health Perspectives* (2003) doi: 10.1289/ehp.6398 (available at http://dx.doi.org/)

This Report does not cover parts of the study undertaken that related to occupational exposures to endocrine disrupting chemicals and hypospadias. Results of occupational analyses can be found in the following papers:

> Van Tongeren M, Nieuwenhuijsen M, Gardiner K, Armstrong B, Vrijheid M, Dolk H, Botting B, "A job exposure matrix for potential endocrine disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias", *Annals of Occupational Hygiene* (2002), 46, pp465-477.

> Vrijheid M, Armstrong B, Dolk H, van Tongeren M, Botting B, "Risk of hypospadias in relation to maternal occupational exposure to endocrine disrupting chemicals", *Occupational and Environmental Medicine* (2003), 60, pp543-50.

A literature review on the prevalence and aetiology of hypospadias, based on Chapter 1 of this Report, can be found in

> Dolk H, "The Epidemiology of Hypospadias", In: Hadidi AT and Azmy AF (Eds) "Hypospadias Surgery: an illustrated guide", (2004) New York, Springer Verlag, pp 51-57.

An earlier version of the hypospadias prevalence and occupational analyses can be found in:

> Dolk H, Vrijheid M, Scott J et al, "An Assessment and Analysis of Existing Surveillance Data on Hypospadias in UK and Europe", (April 2002), Final Report to DH/HSE/DETR Male Reproductive Health research programme Project No. 121/6763.

This Report is limited to 20 EUROCAT registries and the England and Wales National Congenital Anomaly System which took part in the hypospadias survey. Further prevalence data from other EUROCAT registries, updated each year, can be found on http://www.eurocat.ulster.ac.uk/pubdata/ and in EUROCAT Working Group (2002), "EUROCAT Report 8: Surveillance of Congenital Anomalies in Europe 1980-1999", *EUROCAT Central Registry,* University of Ulster.

Summary

Concern about apparent increases in the prevalence of hypospadias, a congenital male reproductive tract abnormality, in the 1960s to 1980s and the possible connection to increasing exposures to endocrine disrupting chemicals, have underlined the importance of effective surveillance of hypospadias prevalence in the population. We report here the prevalence of hypospadias from 1980 to 1999 in 20 regions in 13 countries of Europe with EUROCAT population-based congenital anomaly registers, fourteen of which implemented a guideline to exclude glanular hypospadias. We also report data from the England and Wales National Congenital Anomaly System (NCAS) for 1980-96. Our results do not suggest a continuation of increasing trends of hypospadias prevalence in Europe. However, a survey of the registers and a special validation study conducted for the years 1994-96 in nine EUROCAT registers as well as NCAS identified a clear need for a change in the guidelines for registration of hypospadias. We recommend that all hypospadias should be included in surveillance, but that information from surgeons must be obtained to verify location of the meatus, and whether surgery was performed, in order to interpret trends. Investing resources in repeated special surveys may be more efficient than continuous population surveillance. We conclude that it is doubtful whether we have had the systems in place worldwide for the effective surveillance of hypospadias in relation to exposure to potential endocrine disrupting chemicals.

New EUROCAT Guidelines for Registration of Hypospadias

Registries can choose <u>not to</u> transmit isolated hypospadias to Central Registry if they do not follow the criteria below.

1. Paediatric surgeons <u>must</u> be a source both of notification and of case status and meatal local verification.
2. To allow paediatric surgeon involvement, a delay of 3 years > D.O.B. will be needed for surveillance.
3. ICD10 should be used for coding location of hypospadias. Text information should give further location specification (eg. glanular versus coronal)
4. Glanular cases should be included.
5. Incomplete prepuce should be excluded.
6. Whether surgery is intended or performed should be included in text information.

Objectives

1. To assess the quality of hypospadias surveillance data in Europe, with regard to completeness of ascertainment, validity and standardisation. Specifically, to assess the implementation of a guideline to exclude glanular or Type I hypospadias from registration.

2. To present hypospadias prevalence data in European regions 1980-1999 and comment on temporal trends observed.

Chapter 1

Background: Epidemiology and Aetiology of Hypospadias – A Brief Literature Review

1.1 Definition, Classification and Treatment

Hypospadias is a congenital abnormality of the male genitalia characterised by incomplete development of the urethra so that the external urethral opening (meatus) is on the ventral surface of the penis or on the scrotum, rather than at the tip of the penis. The development of the penile urethra is complete by 12 weeks after ovulation (14 weeks gestation) and depends on the secretion of testosterone by the fetal testes[1].

Hypospadias can be classified according to the location of the meatus, ranging from more distal to proximal locations. Paulozzi has commented that "there is no anatomical marker that defines when normal variation stops and first degree hypospadias begins"[2]. Hypospadias is classified as glanular (or glandular), coronal/peno-glanular, subcoronal, penile (or mid shaft and proximal shaft), penoscrotal, scrotal and perineal (see Appendix 1). Together glanular and coronal types account for approximately two thirds to three quarters of diagnosed cases (see Table 1.1). We use the term "distal" in this report loosely to denote the more distal rather than proximal forms, including glanular and sometimes coronal among distal forms, but the term can also be differently defined[3].

Hypospadias, particularly when proximal, is often accompanied by chordee, curvature of the penis. The more proximal the location, and the greater the associated chordee, the more functional impairment results. Glanular hypospadias is usually of more cosmetic than functional significance. More proximal forms are associated with difficulties in directing the urinary stream. Surgical correction is required, but opinions differ as to whether surgery should be recommended for uncomplicated glanular forms.

There are few reports indicating the proportion of children with hypospadias, particularly distal hypospadias, who undergo surgery, and many of the studies that exist (reviewed in Table 1.1) were not designed to give reliable estimates of the proportion with surgery. Some estimates suggest that less than half of reported cases were undergoing surgery in the 1970's in Hungary and Sweden, and in the 1970s and 1980s in Denmark[4]. More recently in the Netherlands 1998-2000, it was reported[5] that surgery was recommended for 79% of cases - 3 out of 12 glanular cases and virtually all other cases. A study in Southampton and Portsmouth[6] reported that policy was to recommend surgery for virtually all cases, including glanular, but as this study was based on surgery lists it may have missed some very mild cases. It is possible that the proportion of distal cases undergoing surgery has increased over the decades in some countries, encouraged by new surgical techniques such as meatal advancement glanuloplasty for glanular and coronal cases without significant chordee, introduced by Duckett in 1981. A Finnish study[7] however commented for the period from 1970 to 1994 that "no major changes in the treatment policy have occurred…since the 1960s or even earlier, even minor cases of hypospadias have been treated surgically before the children reached school age. More recently, modern operative techniques and equipment have enabled treatment at younger ages". In the 1970s and 1980s there was generally a trend

towards earlier surgery (around one year of age) rather than waiting till the child was out of nappies, partly in the belief that this was better for psychological reasons.

A recent German study[8] has questioned whether surgery for glanular and even many coronal cases is necessary, given their survey of adult men (see 1.2 below) which suggested no functional or psychological consequences for milder forms of abnormality.

1.2 Prevalence

Table 1.1 gives estimates of prevalence rates of hypospadias, and proportion of glanular and coronal cases.

Factors potentially affecting the estimation of prevalence and the proportion of distal cases include study population definition, exclusion or underascertainment of distal forms of hypospadias or cases not referred for surgery, definition of the boundary between "normal" and "abnormal" and other classification issues, underascertainment related to passive rather than active case ascertainment, and lack of validation of information by paediatric surgeons or urologists to avoid inclusion of false positive diagnoses or cases with misclassified location. These factors are further explored in Chapter 2.

Most estimates of prevalence in Europe and US range up to 3 per 1,000 births with two-thirds to three-quarters of cases being glanular or coronal (Table 1.1). A Dutch study reported a prevalence of 3.8 per 1,000[5], which may be related to sensitisation to diagnosis by special training of Child Health Centre physicians for the survey, although it should be noted that the proportion of distal cases was not higher than usual. A study in Bristol[9] reported a prevalence over 3 per 1,000, but cases were not confirmed by paediatric surgical records and may have included false positive diagnoses or abnormalities of prepuce rather than hypospadias. The influential early Rochester study[10] 1940-70 quoted in many paediatric urology and surgery textbooks reported a relatively high prevalence of 4 per 1,000 births but also a high proportion of glanular and coronal cases (87%), suggesting more complete diagnosis of glanular cases and/or a shifted boundary between "normal" and "abnormal". A German study of 500 adult men[8] found that 13% had hypospadias (equivalent to a rate of 65 per 1,000 births) of which 75% had glanular hypospadias, 98% coronal or glanular. It is probable that the high proportion of glanular hypospadias in this study was related to measurement and designation of the "normal/abnormal" boundary, possibly altered in adult men. Many of the men, including those assessed to have coronal hypospadias, had not previously been aware of any penile deformity.

There is some evidence that the prevalence of hypospadias has been increasing in the 1960s, 70s and 80s in Europe[2, 11-14] and in the US[1], although recent reports suggests that these trends might not be continuing[2, 14] (Table 1.1). One of the main difficulties in reliably documenting changes in prevalence of hypospadias is the relatively common occurrence of more distal forms compared with severe forms, and the potential for incomplete ascertainment of the more distal forms. It could be that any reported rising trend simply reflects a more frequent or early diagnosis of more distal forms of hypospadias over time, or an increasing tendency to report them to congenital anomaly registers. This possibility was examined to a limited extent in one US report of a rising prevalence[1], and found not to be a likely explanation. Any of the other factors affecting ascertainment discussed above could also change over time, but would be less likely to result in a consistent increase in many different areas. A Finnish study

found that a previously reported increase in the prevalence of hypospadias in Finland was probably due to general improvement of ascertainment by the congenital anomaly register, since surgical discharge records showed a stable prevalence[7]. Paulozzi[2] has proposed the possibility that, since the foreskin is used in some surgical repair procedures and therefore circumcision must be deferred if hypospadias is present, medicolegal considerations may increasingly cause physicians to examine the penis carefully before circumcision i.e. a change in the detection of mild hypospadias rather than in surgical policy per se.

At the same time as hypospadias prevalence has appeared to be rising, increases in the frequency of new cases of related abnormalities such as cryptorchidism (undescended testes) and testicular cancer have been reported, as well as a fall in male fertility[15]. While there are problems with the interpretation of the changes in frequency of the various disorders, the concomitant increase in apparently aetiologically related disorders and the absence of increases in other congenital anomalies or cancers has tended to strengthen the interpretation of these changes as real phenomena. In addition, there have been some geographical correlations. For example, the hypospadias rate in Finland seems low (Table 1.1.) and Finland also has a low rate of testicular cancer and high semen quality compared to other Scandinavian countries[15], although comparisons are no longer clear in light of the revised Finnish rate[7].

Endocrine Disrupting Chemicals and Hormonal Aetiological Factors

A hypothesis has been proposed that the underlying cause of the change in frequency of all these conditions, as well as reproductive abnormalities observed in fish and other animals, may be exposure to endocrine disrupting chemicals (including xenoestrogens)[14-18]. Endocrine disrupting chemicals are exogenous substances that cause adverse health effects through interference with the endocrine system, either by mimicking hormones (agonists); binding to receptor sites without activation, thereby antagonising endogenous hormones; interfering with the synthesis or degradation of hormones; or in some other way (in)directly interfering with the functioning of hormones. In relation to hypospadias, evidence suggests that an antiandrogen mechanism (one that hampers the activity of male hormones) is most likely[3]. Potential endocrine disrupting chemicals include dioxins and furans, PCBs, and organochlorine pesticides (see Table 1.2), and also dietary phytoestrogens (such as in soy products)[16-18]. Exposure to these substances may occur particularly in the occupational setting but also through more general environmental exposure, exposure in the home, food packaging, and diet[17].

There has been very little research directly investigating the hypothesised relationship between exposure to endocrine disrupting chemicals in the environment and risk of hypospadias. Research to date, both animal and human, has been recently reviewed[3]. The ALSPAC cohort study[9] found vegetarian diet to be a risk factor for hypospadias, with the implication that high soy (a phytoestrogen) intake or pesticide intake might be causal factors although numbers were too small for detailed analysis. To date, no further published studies have looked at vegetarian diet. A study of residents near hazardous waste landfills found an increased risk of hypospadias and some other congenital anomalies, but no specific chemical exposures could be characterised in that study[19].

Since the development of the male genital tract is under hormonal influence, indicators for both endogenous and exogenous endocrine factors have been suggested to play a role in the aetiology of hypospadias[20,21]. Several epidemiological case-control studies of hypospadias

have looked at a range of possible indicators of "fertility" or maternal endocrine function in its broadest sense, including age at menarche, menstrual cycle irregularities, parity, age, previous spontaneous or induced abortions, time to pregnancy, strength of contractions, and other characteristics of delivery. Possibly the most consistent findings have been associations with threatened spontaneous abortion. Low birthweight or intrauterine growth retardation have also been found to be associated with hypospadias[21] consistent with some explanations involving fetal androgen production. Testicular abnormalities and subfertility have been reported to be more prevalent among fathers of children with hypospadias than other fathers[3,22,23]. An international ecological study suggested that differences in prevalence rates between countries might be associated with the relative representation of subfertile couples among parents[22]. It has similarly been suggested that rising prevalence may be a result of improving fertility treatment thereby increasing the number of children born to subfertile men[23].

The main exogenous hormones investigated have been oral contraceptive use in early pregnancy, hormones used in pregnancy tests, and progestagens used on indication of threatened abortion or previous miscarriages. The evidence is not strong for a risk of hypospadias associated with these exposures[24]. It has also been pointed out that oral contraceptive use is not a frequent enough exposure in early pregnancy for any small excess use to explain such a large increase in prevalence of hypospadias[11].

A follow-up of diethyl stilbestrol (DES) exposed offspring has not given strong evidence of a risk of hypospadias[3, 25]. However, a higher risk of hypospadias has been found in sons of women exposed in utero to DES[26]. A consistent picture regarding risk after IVF and other assisted conception techniques has not yet emerged[3,26,27], and interpretation is complicated by confounding by subfertility, multiple births, low birthweight and maternal age.

Studies of Occupation Exposure and Hypospadias

Studies of occupational exposures in relation to hypospadias are few. Farmers and gardeners have been one occupational group of concern because of their work with pesticides, many of which have potential endocrine disrupting properties. Studies have suggested both no relationship between hypospadias risk and parental work in agriculture or gardening[28-30], and a positive relationship[31]. More general studies of occupation and birth defects have identified several occupations with increased risks of hypospadias (paternal work as vehicle mechanics[32] and paternal work in forestry and logging, carpentry and woodwork, and as service station attendants[33]), but these associations are detected in many combinations of occupation and birth defects tested, and thus some spuriously significant results can be expected.

A study analysing the England and Wales National Congenital Anomaly System data on hypospadias in relation to occupational job title, using a job exposure matrix, found little evidence for an increased risk of hypospadias associated with probable exposure to potential endocrine disrupting chemicals although exposure classification was crude[34]. Occupations with probable exposures to potential endocrine disrupting chemicals are shown in Table 1.3. The numerically largest group are hairdressers.

Table 1.1 Review of Studies Giving Hypospadias Prevalence Estimates since 1970, Distribution of Location of Meatus, or Proportion Undergoing Surgery

Type of Study, Place, Time and reference	Prevalence Estimate	Proportion Glanular and Coronal	Proportion with Surgery	Comments
Population-based Congenital Anomaly Register, Italy, 1978-83[35]	2 per 1,000 (168 cases)	Type 1 hypospadias in 75% of cases	-	According to the diagram included in the paper, glanular and coronal cases were included in 'Type I'
Hospital Discharge and Population-based Congenital Anomaly Register records, Denmark 1983-93[29]		-	Of 1345 cases identified, 650 had record of surgical treatment (48%)	No prevalence estimate given – cases ascertained for case-control study
Military hospital discharge records from 15 military hospitals, USA[36]	3.5 per 1,000 (709 cases)	-	-	Not clear what discharge records refer to, or whether multiple episodes could be reliably identified
Population-based Congenital Anomaly Register New York State 1983-95 and hospital discharge data[37]	3.6 per 1,000	-	Surgical repair rate 0.6 per 1,000 suggesting only 17% have surgery	No trend in prevalence or surgical repair. No author comment on low surgical rate
Population-based Congenital Anomaly Register Strasbourg 1979-87[38]	1.5 per 1,000	69% glanular or coronal	-	-
Population-based surgical series, Southampton & Portsmouth 1992-94[6]	2.4 per 1,000 (84 cases)	31% glanular, 75% glanular or coronal	Policy to recommend surgery in virtually all cases of hypospadias	-
Population-based survey, Netherlands 1998-2000[5]	3.8 per 1,000 (53 cases)	25%glanular, 56% glanular or coronal	Surgery for 78%, 3/12 glanular, 14/15 coronal, all more severe anomalies	Special training of Child Health Centre physicians for neonatal examinations and follow-up or referrals to paediatric urologist
Cohort study, Bristol 1991-92[9]	3.2 per 1,000 (51 cases)	-	-	Enrolled women antenatally, hypospadias identified from annual questionnaires to mothers up to age 3, birth notifications and reports of neonatal examinations by paediatricians, cases not confirmed by paediatric surgery/urology records

Hospital discharge database Finland 1970-94[7]	1.4 per 1,000	-	-	Surgery up to 8 years of age. Rate stable over time. PCR based rate in Finland over same time period starts much lower and increased to 1.4 per 1,000
Population-based Congenital Anomaly register and Hospital-based Congenital Anomaly Register, International, 1964-1997[2]	Increase in prevalence during 70's and 80's in USA (up to 3.5 per 1,000), Scandinavia (up to <2 per 1,000) and Japan (up to <0.5 per 1,000). Little evidence of further increase anywhere after 1985	-	-	Limited detail on methodology for individual registries
Hospital series, excluding non-residents Rochester USA, 1940-70[10]	4.1 per 1,000 (113 cases), no temporal trend, 0.5 per 1,000 excluding glanular/coronal	87% glanular or coronal hypospadias	24%, all either penile or with testicular associated anomalies	-
Survey of 500 hospitalised adult men, Germany, mean age 57[8]	65 per 1,000 (13% of men)	75% glanular hypospadias, 98% coronal or glanular, 1 subcoronal	-	It is probable that the high proportion of glanular hypospadias in this study was related to measurement and designation of the "normal/ abnormal" boundary, possibly altered in adult men. Many of the men, including those assessed to have coronal hypospadias, had not previously been aware of any penile deformity
Population-based Congenital Anomaly Register and Hospital-based Congenital Anomaly Register International 1967-82[4]	0.3 per 1,000 Mexico, 0.6 South America, 0.9 Denmark, 1.6-1.7 Spain, Hungary, Italy, 2.0 Sweden	69-85% of cases glanular or coronal	Surgery for 40% of cases in Hungary in 1975, 31% Sweden 1974, 27% Denmark 1974-76	Proportion glanular/coronal did not correlate with prevalence. Increasing trend in Denmark and Hungary. Increasing trend up to 1973 in Sweden
Population-based Congenital Anomaly Register Atlanta 1968-96[1]	Increase from 1.7 per 1,000 to 3.0 per 1,000	74% were first degree (meatus on ventral surface of glans penis)	-	No indication that the proportion of first degree cases had increased during the time period but location was unknown in the majority of cases
Hospital-based Congenital Anomaly Register, USA 1970-93[1]	2.0 per 1,000 rising to 3.5 per 1,000	-	-	Neonatal discharge summaries sole source of information

England and Wales National Congenital Anomaly System, 1964-83[11]	Rising from 0.7 to 1.8 per 1,000	-	-	See Chapters 2 and 3
Population-based Congenital Anomaly Register Victoria, Australia 1983-95[39]	1.7 per 1,000 rising to 2.9 per 1,000	-	-	-

Table 1.2 Categories of Substances with Suspected Endocrine Disrupting Potential, Including Information on Use and Possible Sources of Exposure

Substance Groups	Potential Sources
1 Pesticides	
Herbicides	2,4-D (used on variety of crops, including grains, and on urban parks, golf courses and lawns). Atrazine (mainly used in cornfields). 2,4,5-T, alachlor, amitrole, atrazine, metribuzin, nitrofen, trifluralin.
Fungicides	hexachlorobenzene, mancozeb, maneb, metiram-complex, tributyl tin (TBT), vinclozolin, zineb, ziram. Pentachlorophenol (fungicide extensively used on textiles and as wood preservative)
Insecticides and nematocides	Aldicarb, beta-HCH, carbaryl, chlordane, cypermethrin, DBCP, dicofol, dieldrin, DDT/DDE/DDD, endosulfan, esfenvalerate, ethylparathion, fenvalerate, heptachlor, heptachlorepoxide, lindane, (γ-HCL), malathion, methomyl, methoxychlor, Mirex, oxychlordane, parathion, permethrin and other synthetic pyrethroids, toxaphene, transnonachlor
2 Polychlorinated Organic Compounds	
PCB	Used since 1929 as a heat transfer fluid in large transformers, hydraulic fluid, adhesive, flame retardant, dielectric fluid in capacitors and transformers. May still be present in many older electrical installations. Production was banned in 1977.
Dioxins and Furans	By-product in incineration, paper manufacture, production of chlorinated aromatics.
Hexachlorobenzene	By-product of process that involve organochlorines or elemental chlorine. Also produced in the incineration of chlorinated wastes.
Octachlorostyrene	By-product
3 Phthalates	
Di(2-ethylhexyl) phthalate (DEHP) or di-octyl phthalate (DOP)	Used as plasticisers in many plastics. In the UK no longer used in the manufacture of cling film or other food contact plastics. Most used as additive in PVC for rain wear, footwear, upholstery materials, waterproof gloves, tablecloths, shower curtains, floor tiles, toys, blood bags, beer bottle caps. Used in emulsion paints; in heat-seal coatings on metal foils such as those found on yoghurts, cream and individual portions of milk, and in aluminium paper-foil laminates
Butyl benzyl phthalate (BBP)	Widely used in manufacture of flooring tiles, for cellulose plastics, polyvinyl acetates, polyurethanes and polysulfides and in regenerated cellulose films for packaging. It is also used in vinyl products such as synthetic leathers, floor tiles, acrylic caulking, adhesives for medical devices and in the cosmetics industry. Dispersant or carrier for insecticides, repellents and perfumes component of paper and paperboard in contact with liquid, fatty and dry foods.
Dibutyl phthalate (DBP)	Widely used in PVC and nitrocellulose polyvinyl acetate, carpet backing, paints, inks, glues, insect repellents, hair spray, nail polish and rocket fuel.
Diethyl phthalate (DEP)	Used as a plasticiser for cellulose acetate plastic films. May be used in blister packaging and many moulded and extruded articles such as toothbrushes, car components and toys. May be found in numerous articles such as toiletries (nail polish), insect repellent, adhesives.
4 Alkylphenolic compounds	
Alkylphenol ethoxylate surfactants	Usually nonylphenol ethoxylate or octylphenol ethoxylate. Used for a wide range of detergents and surfactants. Phased out for domestic use in 1976, but are still used in industry. Industrial detergents, such as those used for wool washing and metal finishing. Some detergent-containing petrol. Spermicidal lubricant nonoxynol-9. Various laboratory detergents, including Triton X-100. Emulsifier for grease and lubricating oils. Some shampoos, shaving foams and other cosmetics. In pesticide formulations as surfactant/carrier. Used in paints, pesticide formulations and lubricants. Surfactant/dispersant in textile mills and pulp and paper mills. Surfactant/dispersant in coal processing.

Alkylphenols	Usually nonylphenol or octylphenol. Used as antioxidants in some clear plastics to prevent yellowing, in the form of tris-nonylphenol phosphite. Used in the production of nonylphenol ethoxylates and polymers. Phase out of alkylphenolic detergents to wash wool was expected by 1996. Two industry associations of soap and detergent producers and cleaners called for a phase out of alkylphenol ethoxylates by 1997.
5 Bi-phenolic compounds	
Bisphenol A	Used in the production of epoxy resins and polycarbonate plastics. These plastics are used in many food and drink packaging applications. Resins are commonly used as lacquers to coat metal products such as food cans, bottle tops and water supply pipes. Used in some dental resins
6 Heavy metals	
Cadmium	Mainly used in production of nickel/cadmium batteries. Other uses include coatings, pigments, stabilizers in plastics, alloys. Naturally found in fossil fuels and is emitted during combustion
Lead	Used in lead batteries, paints, pipes, leaded petrol, leaded glass crystal, fishing sinkers, shotgun shot
Mercury	Used in nickel/cadmium batteries, fluorescent lighting, seed coatings, dental amalgams, temperature/pressure devises.
7 Other hormone disrupting substances	
Parabens	Methyl-, ethyl-, propyl, and butyl paraben. Common preservatives in cosmetics such as sun creams.
Butylated hydroxyanisole	Food antioxidant
Phytoestrogens	Produced naturally by plants
Synthetic steroids	Ethinyl oestradiol, contraceptives

Source: Van Tongeren M, Nieuwenhuijsen M, Gardiner K, Armstrong B, Vrijheid M, Dolk H, Botting B. "A job exposure matrix for potential endocrine disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias". *Annals of Occupational Hygiene* 2002, 46:465-477

Table 1.3 Some Examples of Occupations from the NCAS Congenital Malformation Surveillance Database with "Probable" Exposure to Endocrine Disrupting Chemicals

Substance Category	Occupation
Pesticides	Farm workers
Polychlorinated Organic Compounds	Electricians
Phthalates	Plastic workers Painters Electricians Hairdressers Printers
Alkyl Phenolic Compounds	Farmers Painters Laboratory technicians Textile workers Cleaners
Bi-Phenolic Compounds	Plastic workers Dental practitioners
Heavy metals	Dental practitioners Armed forces Petrol pump attendants Traffic wardens Goldsmiths Glass, ceramic and pottery workers Welders

Source: Van Tongeren M, Nieuwenhuijsen M, Gardiner K, Armstrong B, Vrijheid M, Dolk H, Botting B. "A job exposure matrix for potential endocrine disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias". *Annals of Occupational Hygiene* 2002, 46:465-477

Chapter 2

Validation of European Surveillance Data on Hypospadias

2.1 Objective of Chapter 2

In Chapter 2, we report on the methods and results of the first objective of the study: to assess the quality of EUROCAT data on hypospadias and National Congenital Anomaly System (NCAS) data for England & Wales, with regard to completeness of ascertainment, validity and standardisation. Specifically, to assess the implementation of a guideline to exclude glanular or Type I hypospadias from registration.

2.2 Background and Aims of Validation Study

There are two main potential sources of variation in the ascertainment of hypospadias, over time or between registries, which can lead to artefactual differences in prevalence: the inclusion or exclusion of more distal forms of hypospadias, and the sensitivity and specificity of the sources of case ascertainment used.

EUROCAT (European Surveillance of Congenital Anomalies) congenital anomaly registries agreed in 1979 a list of "minor anomalies for exclusion". This list comprised anomalies of little medical, functional or cosmetic importance. The list specifies that hypospadias when the meatus lies before the coronary sulcus, glanular or 1st degree hypospadias is to be excluded unless occurring in combination with specified (major) anomalies. The minutes of the discussion leading to this list are no longer available, but it is likely that this decision was made on the basis that glanular hypospadias may be misidentified at birth, is often not of functional significance, and the perception at the time may have been that surgery was not often recommended for glanular forms.

In 1990, the National Congenital Anomaly System (NCAS) for England and Wales adopted the EUROCAT list of minor anomalies for exclusion. This led to a halving of the reported prevalence of all congenital anomalies, and of hypospadias itself (see Chapter 3). The implementation of the guideline to exclude glanular hypospadias has never been evaluated in either EUROCAT or NCAS.

The aims of the validation study are to assess the sensitivity and specificity of hypospadias registration, and to evaluate the implementation of the guideline to exclude glanular hypospadias.

2.3 General Description of NCAS and EUROCAT

National Congenital Anomaly System

The collection and notification of information on congenital anomalies observed at birth, on a national basis, was proposed by the Chief Medical Officer at the Department of Health in 1963. This was initiated following the thalidomide epidemic in order to detect other hazards more quickly. The National Congenital Anomaly System (NCAS) was set up in 1964 to monitor congenital anomalies in England and

Wales and covers all births, live and still. The system is run by the Office for National Statistics (ONS). The main purpose of NCAS is surveillance, but it also provides the best national data on prevalence. Reporting to the system is voluntary.

In most Health Authorities, Community Trusts notify NCAS by means of a paper form (the SD56 notification form) which contains a written description of the anomaly and details of the birth, along with some demographic information about the parents. There is no time limit for notification to NCAS. Most information is supplied on a monthly basis mainly based on birth notifications prepared by attendants at birth, either physicians or midwives, supplemented by other reports from other sources such as neonatal intensive care units and special care baby units. However, it has long been recognised that there is under reporting. A number of studies have evaluated the completeness of notification to NCAS with respect to specific abnormalities since 1980[41-45].

A review of NCAS in 1993 recommended that 'where good congenital malformation registers exist outside the Office of Population, Censuses and Surveys (now ONS) information should be exchanged with these to improve the completeness and validity of both local and national data'[46]. In 1998 the Congenital Anomaly Register and Information Service (CARIS) in Wales began data exchange with NCAS for all congenital anomalies reported in live or stillbirths known to them from any source. The Trent Congenital Anomaly Register began electronic data exchange in 1999, followed by the Merseyside and Cheshire Congenital Anomaly Survey and the North Thames (West) Congenital Malformation Register in January 2000.

EUROCAT

The EUROCAT network of population-based congenital anomaly registers is the main source of epidemiological data on congenital anomalies in Europe since 1979. A brief general description of EUROCAT and map of EUROCAT registries can be found in Appendix 3.

EUROCAT congenital anomaly registers are population-based, covering defined areas of Europe. Registers use active methods of case ascertainment, accessing multiple sources of information for both initial case notification and verification of diagnostic information. The populations covered by EUROCAT registers are given in Table 2.1 and more extensive information on registration practice can be found in Appendix 3. EUROCAT Report 7 reports on the prevalence of congenital anomalies in EUROCAT registries during the period 1980-1994[47]. A report of prevalence rates of congenital anomalies in EUROCAT regions from 1980 to 1999 is available (EUROCAT Report 8)[48].

EUROCAT registries annually send a file of individual case records corresponding to each new birth year to the EUROCAT Central Registry, along with appropriate denominators (no. of live and stillbirths in the region). Case records include a standard dataset, with standard coding (EUROCAT Guide 1.1, 1.2[49,50]). Four of the registers shown in Table 2.1 are associate members, sending only aggregate data to the Central Registry. All data sent to the Central Registry is anonymous, and any identification of cases in order to collect further information is done at local registry level.

Table 2.1 EUROCAT Registry Populations

Registry	No. of Births (1999)	Year Joined EUROCAT	Population Definition (Population-†/Hospital-based)	Geographical Area	Stillbirth Definition for Denominators	Maximum Age at Diagnosis for Notification to Registry
Austria: Styria	10,800	1995	Population-based I	Province of Styria	Late fetal death from a Crown Foot Length>=35 cm. From 01.01.95 limit of >=500g introduced by law	Up to 1 year
Belgium: Antwerp	17,719	1990	Population-based I	Province of Antwerp	>180 days	Recorded up to 1 year
Belgium: Hainaut-Namur	12,097	1979	Population-based II	Provinces of Hainaut (South) & Namur	28 weeks or 180 days	Recorded up to 1 year
Croatia: Zagreb	6,033	1983	Population-based I	Cities of Rijeka, Varazdin, Koprivnica & Region of Pula	22 completed gestational weeks/500g	Recorded up to 1 week
Denmark: Odense	5,689	1979	Population-based I	County of Funen	Gestation age at 28 weeks or more. No sign of life at birth (breathing or heart beats or movements)	Up to 7 years for cases seen at paediatric department
France, Paris	38,200	1982	Population-based III	Greater Paris	22 weeks after LMP	Recorded up to 1 week (hospital discharge)
France: Strasbourg	13,656 (1998)	1982	Population-based III	Department of Bas-Rhin	Before 1993: 180 days. After 1993: 22 gestational weeks	2 to 5 years
Germany: Mainz	3,275	1992	Population-based II	Mainz District (Land Rheinfalls)	Weight < 500g	Recorded up to 1 week
Germany: Saxony-Anhalt	11,500	1992	Population-based III	Federal State Saxony-Anhalt	Weight >=500g introduced by law 1.4.94 (before 1.4.94 >=1000g	Recorded up to 1 week.
Ireland: Dublin	20,746	1980	Population-based I	Eastern Regional Health Authority Region	Gestation >=24 weeks or weight >=500g	5 years

Ireland: Galway	2,655	1981	Population-based I	County of Galway	Gestation >=24 weeks or weight >=500g	5 years
Italy: Emilia Romagna	24,003	1980	Population-based II	Region of Emilia Romagna	Gestational age of 28 weeks	Recorded up to 1 week (after 1 week for selected malformations eg. Downs Syndrome, cardiovascular defects, cleft palate. Follow up for selected congenital anomalies)
Italy: ISMAC	16,922 (1998)	1997	Hospital-based	Sicily	180 days	Recorded up to and after 1 year
Italy: North East	54,364	1985	Population-based II	Veneto, Friuli-Venezia, Giulia, Trentino-Alto, Adige Regions	>=26 weeks	Varies by malformation
Italy: Tuscany	26,059	1979	Population-based I	Region of Tuscany	180 days	Recorded up to and after 1 year
Malta	4,339	1986	Population-based I	Country of Malta	Gestation age >22 weeks or weight >500g	Recorded up to 1 year
Northern Netherlands	20,167	1981	Population-based I	Provinces of Groningen, Friesland and Drenthe	Gestational age >=24 weeks	Unlimited.
Spain: Basque Country	16,169 (1998)	1990	Population-based III	Basque Country region, Northern Spain	Gestational age of 22 weeks or weight >500g	Recorded up to 1 year
Switzerland: Vaud	7,465	1988	Population-based I	Canton of Vaud	Gestational age >=27 weeks or length >=30 cm	Recorded up to and after 1 year. No limit
UK: Glasgow	9,721	1978	Population-based I	Greater Glasgow	Gestational age >24 weeks	Recorded up to and after 1 year. No specified time limit

†Population-based: I = All mothers resident in defined geographic area, II = All mothers delivering within defined geographic area, irrespective of place of residence, III = All mothers delivering in defined geographic area excluding non-residents of that area

2.4 Methodology of the Validation Study: NCAS Data

In order to determine the proportion of hypospadias cases notified to ONS-NCAS (ie. the sensitivity of NCAS), comparisons were made with surgery lists from paediatric surgery centres. Surgery lists were requested from paediatric surgery centres in Newcastle, Sheffield, Southampton, and Birmingham, all centres with which one of the investigators (JES) had previous professional contact. Details of all hypospadias cases operated in 1996 were requested, irrespective of year of birth, on the understanding that year of surgery indexing would simplify the task. All centres except Birmingham responded with a complete list. In addition to the list, a form was filled out for each case specifying the location of hypospadias and other details (Appendix 1). This form was designed by one of the investigators (JES), again balancing ease and speed of completion with amount of information desired.

Surgery lists were matched with NCAS notifications by date of birth and postcode. This was done at NCAS to preserve confidentiality. Since postcode in surgery lists was postcoded at time of surgery rather than at birth, cases with the same date of birth and a nearby postcode (in the same general catchment area as judged from other postcodes) were considered possible matches. From 1995 on, the first three initials of the first and last name in the NCAS records could also be used to match records.

A surgery list for all cases born 1992-94 operated in Southampton and Portsmouth, irrespective of place of residence, was obtained from Southampton, in relation to a previously published study[6]. This list overlapped with the above list from Southampton for any children born 1992-94 who were operated on in 1996.

In order to determine the specificity of NCAS hypospadias notifications, it was necessary to confirm the hypospadias status and location of a sample of all notified cases. All hypospadias notifications to NCAS for the Health Authorities mainly served by the four paediatric surgery centres above were extracted. These Health Authorities were Southampton and South West Hampshire, Newcastle and North Tyne, Gateshead and South Tyneside and Sheffield. For all cases not matching with the surgery lists above, and born in the years 1993-96, the anonymous notification forms were sent back by NCAS to the HA's who had notified the cases, asking for identification of the children and the clinicians responsible for treatment. Three districts were able to supply this information. Clinicians and medical records departments were contacted by one of the investigators (JES) to find out case status (whether hypospadias or not) and location of hypospadias. The remaining district (Sheffield) was uncertain about how to trace cases and the need for patient consent which led to an indefinite delay in response.

2.5 Methodology of the Validation Study: EUROCAT Data

Part A: Survey of Registration Practice in EUROCAT Registries

A questionnaire was sent in mid 1999 to all EUROCAT registries to ask about registration practice. The questionnaire is given in Appendix 2. Questions covered whether and how registries implemented the guideline to exclude glanular hypospadias, and sources of information for registration of hypospadias.

Part B: Validation of Case Registration 1994-96

Eleven registries agreed to participate in a special retrospective validation study of cases registered between 1994 and 1996. Data collection for this validation study took place in 1999-2000.

The registries were asked to contact the paediatric surgeons who had treated the hypospadias cases, asking them to fill in a succinct questionnaire (Appendix 1), the same as used for the NCAS part of the study, relating to when operation was planned/performed, and the location of hypospadias. The surgeons were also to be asked if they had operated on any further cases who fulfilled the registration criteria (born 1994-96 within the geographical region concerned, excluding glanular cases) but which were not on the case list given to them.

The Mainz Registry, which differs from other registries in that diagnostic information in liveborn babies comes mainly from a standardized paediatric assessment at birth carried out by the three registry paediatricians, did not request data from paediatric surgeons but filled in their own assessment.

One registry did not carry out the study (Strasbourg), and another (Glasgow) could not gain sufficient response from paediatric surgeons.

A workshop was held in conjunction with the EUROCAT Registry Leaders Meeting on June 1 2001 to discuss the results of the study. The participants were Dolk (Chair, UK), Garne (Odense), De Vigan (Paris), Addor (Switzerland), Pierini (Tuscany), Calzolari (Emilia Romagna), Lillis (Galway), Bielenska (Poland).

A different method was used for validation of the Northern Ireland EUROCAT registry. One of the investigators (JES) requested a 1996 surgery list from a paediatric surgery centre in Northern Ireland, and a description of each case using the standard form (Appendix 1). This surgery list was then compared with the case list from the Belfast EUROCAT registry held at the EUROCAT Central registry, matching by date of birth only. This was therefore similar to the methodology used for validation of the NCAS register.

2.6 Results of the Validation Study: NCAS Data

The Proportion of Cases With Surgery Who Had Been Notified to NCAS at Birth

Newcastle: 75 operations were performed in 1996 for hypospadias of which 55 children were having their first operation for hypospadias (Table 2.2). Of these, 47 were for children born 1993-95, of which 31 were non-glanular. Three non-glanular cases matched with NCAS notifications, with 4 further possible matches with postcodes in the Newcastle area. A maximum 23 % of cases with non-glanular hypospadias (including matches and possible matches) born 1993-95 and first operated 1996 were notified to NCAS.

Table 2.2 Cases of Hypospadias Operated in Three UK Centre 1996 and Notifications to NCAS Among Non-Glanular Cases

	Total Ops 1996	1st Operated 1996	1st Op 1996, born 1993-95	Non-Glanular	% Non-Glanular	Match NCAS	Possible Match NCAS	% Match or Possible Match
RVI	75	55	47	31	66.0	3	4	22.6
Sheffield	79	72	59	42	71.2	4	12	38.1
Southampton	78	66	53	41	77.4	3	4	17.1
TOTAL	232	193	159	114	71.7	10	20	26.3

Table 2.3 Location of Hypospadias in Four UK Centres Patients with First Operation in 1996, Born 1993-1995

	RVI No.	Sheffield No.	Southampton No.	Total (3 Centres) No.	Total %	Belfast	
						No.	%
Preputial	3	2	-	5	3.1	0	-
Glanular	13	15	12	40	25.2	0	-
Peno-glanular	24	21	24	69	43.4	35	74.5
Mid-shaft	4	16	13	33	20.8	10	21.3
Proximal shaft	2	2	-	4	2.5	0	-
Penoscrotal	1	2	4	7	4.4	1	2.1
Scrotal	-	1	-	1	0.6	1	2.1
TOTAL	47	59	53	159	100.0	47	100.0

Southampton: 78 operations were performed for hypospadias in 1996 in Southampton General Hospital of which 66 were first operations (Table 2.2). 53 operated children were born 1993-95 of which 41 had non-glanular hypospadias. There was an additional case with type of hypospadias unspecified. 3 of the 41 matched and 4 possibly matched with NCAS notifications. A maximum 17% of cases with non-glanular hypospadias (including matches and possible matches) born 1993-95 and first operated 1996 were notified to NCAS. 174 children were born 1992-94 who later had surgery for hypospadias in either the Southampton or Portsmouth hospitals. Of these, 12 matched and 21 possibly matched with NCAS records, a total of 19%. This figure agrees quite well with that based on the 1996 surgery list for Southampton.

Sheffield: 79 operations were performed in 1996 of which 72 were first operations (Table 2.2). 59 were born 1993-95, of which 42 were non-glanular cases. 4 of the 42 matched and 12 possibly matched with NCAS records. A maximum 38% of cases with non-glanular hypospadias (including matches and possible matches) born 1993-95 and first operated 1996 were notified to NCAS.

Of 277 unmatched cases on any of the four surgery lists (born any year), all but 224 had the same date of birth as one or more other children born in England with hypospadias. It is expected that as there were at this time 520 cases reported to NCAS per year and 365 days in a year, most would find a matching date of birth. It is possible that some of these were

children notified to NCAS who had moved outside their area of birth and were therefore unmatched. However, of the 54 of these children born in 1995, where initial of first and last name could be looked at as a further matching variable, none of these children had the same first and last name initial, nor even first name initial. This suggests that few if any of the unmatched children were unmatched because they had moved to a distant postcode.

Overall, in the three large centres (Newcastle, Southampton and Sheffield), of 159 cases first operated in 1996 and born 1993-95, 26.3% matched or possibly matched with NCAS records. Variation between the centres was not statistically significant ($p > 0.05$).

Location of Hypospadias and Average Age at Operation, Based on 1996 Surgery Lists

Table 2.3 shows the distribution of hypospadias location of the 159 cases born 1993-95, first operated in 1996 in three paediatric surgery centres. 3.1% were preputial (i.e. not hypospadias) and 25.2% were glanular. The difference between these three centres in the distribution of location of hypospadias was not statistically significant ($p>0.05$).

The average age at first operation 1996 (any birth year) was 22.7 months in Newcastle (range 6-151), 27.7 months in Sheffield (range 11-153) and 30.4 months in Southampton (range 10-131). The average age at operation across all three centres was 30 months.

The Proportion of NCAS Cases Verified as Non-Glanular Hypospadias

In the adjoining HA's of Newcastle and North Tyneside, and Gateshead and South Tyneside, 23 cases had been notified to NCAS born 1993-95 (Table 2.4). Four of these did not have hypospadias. 12 were glanular, despite the guideline not to notify glanular cases. One could not be traced. Only 6/22 (27%) therefore were verified as cases of hypospadias eligible for notification to NCAS.

In Southampton and South West Hampshire, 21 cases had been notified to NCAS born 1993-95. Three of these were not hypospadias. Four were glanular. Three could not be traced. Only 11/18 (61%) could therefore be verified as cases of hypospadias eligible for notification to NCAS.

In summary, of the 44 cases surveyed born 1993-95 in these three districts and reported to NCAS, 16% were not hypospadias, and 36% were glanular and therefore not eligible for notification. The prevalence rate of hypospadias in these three districts 1993-95 was 1.0 per 1,000, higher than the average England and Wales prevalence for that period (see Table 3.1).

Table 2.4 Verification of Hypospadias Cases reported to NCAS, 1993-95

Health Authority	Number	Not Hypospadias	Glanular	Not Traced
Newcastle & North Tyneside, Gateshead & South Tyneside	23	4	12	1
Southampton & SW Hampshire	21	3	4	3
TOTAL	44	7 (16%)	16 (36%)	

2.7 Results of the Validation Study: EUROCAT Data

Part A: Survey of Registration Practice in EUROCAT Registries

Table 2.5 shows the results of the questionnaire to EUROCAT registries on registration practice. 25 full member registries completed the questionnaire and one further registry noted that they did not register hypospadias at all. A wide variation in practice can be seen, particularly in the implementation of the exclusion criterion. 9/25 registries did not implement the exclusion criterion in the most recent data transmission. Two (Vaud and Styria) excluded distal (glanular) hypospadias only when there had been no surgical intervention and Glasgow also did this up to 1990. Some registries reported that it could be difficult to distinguish whether hypospadias was on or before the coronary sulcus. Some registries asked their notifiers to exclude glanular hypospadias (thereby pushing the guideline back one further stage in the reporting chain). Other registries excluded glanular hypospadias after they had been reported to them. However, among these registries practice was variable as to how successfully cases of hypospadias of unspecified location could be followed up in order to establish location, and whether unspecified cases were excluded or included among registrations. Other limitations were whether registries used paediatric surgeons or other surgeons as a source of reporting new cases of hypospadias and whether registries used sources of information which covered the first week of life only. In one registry (Mainz) registration involves a special examination by registry paediatricians in the first week (see 2.5 above). All registries other than Mainz rely on examinations carried out as part of normal health services, and subsequent reporting of results to the register.

Table 2.5 Responses to Questionnaire Regarding Hypospadias Registration Practice in EUROCAT Registries

Registry	Do you record cases of isolated distal hypospadias (for transmission to EUROCAT)?	If the type (severity) of hypospadias is not specified in the notification, do you verify that the case is proximal before including it on the register?	Despite the exclusion criteria do you think that cases of isolated 'minor' hypospadias may be included on the register?	Who notifies most cases?	Age at first notifications of most cases	Glanular excluded by registry or notifers
Participants in Validation Study						
Odense	No	Yes	Yes, quite a few	Midwives on birth certificate and hospital discharge records	<10 days (then followed up with paediatric surgeons)	Registry
Paris	No	No, unspecified cases included, though more care not to register glanular cases in later years	Yes, quite a few	Midwife notifications and consultation of maternity records	<10 days	Notifier
Tuscany	No	Yes	Yes, before 1992 when type not specifically coded	Notifications by paediatricians	<10 days	Notifier and Registry
Northern Netherlands	No	Yes	No	Midwife birth registrations and notifications by paediatric surgeons	From birth to 3 years	Notifier and Registry
Emilia Romagna	Yes, but not transmitted to EUROCAT	Yes		Paediatricians	<10 days	Registry
Switzerland	Yes, if with surgery	Yes	Yes, occasional one	Notifications by paediatric surgeons	Time of surgical repair	N/A
North East Italy	No, nor coronal	Yes	Yes, occasional one	Paediatricians at birth	<10 days	Notifier
Basque Country	No	Yes	Yes, occasional one	Paediatrician registration book and neonatal unit and paediatric surgery dept discharge reports	<10 days	Registry
Mainz	Yes	Severity is known in all cases	Yes	Registry paediatricians examine all babies. No follow-up after this	<10 days	N/A

Other EUROCAT Members						
Hainaut	Only if surgical correction planned/ performed	Yes	Yes, occasional one	Consultation of maternity and paediatric dept records	<10 days	Registry
Dublin	Yes	All cases included	Yes	Hospital discharge records	<10 days and 3-12 months	N/A
Galway	No	No, unspecified cases included	Yes, occasional one	Consultation of maternity unit records	<10 days	Registry
Glasgow	Not since 1990	Yes	Yes, before 1990 if had surgery	Hospital discharge prints and health visitor follow-up forms	Most 1-3 years	Registry
Strasbourg	Not since 1993	Yes	No	Systematic consultation of records at maternity units, paediatric depts and paediatric surgery depts	<10 days, but verify later	Registry
Zagreb	Yes	Yes	Yes, because neonatologist diagnosis, not surgeon	Paediatricians and Maternity records	10 days – 3 months	Registry
Malta	No,	Unverifiable cases are included on the register	Yes, occasional one	95-97 by consultation of maternity unit records, from 1998 notifications by paediatric surgeons	<3 months	Notifer and Registry
Antwerp	No	Unspecified cases are excluded	Yes, occasional one	Consultation of maternity and paediatric dept records	3-12 months (depending on frequency of visits to consult records)	Notifiers and Registry
Asturias	No	Very few unspecified, assume proximal	Very few	Paediatricians and Surgeons	<10 days or 1-3 years	Notifiers
Saxony Anhalt	Yes	All cases included	Yes	Paediatricians/obstetrician notifications	<10 days	Registry since 1995
Barcelona	Yes	All cases included	Yes	Consultation of birth records at maternity unit	<10 days	N/A
Styria	Only if surgical correction performed	-	-	Search paediatric surgery records	3-12 months	-

43. North Thames North Thames Sicily – ISMAC Campania Merseyside & Cheshire South Wales – CARIS	Do not register proximal or distal hypospadias Yes Yes, up to 1997 only Yes Yes (except early 1998)	All cases included ? No All cases included	Yes Yes, quite a few Yes Yes	Notification by paediatricians and paediatric surgeons Paediatricians Midwives Midwives	10 days – 1 year <10 days <10 days <3 months	N/A Registry N/A Some notifiers probably exclude due to NCAS exclusion list. Glanular hypospadias is only minor anomaly recorded by CARIS despite NCAS exclusion list
Associated Members Finland Norway	 Yes Yes	 All cases included All cases included	 Yes, but minors excluded in specific tables Yes	 Notifications by paediatrician. Access medical birth registry since 1991 and hospital discharge records since 1994 Notification by midwives	 <10 days	 N/A

Old Members *						
South Western Netherlands *	No	Yes	No	Consultation of maternity unit and paediatric dept records and hospital discharge records	3 months – 3 years	Notifier and Registry
Bouches du Rhone *	Do not register proximal or distal hypospadias					

* Prevalence data not reported in this report, but can be found in EUROCAT Reports 6, 7 and 8 [47, 48, 51].

Part B: Validation of Case Registration 1994-96

Table 2.6 shows the results of the validation study in nine registers. A total of 382 cases were included in the survey (including extra cases found as a result of the survey).

The source of initial notification was maternity units in Paris, Emilia Romagna and Tuscany (100%), frequently the plastic surgeon in N Netherlands (15/41), the paediatrician or paediatric surgeon in half of Vaud cases, and the paediatrician in 100% of Mainz and Basque Country cases. In Paris, Tuscany, Emilia Romagna, N E Italy and Mainz, cases were reported to the register in the first month of life. In N Netherlands only 5 of 32 cases where this information was known were reported in the first month of life and 15 were reported after the first year of life. In Vaud, 14 of 26 cases were reported in the first month, a further 8 up to 1 year of age, and 4 at later ages.

The response rate from paediatric surgeons and paediatricians varied from 45% to 100%. Reasons for non-response included death or change of address of child, not being able to identify the clinician responsible for the child's treatment, and the clinician not sending back a questionnaire. It is difficult to be sure that the initial diagnosis of hypospadias was correct in these cases. As with NCAS data, anonymity of cases at registration in some registries (Tuscany, North East Italy) complicated the follow-up process.

A low proportion of cases were incorrectly registered as hypospadias – 4% of cases in Paris and 11.1% in Mainz (the latter were preputial). It is possible however that incorrectly registered cases were mainly in the non-response category.

Up to a third of cases in any one registry 1994-96 were additional cases added to the registers as a result of the survey. In Odense, the additional cases were known to the register but awaiting verification, and consultation of paediatric surgery lists showed no further cases were missing. In Northern Netherlands the extra cases included late registrations rather than cases which would not have ordinarily come to the attention of the register.

Between 64% and 91% of cases in the different registries were isolated anomalies (or associated with other genital anomalies including chordee).

Two of the registers (Vaud and Mainz) reported 33% and 46% respectively of glanular cases among cases of isolated hypospadias. These registers were not implementing the EUROCAT guideline for exclusion, although this was not known to the Central Registry. Four registers found that on further verification of isolated cases, a proportion of registered cases transmitted to the central EUROCAT database were glanular (23% of cases of known location in Paris, 17% in Emilia Romagna, 29% in North East Italy and 12% in Basque Country). Tuscany, Northern Netherlands and Odense found no glanular cases among registered isolated cases. However, in Tuscany the original registry records noted 10 cases as glanular, 4 of which were peno-glanular at follow-up and the remaining unknown (non-response).

Table 2.6 shows the prevalence rates of hypospadias before and after exclusion of known isolated glanular cases. Total prevalence rates varied from 0.5 per 1,000 (NE Italy) to 2.4 per 1,000 (Mainz), and without glanular cases from 0.5 per 1,000 to 1.3 per 1,000. Prevalence rates excluding glanular cases are overestimated in registries with a low response rate regarding verification of location. Three small registries with good ascertainment and response (Vaud, Odense, Mainz) found prevalence rates of 1.3 per 1,000 excluding glanular

cases. Vaud and Mainz were the only registers where a total prevalence rate including cases of all locations could be estimated: 1.7 per 1,000 in Vaud and 2.4 per 1,000 in Mainz.

The average age at first operation varied considerably from 13.6 months to 61.5 months (Table 2.6). Use of surgical records can thus expect to pick up cases up to 5 years of age. Whether a one or two stage operation was performed or planned also varied (Table 2.6).

The distribution by location for all registries is shown in Table 2.7. Table 2.8 shows whether hypospadias was accompanied by chordee, which would influence the need to operate to restore normal function. In general more distal forms have no chordee, and more proximal forms have severe chordee. Of the 251 known cases, 123 had no chordee, 82 mild chordee and 46 severe chordee.

Table 2.6 EUROCAT Validation Study – Results from 9 Registries

	Implementing guideline							Not implementing guideline	
	Paris	Tuscany	N Netherlands	Emilia Romagna	Odense	NE Italy	Basque Country	Mainz	Vaud
Total cases [a] (n)	75	60	41	44	23	58	28	27	26
Births (n)	74121	73613	57612	55232	18136	108355	30754	11042	15427
Reported Prevalence per 1000 births	1.0	0.8	0.7	0.8	1.3	0.5	0.9	2.4	1.7
Prevalence excluding isolated glanular/normal	0.8	0.8	0.7	0.8	1.3	0.5	0.9	1.3	1.3
Registered as result of survey (n)	0	20	10	0	9	0	0	0	9
(%)	0	33.3	24.4	0.0	39.1	0.0	0.0	0.0	34.6
Response to survey (n)	57	47	32	21	22	26	25	27	26
(%)	76.0	78.3	78.0	47.7	95.7	44.8	89.3	100.0	100.0
Isolated (n) [b]	64	45 [c]	30	28	19	53	21	22	18
(%)	85.3	75.0	73.2	63.6	82.6	91.4	75.0	81.5	69.2
Isolated, location known (n)	47	32 [c]	24	12	16	24	17	22	18
Isolated Glanular (n)	11	0	0	2	0	7	2	10	6
(%)	17.2	0.0	0.0	7.1	0.0	13.2	9.5	45.5	33.3
Normal (n)	3	0	0	0	0	0	0	3	0
Mean age at surgery (months)	16.4	36.0	19.5	24.7	61.5	34.0	34.2	22.4	13.6
Ratio 1:2 stage operations	37:1	37:1	13:17	9:2	13.5	3:6	16:3	11:2	15:0

[a] Non-chromosomal liveborn cases only

b Isolated includes association with other genital anomalies but excludes cases associated with other major malformations

[c] Including 20 cases not known if isolated (extra cases reported by surgeons)

Table 2.7 EUROCAT Validation Study Location of Hypospadias in 9 Registries

	Paris	Tuscany	N Netherlands	Emilia Romagna	Odense	NE Italy	Basque Country	Mainz	Vaud
Normal	3							3	
Glanular	15	1	1	3		7	3	11	10
Peno-glaular	23	20	11	4	11	7	11	12	12
Mid-shaft	11	8	12	7	3	4	6	1	4
Proximal shaft	3	1	3		1	1	1		
Peno-scrotal	1	7	1	1	2	3	2		
Scrotal		2	4	1		1	1		
Perineal	1				1	2			
Unknown	18	21	9	28	5	33	4		
Total	75	60	41	44	23	58	28	27	26

Table 2.8 Urethral Meatus Position by Whether Chordee was Present

	No Chordee	**Mild**	**Severe**	**Not Known**	**TOTAL**
Normal	5	1			6
Glanular	39	6	2	1	48
Peno-Glanular	60	42	5	3	110
Mid-Shaft	16	25	12	3	56
Proximal Shaft		3	7		10
Peno-Scrotal	1	3	12	1	17
Scrotal	1	2	6		9
Perineal			2		2
Not Known	1			123	124
TOTAL	123	82	46	131	382

Results for the Belfast EUROCAT Register

79 children with hypospadias had been operated on in 1996 in one Northern Irish paediatric surgery centre, of whom 49 were born 1993-95. All but two of these 49 cases were first time operations for hypospadias. (In contrast, 10 of the remaining 30 older cases were second or third operations). Ten of the 49 cases (20.4%) had been registered by the Belfast EUROCAT registry. The distribution of location were 35 peno-glanular, 10 mid-shaft, 1 penoscrotal and 1 scrotal (Table 2.3). The 2 most proximal cases had been registered. Two of the mid shaft and six of the penoglanular had also been registered. The average age at operation for first operations in 1996 (any birth year) was 37.9 months (range 3-135 months).

It was not possible to follow up the cases on the Belfast register to see what proportion were glanular hypospadias or were not hypospadias. The total prevalence rate recorded by the Belfast EUROCAT registry 1993-95 was 0.7 per 1,000 (52 per 73,500 births). These were the last years of data transmission from the Belfast registry to the Central Registry, and reported prevalence of many congenital anomalies had been falling (EUROCAT Report 7)[47].

2.8 Discussion

The Need for Validation of Surveillance Data

It is a precondition for effective epidemiologic surveillance of hypospadias that comparisons over time and between countries should be based on comparable data in terms of definition and ascertainment. We have investigated the degree of under and overascertainment of hypospadias in European registries, and the success with which a guideline to exclude "minor" distal (glanular) cases has been implemented.

Retrospective data validation studies are difficult to carry out successfully. They encounter problems of data confidentiality and protection, resistance of health professionals to completing more paperwork, and problems with retrieval of information and tracing of cases. Data validation therefore has to be built into surveillance systems on a prospective basis. We suggest more use could be made in surveillance systems of continuous programmes of data validation on random samples of cases, or samples of cases born or treated between specified dates.

NCAS (England and Wales) registers cases anonymously. Theoretically, cases can be traced by writing t o notifying Health Authorities. In reality, many HA's either do not keep adequate records to identify these cases, or are doubtful about the data protection implications and need for patient consent (further clarification of this issue in the UK is awaited), or are too busy to respond to requests. It should be recognized in the design of surveillance systems that both anonymity and patient consent can greatly increase the difficulty and expense of carrying out data validation.

At the time this study was done, coding of congenital anomalies was in the International Classification of Diseases version 9, which did not differentiate location of hypospadias. Most registries now employ or will shortly employ ICD10, where location is specified. This should make it more straightforward to validate hypospadias data, although the accuracy of location data will still need evaluation.

Implementation of the Guideline to Exclude Glanular Hypospadias

It is a well known phenomenon in health services research that the existence of guidelines does not guarantee their implementation. Impediments to implementation need to be assessed. Registries and routine data systems must follow through their guidelines to encourage and evaluate their implementation.

The guideline issued by EUROCAT since 1980 and by NCAS since 1990 for the exclusion of glanular hypospadias was not implemented consistently across registries. In the NCAS data, we found that 36% of the 44 cases reported from three sample districts 1993-95 were glanular hypospadias, despite the exclusion criterion. Although our study sample was not necessarily representative, it clearly demonstrates that implementation of the guideline is poor in the NCAS system. A number of factors may explain this. Some cases may have been identified as peno-glanular at birth which were later reclassified as glanular when seen by a surgeon. Secondly, midwives filling in the SD56 forms and sending them to their district to be forwarded to ONS may be unaware of the exclusion guideline, and may not specify type of hypospadias on the form. Thirdly, personnel processing SD56 forms in the Health Authority may not always be aware of the exclusion guideline. Finally, personnel processing SD56 forms at HA level may be aware of the guideline but not have the location information to implement it, resulting in them either not notifying any hypospadias cases, or notifying all hypospadias cases regardless of location.

Among the nine registries taking part in the EUROCAT validation study, one did not implement the guideline to exclude glanular hypospadias (Mainz), and one did not exclude glanular cases if they had surgery (Switzerland). Some registries following the exclusion guidelines nevertheless reported a substantial number of glanular cases on further verification. A relatively high proportion of glanular cases were inadvertently reported from Paris (23%) and North East Italy (29%), the larger of the EUROCAT registries in terms of annual no. births surveyed. Only three of the nine registries had successfully excluded all glanular cases.

A major impediment to implementation of the exclusion guideline has been the perception that, if surgery is performed or planned for glanular hypospadias, hypospadias is by definition not "minor" and therefore should not be excluded. There are few reports indicating the proportion of children with hypospadias, particularly distal hypospadias, who undergo surgery. These are reviewed in Chapter 1.1 and Table 1.1. A prospective survey in the Netherlands,1999-2000 reported that 79% of cases had surgery planned or performed[5]. The Dutch study was the only one to specify the location of cases with and without surgery: 3 out of 12 glanular cases, 14 of 15 coronal cases and all others had surgery. A study in Southampton and Portsmouth[6] reporting on the prevalence of hypospadias 1992-94 considered that effectively all cases, including glanular cases, would have surgery. The two EUROCAT registries registering glanular hypospadias (Mainz and Vaud) reported that surgery was usual in cases of glanular hypospadias, but cases of glanular hypospadias without surgery were likely to be missed by the Vaud registry. In contrast, the Belfast EUROCAT registry rarely performed surgery for glanular hypospadias, a fact reflected in the 1996 surgery list which contained no cases of glanular hypospadias. It is quite possible that "fashions" regarding surgery for glanular hypospadias, which is of cosmetic rather than functional importance, will continue to vary over time and between places. A recent German study[8] has for example questioned whether surgery for glanular cases is necessary, given their survey of adult men and suggested no functional or psychological consequences for milder forms of abnormality.

Doubt was expressed by some of the respondents to the EUROCAT registration practice survey as to whether cases with the opening on (rather than before) the coronal sulcus should be reported and whether the distinction between glanular and coronal (or penoglanular) could be reliably made by registries. Moreover, the EUROCAT exclusion criterion specifies glanular or Type 1, but Type 1 or first degree seems to include coronal cases in many classifications. In Mainz and Vaud, the two registries not excluding glanular hypospadias, glanular location accounted for 40% of cases of isolated hypospadias. In the English surgery lists we analysed, the proportion of glanular hypospadias was 25.2% and the proportion of peno-glanular was 43.4%. An Italian study[35] reported Type 1 hypospadias to account for 75% of cases (although it is difficult to see in the classification diagram whether Type 1 referred to glanular only or glanular and coronal combined), and a review reported 70-80% of glanular cases[2]. A Dutch study found 23% glanular and 28% coronal[5]. Glanular or coronal cases (combined) have been reported to account for 69%[36] and 69-85%[38]. The difficulty of distinguishing in reporting systems between glanular and coronal cases was noted in a previous study[4]. While surgeons may be expected to assess and record location accurately and consistently (although this has yet to be evaluated), reporting systems which rely on a wider net of information sources are unlikely to be able to implement a guideline relying on the distinction between glanular and coronal/peno-glanular cases. Thus, implementation of the EUROCAT exclusion guideline may have resulted in exclusion of some or all coronal/peno-glanular cases, which would lead to marked lowering of prevalence rates.

Underascertainment of Eligible Cases for Registration (False Negatives)

Underascertainment of hypospadias by registries could only be judged for non-glanular hypospadias in this study. Our study suggests that in 1993-95, only approximately one quarter of eligible cases of non-glanular hypospadias were notified to NCAS and one fifth to the Belfast EUROCAT register. Five of the nine EUROCAT registers involved in the validation study did not find extra cases after consulting paediatric surgeons and estimated their completeness at 100%, but this method of assessment is unreliable compared to direct comparisons with surgery lists. Two registries (Tuscany and Vaud) assessed their completeness of ascertainment to be 66% after consultation with paediatric surgeons. In the only previous study considering underascertainment, an international study of registries[4] estimated that the proportion of missed cases among those severe enough to be operated was 46% for Hungary 1975, 30% for Sweden 1974, and 64% for Denmark 1974-76.

Overascertainment of Hypospadias (False Positives)

Overascertainment (or incorrect notification) of hypospadias may result if registry information is based solely on neonatal examinations or may result from coding errors. In our small data sample of 44 notifications to NCAS, 16% of notified cases did not have hypospadias. Among the 382 notifications in the EUROCAT sample, 6 cases were not hypospadias. However, it is possible that incorrectly notified cases were amongst those cases that could not be followed up by EUROCAT registries, especially where the reason for non follow-up was the impossibility of identifying a paediatric surgeon responsible for the case. The non-response category was particularly large in two of the Italian registries, where anonymous data are kept. A previous international study of registries[4] found that in Sweden in 1974, 5% of cases were false positives, and in Hungary in 1975, 21% of cases were false positives. The existence of false positives also indicates that validation studies should make their comparisons on a case by case basis, rather than comparing total numbers or prevalence. Thus, comparisons made in Southampton and Portsmouth[6] suggested that 38% of eligible

cases were notified to NCAS 1992-94, while we estimate 19% from the same data. A further study[52]evaluated NCAS data for 1977-78 by comparing total prevalence with the literature, and concluded that ascertainment was high, although the potential for false positives was not taken into account. A study in Birmingham[53] 1972-78 did a case by case comparison with ONS data (before the implementation of the exclusion guideline) and found a false positive rate of 14%.

A particular category of over-notification is notification of incomplete prepuce as hypospadias. This is sometimes called "preputial hypospadias" or "hypospadic prepuce" but does not routinely require surgery, and the meatal location is normal. It is interesting that in Odense, 10 cases of hypospadias notified by midwives were found on follow-up to be incomplete prepuce, as against 18 "true" hypospadias born during the same time period. This high ratio emphasises the need to ensure accurate identification and exclusion of incomplete prepuce, by verification of location by appropriate sources such as paediatric surgeons or urologists. A recent Dutch study[5] trained 30 Child Health Centre physicians in standardised examination of newborns to detect hypospadias. Of the 60 boys referred to the paediatric urologist/ endocrinologist as cases of hypospadias, 7 had a preputial abnormality only.

Recommendations for Future Surveillance

On the basis of the results of this study, we recommend the following practice for the surveillance of hypospadias by registries:

1. Information on location of hypospadias should be completely recorded for all cases, coded to ICD10. Increasing possibilities for transmission of digital images may be helpful for special hypospadias prevalence surveys.
2. All cases of hypospadias should be registered, regardless of location. Considerable attention however should be given to cases on the borderline between hypospadias and incomplete prepuce, to exclude the latter.
3. In order to ensure complete ascertainment of hypospadias, and in order to verify location and exclude incomplete prepuce, paediatric surgeons should be one of the multiple sources of information for all cases. This may imply a delay before completing registration, especially in countries where surgery is conducted later in the first five years of life.
4. Information on whether surgery has been planned or performed should be recorded.
5. Analyses of trends in prevalence should consider changes in the distribution of location of recorded cases, as well as changes in the proportion undergoing surgery by location.

In the light of the above guidelines, registries could consider whether hypospadias registration should be the subject of periodic intensive ad-hoc surveys, or continuous registration. This may depend on the size of the registry, the methods and sources of information usually used, and the resources routinely available.

For NCAS, it is probably not feasible to follow the guidelines above on a routine basis, but consideration should be given to lifting the exclusion criterion for glanular hypospadias.

2.9 Summary of Main findings and Conclusions

Main Findings

- The EUROCAT and NCAS guideline for exclusion of glanular hypospadias has been variably and often poorly implemented.
- Where the intention was to implement the guideline, particular problems included:
    - whether cases "on" the coronary sulcus should be excluded
    - whether distal cases undergoing surgery should be excluded
    - whether the registry could routinely verify meatal location
    - access to appropriate sources of information for verification of diagnosis.
- The degree of underascertainment and overascertainment of hypospadias in NCAS and EUROCAT registries is variable. NCAS registered 25% of eligible cases in the sample of districts studied, and 16% of registered cases were not hypospadias.

Main Conclusions

- Systems of data validation should be built into surveillance systems on a prospective basis. Confidentiality requirements should take this into account.
- Exclusion of glanular hypospadias cases is neither reliable nor desirable for the following reasons:
    - the distinction between glanular and peno-glanular or coronal cases is open to considerable inter-observer variation.
    - glanular hypospadias are frequently operated on and thus cannot be considered a "minor" anomaly for exclusion.
- If all hypospadias cases are to be registered, then the following problems should be taken into account:
    - incomplete prepuce may be incorrectly identified as hypospadias and follow-up of cases is needed to exclude these "false positives"
    - Hypospadias must be verified by a paediatric surgeon/urologist or equivalent, recording meatal location.
    - Waiting for case verification by paediatric surgeons may imply a delay in surveillance
- We recommend that hypospadias surveillance should in future take the form of focused regular surveys, including paediatric surgeons as one source of information. These surveys can be undertaken by congenital anomaly registers if they follow a special protocol for hypospadias. Surveys should record details of location, source of information for verification of location, and whether referred for surgery.

Chapter 3
Temporal Trends, Seasonal, Geographical and Socio-Economic Differences in Prevalence of Hypospadias

3.1 Objectives of Chapter 3

In Chapter 3, we address the second objective of the study: to present hypospadias prevalence data in European regions 1980-1999 and comment on temporal trends observed. We discuss results for England and Wales (NCAS data) and Europe (EUROCAT data) separately.

3.2 NCAS Data

Data from the National Congenital Anomaly System (NCAS) was used to investigate time trends, seasonal patterns and socio-economic differences in the prevalence of hypospadias. This system covers around 650,000 births per year in England and Wales. Data for all live and stillbirths in England and Wales has been used as denominator data (from NCAS DH3 publications). Data from 1980-1996 have been analysed.

- Time Trends

Table 3.1 and graph 3.1 show the prevalence rates of hypospadias by year of birth in our study as well as an earlier publication covering the period 1964-83[11]. A sharp fall in prevalence rates is seen starting in 1990 and 1991. In 1990 NCAS introduced new guidelines for the exclusion of 'minor' forms of hypospadias (see 2.2) which led to a drop in hypospadias cases from around 1100 per year in 1980-89 to 550 per year in 1992-96. The exclusion criteria for a range of minor anomalies also led to an equivalent fall in the prevalence of all congenital anomalies. The years 1991-92 were a transition period and have not been included in analyses of time trends or any other analyses of these data. These results suggest that previously reported trends in the same data between 1964 and 1983[11] are not continuing and moreover, that 1983 was a peak year for prevalence.

As shown in Chapter 2, the guidelines for exclusion of Hypospadias has not been well implemented in the sample of HA's we studied and it is doubtful whether full implementation is feasible in routine recording systems. Whereas a simple interpretation of NCAS trends would suggest that the halving of prevalence rates reflects the exclusion of glanular cases, we now interpret this differently. Glanular cases probably represent only about one quarter to one third of all true cases. The stronger drop in rate may reflect a combination of different practices in different HA's, including:

- Exclusion of many cases which are of unspecified location
- Inclusion of cases of unspecified location
- Exclusion of coronal as well as glanular cases
- Complete lack of recording of hypospadias due to the difficulty of collecting data about location
- Disregard of the exclusion guideline and recording of all cases

We could not assess variation across HA's with regard to possible differences in practice statistically, since HA boundaries have changed several times and yearly data within each HA would provide Hypospadias rates based on very small numbers with low statistical stability.

Figure 3.1: Hypospadias Prevalence Rates by Year of Birth - 1980-96 NCAS Data

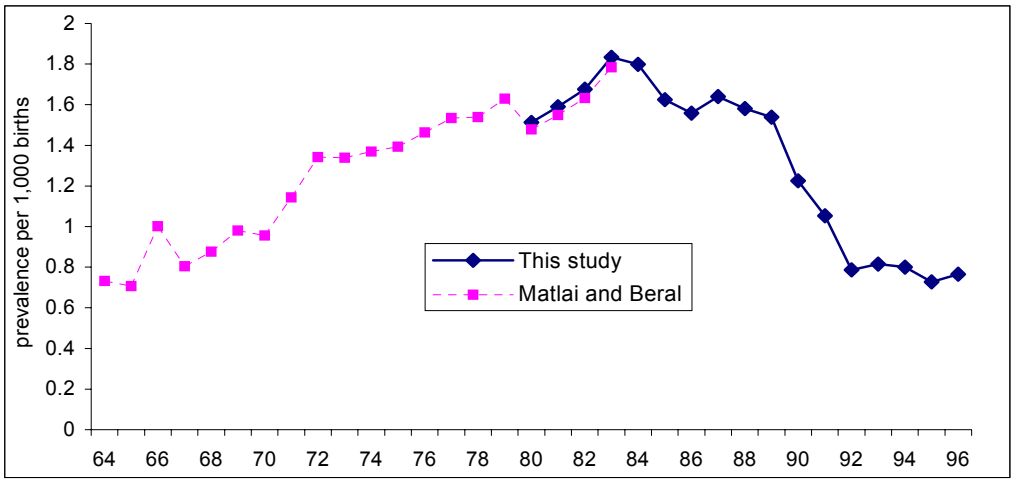


Table 3.1 : Hypospadias Prevalence Rates by Year of Birth - 1980-96 NCAS Data

year	births	hypospadias	
	N	N	rate/1,000
1980	661016	1000	1.5
1981	638699	1016	1.6
1982	629874	1056	1.7
1983	632766	1160	1.8
1984	640468	1152	1.8
1985	660062	1072	1.6
1986	664567	1036	1.6
1987	684934	1123	1.6
1988	696959	1102	1.6
1989	690961	1063	1.5
subtotal 1980-89	6600306	10780	1.6
	p value heterogen 1980-89=		0.001
	p value trend 1980-89=		0.249
1990	709396	869	1.2
1991	702471	740	1.1
1992	692600	545	0.8
1993	675090	551	0.8
1994	668072	535	0.8
1995	651598	474	0.7
1996	653028	500	0.8
subtotal 1992-96	3340388	2605	0.8
	p value heterogen 1992-96=		0.402
	p value trend 1992-96=		0.229
total	17952867	25774	1.4

3.2.2 Geographical Variation

Within the ONS congenital malformation data we examined variation in the hypospadias prevalence rates between regions, based on Regional Health Authority (RHA) areas. Table 3.2 and Figure 3.2 show the prevalence of hypospadias by RHA for the 1980-89 and 1992-96 periods separately. The prevalence of hypospadias varies significantly between regions, from 1.1 to 2.3 per 1,000 births in 1980-89 and from 0.5-1.3 per 1,000 births in1992-1996. In both time periods the region of Trent reported the highest prevalence of hypospadias. The lowest prevalences were reported by Oxford 1980-89 and North West Thames 1992-96. As Chapter 2 discusses, both under and overascertainment of hypospadias cases is likely to have occurred in the NCAS data. These ascertainment problems are likely to vary according to the reporting district, which makes regional differences difficult to interpret.

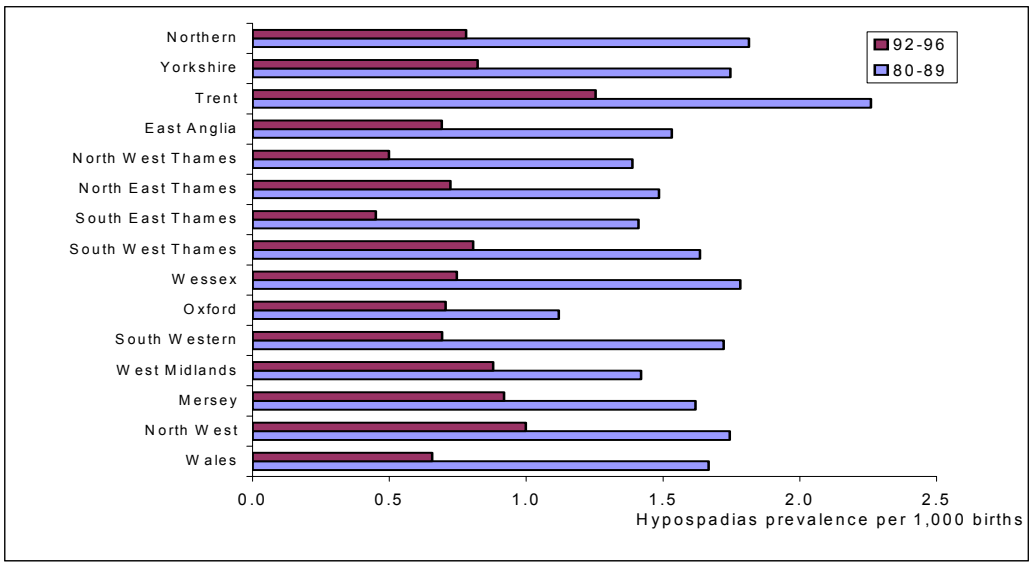
Table 3.2 : Hypospadias Prevalence Rates by Region - 1980-96 ONS Data

Region	births	hypospadias cases	rate/1,000	births	hypospadias cases**	rate/1,000
Northern	401900	729	1.8	188179	147	0.8
Yorkshire	481521	841	1.7	239507	197	0.8
Trent	595027	1345	2.3	299134	375	1.3
East Anglia	246770	378	1.5	127226	88	0.7
North West Thames	479767	666	1.4	252611	126	0.5
North East Thames	528724	785	1.5	281826	204	0.7
South East Thames	472259	666	1.4	251087	113	0.5
South West Thames	366317	599	1.6	195976	158	0.8
Wessex	352411	628	1.8	188928	141	0.7
Oxford	332613	372	1.1	175566	124	0.7
South Western	380969	656	1.7	197609	137	0.7
West Midlands	707327	1004	1.4	347167	305	0.9
Mersey	325668	527	1.6	150248	138	0.9
North West	554021	966	1.7	266526	266	1.0
Wales	370859	618	1.7	179773	118	0.7
		chisq for heterogenity= 280.5			chisq for heterogenity= 178.5	
		p value for heterogeneity= 0.000			p value for heterogeneity= 0.000	

* Based on regional health authorities as at 1980

** Hypospadias cases as registered in Jan 2001

Figure 3.2 : Hypospadias Prevalence Rates by Region - 1980-96 NCAS Data



3.2.4 Socio-Economic Variation

For the analysis of socio-economic variation in the risk of hypospadias we made use of the following measures of socio-economic status:

1. Individual social class of the mother and father. Parental occupation is recorded for congenital anomaly cases in the NCAS data and a random 10% of all births. Six standard social class groups are calculated directly from occupation.
2. Deprivation index of area of residence. Congenital anomaly cases and births were linked through their postcode at birth to the Carstairs deprivation index of their census enumeration district (ED) of residence. The Carstairs index combines census information on access to car, unemployment, overcrowding, and social class of head of household.

The following analyses of socio-economic variation in risk of hypospadias were carried out:

- The proportion of hypospadias cases out of all congenital anomaly cases for whom occupation was recorded by social class of the mother and father and the deprivation index (1980-89 and 1992-96). See for further details the methods section of Chapter 5 on proportional analysis. Results are shown in Table 3.3.
- The proportion of hypospadias cases out of a 10% sample of all live births for whom occupation is recorded by social class of the mother and father and the deprivation index (1992-1996). Results are shown in Table 3.4.

Analyses using births as denominators were based on the 1992-1996 period only, because the recording of maternal occupation in the births data did not start until 1986 and was relatively incomplete in the early years of recording. Also, we were not able to use the deprivation index in the 1980-89 data because full postcoding of the congenital anomaly data did not start until 1983 making linking of census variables in early years impossible.

Table 3.3 Socio-economic Variation in Hypospadias as Proportion of All Congenital Malformations

				1980-89+1992-96		1980-89			1992-96		
	all cases	*hyposp*	*% hyposp*	*OR**	*95% CI*	*OR**	*95% CI*		*OR**	*95% CI*	
Social class of mother											
I: professional	751	69	9.19	1.00		1.00			1.00		
II	9282	843	9.08	0.99	0.76 - 1.28	1.04	0.75	1.43	0.91	0.57 - 1.44	
IIINM	15051	1454	9.66	1.05	0.81 - 1.36	1.12	0.82	1.54	0.89	0.56 - 1.40	
IIIM	2995	311	10.38	1.12	0.85 - 1.48	1.10	0.78	1.55	1.27	0.77 - 2.09	
IV	6283	637	10.14	1.08	0.83 - 1.41	1.13	0.82	1.57	0.98	0.60 - 1.60	
V: unskilled	1562	154	9.86	1.03	0.76 - 1.40	1.08	0.75	1.55	0.97	0.54 - 1.72	
other	38	3									
				trend (I-V) p= 0.17		trend (I-V) p= 0.32			trend (I-V) p= 0.32		
Social class of father											
I: professional	2205	188	8.53	1.00		1.00			1.00		
II	6744	637	9.45	1.11	0.94 - 1.32	1.07	0.88	1.29	1.34	0.90	2.01
IIINM	4178	400	9.57	1.12	0.93 - 1.35	1.03	0.84	1.26	1.63	1.06	2.49
IIIM	9948	992	9.97	1.16	0.98 - 1.37	1.09	0.91	1.31	1.48	0.99	2.20
IV	4818	476	9.88	1.14	0.95 - 1.37	1.06	0.87	1.30	1.51	0.98	2.31
V: unskilled	1525	155	10.16	1.16	0.92 - 1.46	1.07	0.83	1.37	1.64	0.97	2.79
other	6544	623									
				trend (I-V) p= 0.13		trend (I-V) p= 0.45			trend (I-V) p= 0.06		
Deprivation quintile (1992-96 only)											
1: affluent	1351	132	9.77						1.00		
2	1416	147	10.38						1.08	0.84 - 1.39	
3	1527	152	9.95						1.01	0.79 - 1.30	
4	1352	148	10.95						1.14	0.88 - 1.47	
5: deprived	939	90	9.58						0.97	0.72 - 1.31	
other	127	8	6.30						0.60	0.29 - 1.27	
									trend (I-V) p= 0.88		

*adjusted for year of birth, maternal age, region.

In the proportional analyses we find little evidence for socio-economic variation in the proportion hypospadias cases out of all congenital anomaly cases (Table 3.3). Only in the 1992-1996 period we find a trend (not statistically significant) of increasing proportion hypospadias with lower social class of the father. Social class of the mother and deprivation quintile do not show a clear trend in any of the time periods. The main reason for using a proportional analysis here is to use the same source of data for maternal occupation in numerator and denominator data thereby limiting information bias. However, the congenital anomalies included in the denominator data may show an association with socio-economic status also. If this was the case we would in the proportional analyses underestimate a true relationship between hypospadias and socio-economic status. There is some evidence in the literature that all congenital anomalies show an increased risk with lower socio-economic status[54] and we can not exclude the possibility that these proportional analyses underestimate socio-economic variation in risk of hypospadias.

Analyses using births as denominator show statistically significant trends of increasing risk of hypospadias with lower social class of the mother and father (Table 3.4). The odds ratio for social class V vs. I is 2.44 (95% CI 1.53-3.91) using social class of the mother, and 1.56 (95% CI 1.02-2.39) using social class of the father. There is little evidence for a trend in hypospadias risk with deprivation quintile: the risk is increases from quintile 1 to 4 but than drops in quintile 5. Since social class is based on occupation stated at birth registration for all births, but occupation is stated in antenatal notes for Hypospadias cases, it is possible that the lower risk for higher social classes reflects differences in the recording of occupation during

pregnancy and at birth, and for mothers in particular possible differences between social classes in whether they give up their earlier occupation during pregnancy. The absence of a trend with deprivation quintile which is free of such bias supports this explanation. We have shown in a previous study that area deprivation is as good as, if not better than, social class in revealing socio-economic trends in other birth outcomes (i.e. low birth weight)[55]. Our ability to detect socio-economic variation in risk may also be limited by the considerable degree of over and underascertainment of Hypospadias by NCAS varying from health authority to health authority (see Chapter 2).

We conclude that the data available do not clearly point to socio-economic variation in risk of Hypospadias, but that data limitations restrict our ability to draw a solid interpretation.

NCAS plans to link congenital anomaly and births data. This should enable more meaningful analysis of social class in future.

Table 3.4 Socio-Economic Variation in Hypospadias Using 10% of Births as Denominator (92-96)

	births	*hyposp*	*OR**	*95% CI*	
Social class of mother					
I: professional	7582	35	1.00		
II	58899	261	0.90	0.63	1.29
IIINM	69414	335	0.96	0.68	1.37
IIIM	16980	95	1.06	0.72	1.57
IV	25901	126	0.89	0.61	1.29
V: unskilled	2849	36	2.44	1.53	3.91
other	1	339			
			trend (I-V) p=		0.05
Social class of father					
I: professional	16821	53	1.00		
II	49435	181	1.15	0.85	1.56
IIINM	19568	107	1.69	1.21	2.35
IIIM	51570	227	1.30	0.96	1.75
IV	24547	117	1.36	0.98	1.89
V: unskilled	6444	35	1.56	1.02	2.39
other	13579	169			
			trend (I-V) p=		0.02
Deprivation quintile					
1: affluent	40096	172	1.00		
2	40839	198	1.09	0.89	1.34
3	39413	195	1.09	0.88	1.34
4	34945	193	1.20	0.97	1.47
5: deprived	26231	121	0.94	0.74	1.19
other	440	10			
			trend (I-V) p=		0.87

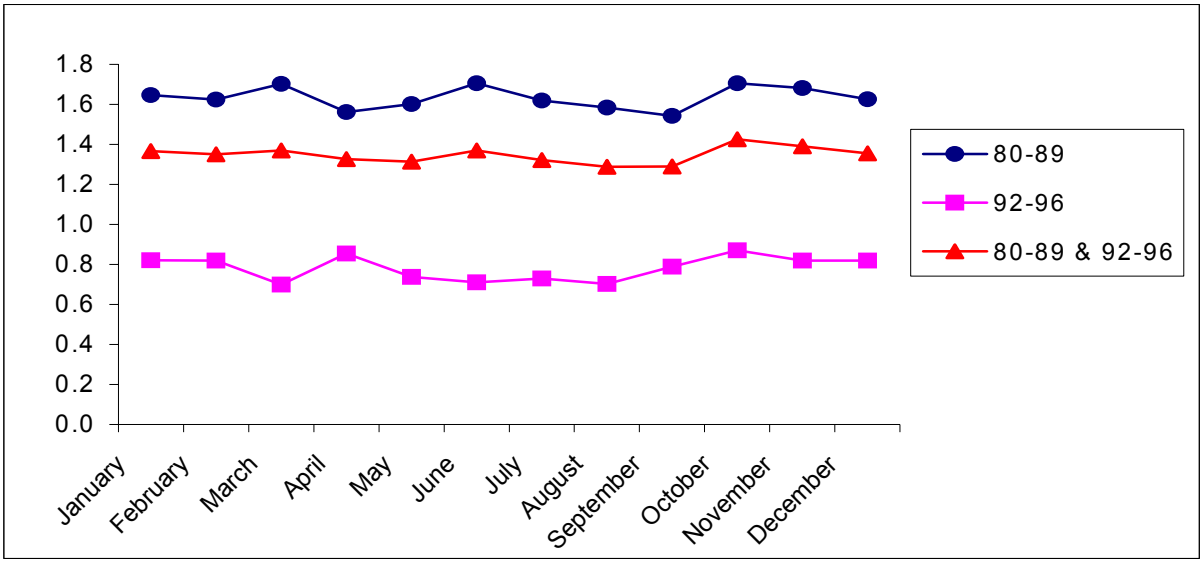
*adjusted for year of birth, region.

3.2.3 Seasonal Patterns

Figure 3.3 shows the monthly variation in hypospadias rates. There was no evidence for variation in Hypospadias rates between months. P-values for heterogeneity between months were 0.37 for the 1980-89 period, 0.18 for 1992-96, and 0.41 for the periods combined. We tested for seasonality in this data by fitting sinus and cosinus Fourier terms. Terms relating to cycles of annual and sub-annual (1/2, 1/3 of a year) periodicity were fitted. There was little evidence for seasonality in the 1980-89 period or the periods combined (p >0.1). In the 1992-

96 period a statistically significant annual cycling was found (p=0.04). There were no sub-annual cycles in that same period. In the 1992-96 period hypospadias rates are highest for babies born in the winter months (Oct-Feb) and lowest in the summer months (May-August).

Figure 3.3 : Hypospadias Prevalence Rates (per 1,000 Births) by Month of Birth



3.3 EUROCAT Data – Geographical Variation and Time Trends

3.3.1 Geographical and Temporal Variation

Fourteen of the 20 registries analysed were implementing the guideline to exclude glanular cases or Type 1 cases (Table 3.5). Of the ten with consistent application of the guideline over the time period, N Netherlands and NE Italy recorded a decreasing trend in prevalence, and Galway an increasing trend. Prevalence in the two French regions seemed to peak in the early 1990s with no overall trend (Figure 3.1). Three registries implemented the guideline for only the latter part of the study period, and recorded a decreasing trend in prevalence at least in part associated with this change (Glasgow, Tuscany, Zagreb; Table 3.5). An increasing trend in Malta was associated at least in part with a change in sources of information for case ascertainment (Table 3.5). By 1995-99, the total prevalence across the 14 registries implementing the guideline was 0.80 per 1,000 (95%CI 0.75-0.86) with significant variation ($p<0.001$) between registries from 0.5 in Tuscany to 1.9 in Strasbourg.

Six registries were not implementing the guideline, two of these registering glanular cases who had surgery (Vaud, Styria), the other four registers registering all glanular cases reported to them (Table 3.5). There was a significant upward trend in two registries (Styria and Dublin), although the prevalence in Styria seemed to peak in the early 1990s. There was a downward trend since 1990 in Mainz. In 1995-99, the total prevalence rate across these registers was 1.64 (95%CI 1.51-1.79) with a higher rate among those registering all hypospadias (1.73 per 1,000, 95%CI 1.57-1.91) than those registering only those with surgery (1.43 per 1,000, 95%CI 1.21-1.69).

Table 3.5 Hypospadias Prevalence per 1,000 Births in EUROCAT Registries, 1980-99

Registry	Years of Data	Number of Cases	Total Births	Prevalence per 1,000	1980-1984	1985-1989	1990-1994	1995-1999	Trend [c]
Implementing Guideline to Exclude Glanular Hypospadias [a]									
Antwerp (Belgium)	1990-1999	78	108753	0.7	-	-	0.69	0.73	no trend
Hainaut (Belgium) [b,s]	1980-1999	248	214340	1.2	0.93	1.31	1.06	1.30	no trend
Basque Country (Spain)[s]	1990-1998	117	144316	0.8	-	-	0.85	0.77	no trend
Emilia Romagna (Italy)	1981-1999	281	445289	0.6	0.71	0.56	0.54	0.74	no trend
N E Italy [d]	1981-1999	554	894344	0.6	0.76	0.72	0.64	0.45	↓ p<0.05
Galway (Ireland)	1981-1999	24	54509	0.4	0.22	0.20	0.62	0.77	↑ p<0.01
N Netherlands	1981-1999	285	288012	1.0	1.73	0.87	0.90	0.92	↓ p<0.01
Odense (Denmark)	1980-1999	121	105848	1.1	1.30	0.85	0.95	1.45	no trend
Paris (France)	1981-1999	839	698681	1.2	1.05	1.10	1.63	1.00	no trend
Strasbourg (France) [s]	1982-1998	481	225983	2.1	1.30	2.336	2.62	1.87	no trend
Changes in guideline implementation[a] or ascertainment[e]									
Glasgow (UK) [a, s]	1980-1999	313	243634	1.3	1.64	1.87	0.90	0.58	↓ p<0.05
Tuscany (Italy) [a]	1980-1999	233	306517	0.8	1.07	1.43	0.70	0.46	↓ p<0.05
Malta[e, s]	1986-1999	94	71354	1.3	-	0.96	1.33	1.63	↑ p<0.05
Zagreb (Croatia) [e]	1983-1999	111	103255	1.1	0.99	1.52	1.09	0.64	↓ p<0.001
Not Implementing Guideline to Exclude Glanular Hypospadias									
Vaud (Switzerland) [b, s]	1988-1999	106	84471	1.3	-	1.11	0.94	1.61	no trend
Styria (Austria) [b, s]	1985-1999	269	192348	1.4	-	0.75	2.11	1.32	↑ p<0.001
Dublin (Ireland)[s]	1980-1999	603	420564	1.4	1.50	1.00	1.38	1.86	↑ p<0.01
Mainz (Germany)[f]	1990-1999	90	37968	2.4	-	-	2.85	1.83	↓ p<0.01
Saxony-Anhalt (Germany)	1987-1999	236	143044	1.6	-	1.45	1.73	1.78	no trend
Sicily (Italy)[s]	1991-1998	237	152237	1.6	-	-	1.61	1.50	no trend

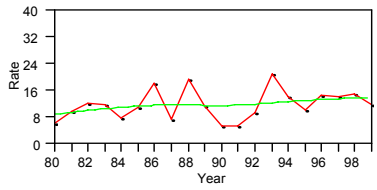
a Implementation of exclusion guideline only since 1990 in Glasgow (previously registering glanular cases who had surgery), since 1992 in Tuscany
b Glanular cases with surgery registered
c ↑ = rising trend, ↓ = decreasing trend
d North East Italy excludes glanular and coronal cases
e Zagreb included cases of unspecified location, and access to information about location improved during the study period, Malta started obtaining several new sources of information since 1993 including hospital activity analyis records covering paediatric surgery discharges.
f Mainz conducts special standardised examination of all newborns for registration and research purposes
s Registry which obtains case notifications, among multiple sources, from paediatric surgeons or hospital discharge records including paediatric surgery.

3.3.2 Interpretation

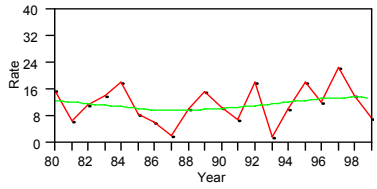
During the period 1980-99 prevalence rates of hypospadias have been influenced by differing interpretations of the guideline to exclude glanular hypospadias, differing levels of ascertainment of hypospadias, whether proximal or distal, and differing sources of information for confirmation of case status and location of hypospadias (see Chapter 2). It is difficult to retrospectively disentangle these factors in order to estimate reliable prevalence rates. The importance of this study has been to show the need for a new set of guidelines for the future surveillance of hypospadias (see Chapter 2). EUROCAT data also suggest that previously reported increasing trends in the prevalence of hypospadias have not been continuing in more recent years.

Figure 3.1 Hypospadias: Line Graphs of Total Prevalence Rates Per 10,000 Births Over Time, Per Registry, 1980-99

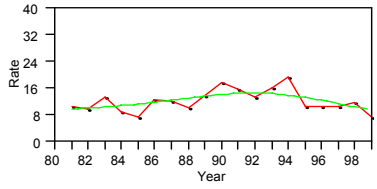
Hainaut



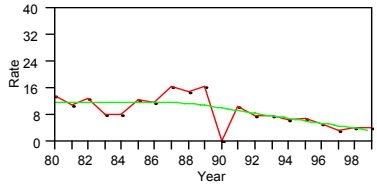
Odense



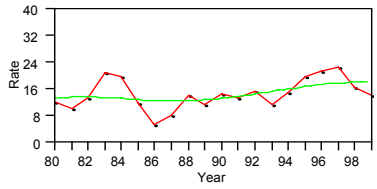
Paris



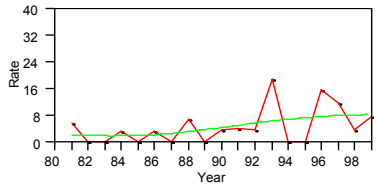
Tuscany



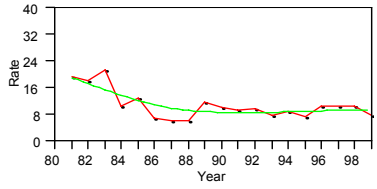
Dublin



Galway

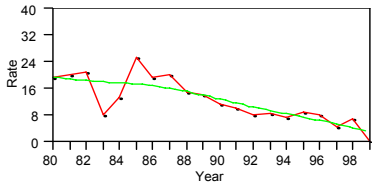


Northern Netherlands

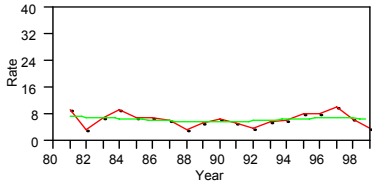


----- Spline Fit Line

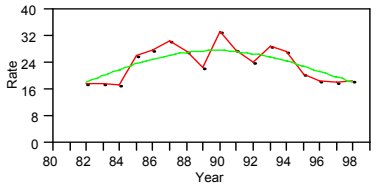
Glasgow



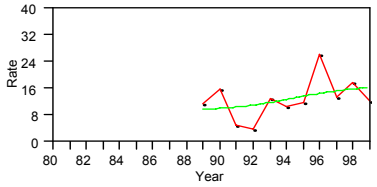
Emilia Romagna



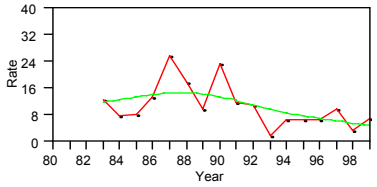
Strasbourg



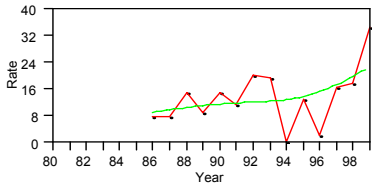
Vaud



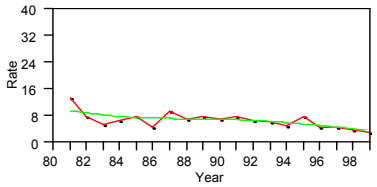
Croatia



Malta

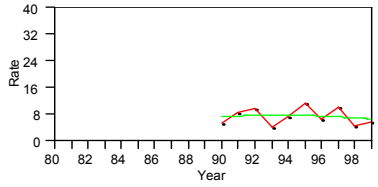


North East Italy

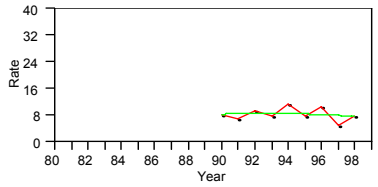


----- Yearly Total Prevalence Rates

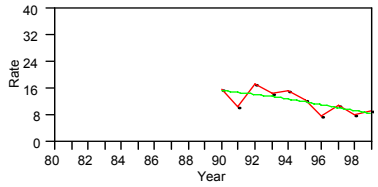
Antwerp



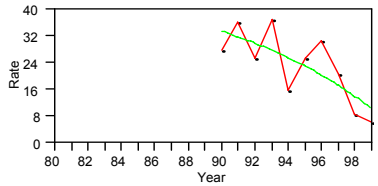
Basque Country



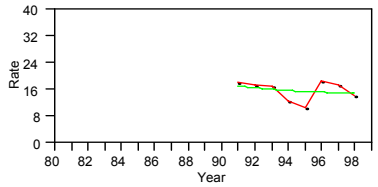
Asturias



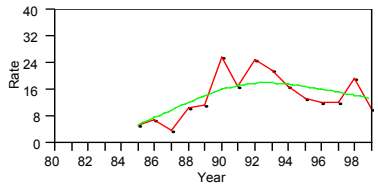
Mainz



South East Sicily



Styria



----- Yearly Total Prevalence Rates
----- Spline Fit Line

Source: EUROCAT **(2002)**, "EUROCAT Report 8: Surveillance of Congenital Anomalies in Europe 1980-1999", *EUROCAT Central Registry*, University of Ulster

References

1. Paulozzi LJ, Erickson JD, Jackson RJ, "Hypospadias Trends in Two US Surveillance Systems", *Pediatrics* (1997), 100(5), pp831-834.

2. Paulozzi LJ, "International Trends in Rates of Hypospadias and Cryptorchidism", *Environmental Health Perspectives* (1999), 107, pp297-302.

3. Baskin LS, Himes K, Colborn T, "Hypospadias and Endocrine Disruption: Is There a Connection?", *Environmental Health Perspectives* (2001), 109, pp1175-1183.

4. Kallen B, Bertollin R, Castilla E et al, "A Joint International Study on the Epidemiology of Hypospadias", *Acta Paediatrica Scandinavica* (1986), suppl 324, pp 5-52.

5. Pierik FH, Burdorf A, Nijman, JMR, De Muinck Keizer-Schrama SMPF, Juttmann RE, Weber RFA, "A High Hypospadias Rate in The Netherlands", *Human Reproduction* (2002), 17 (4), pp1112-1115.

6. Chambers EL, Malone, PSJ, "The Incidence of Hypospadias in Two English Cities: A Case-Control Comparison of Possible Causal factors", *BJU International* (1999), 84, pp95-98.

7. Aho M, Koivisto A-M, Tammela TLJ, Auvinen A, "Is the Incidence of Hypospadias Increasing? Analysis of Finnish Hospital Discharge Data 1970-1994", *Environmental Health Perspectives* (2000), 108, pp463-465.

8. Fichtner J, Filipas D, Mottrie AM, Voges GE, Hohenfellner R, "Analysis of Meatal Location in 500 Men: Wide Variation Questions Need for Meatal Advancement in All Pediatric Anterior Hypospadias Cases", *J Vrology* (1995), 154, pp833-834.

9. North K, Golding J and The ALSPAC Study Team, "A Maternal Vegetarian Diet in pregnancy is Associated with Hyspopadias", *BJU International* (2000), 85, pp107-113.

10. Sweet RA, Schrott HG, Kurland R, Culp OS, "Study of the Incidence of Hypospadias in Rochester, Minnesota, 1940-70, and a Case-Control Comparison of Possible Aetiological Factors", *Mayo Clinical Proceedings* (1974), 49, pp52-58.

11. Matlai P, Beral V, "Trends in Congenital Malformations of External Genitalia", *The Lancet* (1985), 1, pp108.

12. Czeizel A, "Increasing Morbidity in the Male Reproductive System", *Lancet* (1985), 1, pp462-463.

13. Kallen B, Winberg J, "An Epidemiological Study of Hypospadias in Sweden", *Acta Paediatrica Scandinavia* (1982), 293, S1-S21.

14. Toppari J, Larsen JC, Chrostiansen P, Giwercman A, Grandjean P, Guillette LJ, Jegou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Muller J, Rajpert-De-Meyts E, Scheike T, Sharpe R, Sumpter J, Skakkebaek NE, "Male

Reproductive Health and Environmental Xenoestrogens. *Environmental Health Perspectives* (1996), 104(suppl 4), pp741-803.

15. Sharpe RM, Skakkebaek NE, "Are Oestrogens Involved in Falling Sperm Counts and Disorders of the Male Reproductive Tract?", *The Lancet* (1993), 341, pp1392-1395.

16. Colborn T, "Environmental Estrogens: Health Implications for Humans and Wildlife", *Environ Health Perspect* (1995), 103(suppl 7), pp135-136.

17. Burdorf A, Nieuwenhuisen MJ, "Endocrine Disrupting Chemicals and Human Reproduction: Fact or Fiction?", *Annals of Occupational Hygiene* (1999), 43(7):435-437.

18. Joffe M, "Are Problems with Male Reproductive Health Caused by Endocrine Disruption?", *Occup Environ Med* (2001), 58:281-288.

19. Dolk H, Vrijheid M, Armstrong B, Abramsky L, Bianchi F, Garne E, Nelen V, Robert E, Scott JES, Stone, D, Tenconi R, "Risk of Congenital Anomalies Near Hazardous-Waste Landfill Sites in Europe: The EUROHAZCON Study", *The Lancet* (1998), 352, pp 423-427.

20. Dolk H, "Rise in Prevalence of Hypospadias", *Lancet* (1998), 351, pp770.

21. Moller H, Weidner IS, "Epidemiology of Cryptorchidism and Hypospadias", *Epidemiology* (1999), 10(4):352-354.

22. Kallen B, Castilla EE, Kringelbach M, Lancaster PAL, Martinez-Frias ML, Mastroiacovo P, et al, "Parental Fertility and Infant Hypospadias: An International Case-Control Study", *Teratology* (1991), 44:629-634.

23. Fritz G, Czeizel AE, "Abnormal Sperm Morphology and Function in the Fathers of Hypospadias", *J Reprod Fertil* (1996), 106(1), pp63-66.

24. Raman-Wilms L, Lin-in Tseng A, Wignardt S, Emarson TR, Koren G, "Fetal Geneital Effects of First-Trimester Sex Hormone Exposure: A Meta-Analysis", *Obstetrics & Gynecology* (1995), 85(1), pp141-149.

25. Henderson BE, Benton B, Cosgrove M, Baptista J, Aldrich J, Townsend D, Hart W, Mack TM, "Urogenital Tract Abnormalities in Sons of Women Treated with Diethylstilbestrol", *Pediatrics*, (1976), 58(4), pp 505-507.

26. Klip H, Verloop J, Van Gool J et al, "Increased Risk of Hypospadias in Male Offspring of Women Exposed to Diethylstilbestrol In Utero", *Paediatric & Perinatal Epidemiology* (2001), 15, pp A1-A38.

27. Silver RI, Rodriguez R, Chang TS, Gearhart JP, "In Vitro Fertilization is Associated with an Increased Risk of Hypospadias", *Journal of Urology* (1999), 161(6), pp 1954-1957.

28. Schwartz DA, Newsum LA, Markowitz Heifetz R, "Parental Occupation and Birth Outcome in an Agricultural Community", *Scandinavian Journal of Work and Environmental Health* (1986), 12, pp51-54.

29. Weidner IS, Moller H, Jensen TK, Skakkebaek NE, "Cryptorchidism and Hypospadias in Sons of Gardeners and Farmers", *Environmental Health Perspectives* (1998), 106(12), pp793-6.

30. Garcia AM, Fletcher T, Benafvides FG, Orts E, "Parental Agricultural Work and Selected Congenital Malformations", *American Journal of Epidemiology* (1999), 149(1), pp64-74.

31. Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L, "Birth Defects Among Offspring of Norwegian Farmers, 1967-1991", *Epidemiology* (1997), 8(5), pp537-44.

32. Irgens A, Kruger K, Skorve AH, Irgens LM, "Birth Defects and Paternal Occupational Exposure. Hypotheses Tested in a Record Linkage Based Dataset", *Acta Obstet Gynecol Scand* (2000), 79(6), pp465-70.

33. Olshan AF, Teschke K, Baird PA, "Paternal Occupation and Congenital Anomalies in Offspring", *Am J Ind Med* (1991), 20, pp447-475.

34. Vrijheid M, Armstrong B, Dolk H, van Tongeren M, Botting B, "Risk of hypospadias in relation to maternal occupational exposure to endocrine disrupting chemicals", *Occupational and Environmental Medicine* (2003), 60, pp543-550.

35. Calzolari E, Contiero MR, Roncarati E, Mattiuz PL, Volpato S, "Aetiological Factors in Hypospadias", *J Med Genet* (1986), 23, pp333-337.

36. Gallentin ML, Moreu AF, Thompson Jnr IM, "Hypospadias: A Contemporary Epidemiologic Assessment", *Pediatric Urology* (2001), 57(4), pp788-790.

37. Choi J, Cooper KL, Hensle TW, Fisch H, "Incidence and Surgical Repair Rates of Hypospadias in New York State", *Pediatric Urology* (2001), 57, pp151-153.

38. Stoll C, Alembik Y, Roth MP, Dott B, "Genetic and Environmental Factors in Hypospadias", *J Med Genet* (1990), 27, pp559-563.

39. Riley MM, Halliday JL, Lumley JM, "Congenital Malformations in Victoria, Australia 1983-95: An Overview of Infant Characteristics", *J Paediatr Child Health* (1998), 34, pp 233-240.

40. Van Tongeren M, Nieuwenhuijsen M, Gardiner K, Armstrong B, Vrijheid M, Dolk H, Botting B, "A job exposure matrix for potential endocrine disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias", *Annals of Occupational Hygiene* (2002), 46, pp465-477.

41. Rahi JS, Botting B, "Ascertainment of Children with Congenital Cataract Through the National Congenital Anomaly System in England and Wales", *Br J Ophthalmol* (2001) Sep, 85(9), pp1049-51.

42. Murphy M, Seagroatt V, Hey K, O'Donnell M, Godden M, Jones N, Botting B, "Neural Tube Defects 1974-1994 - Down But Not Out", *Arch Dis Child Fetal Neonatal Ed* (1996) Sep,75(2), ppF133-4.

43. Hey K, O'Donnell, Murphy M, Jones N, Botting B, "Use of Local Neural Tube Defect Registers to Interpret National Trends", *Arch Dis Child Fetal Neonatal Ed* (1994) Nov,71(3), ppF198-202.

44. Busby A, Dolk H, Collin R, Jones B, Winter R, "Compiling a National Register of Babies Born With Anopthalmia/Micropthalmia in England 1988-94", *Arch Dis Child Fetal Neonatal Ed* (1998), 79, pp168-173

45. Dutton SJ, Owens JR, Harris F, "Ascertainment of Congenital malformations: A Comparative Study of Two Systems", *Journal of Epidemiology & Community Health* (1991), 45, pp294-298.

46. The OPCS Monitoring Scheme for Congenital Malformations, Occasional Paper 43, OPCS 1995.

47. EUROCAT Working Group, "EUROCAT Report 7: 15 Years of Surveillance of Congenital Anomalies in Europe, 1980-1994", Brussels: Scientific Institute of Public Health - Louis Pasteur, (1997).

48. EUROCAT "EUROCAT Report 8: Surveillance of Congenital Anomalies in Europe 1980-1999", *EUROCAT Central Registry*, University of Ulster (2002).

49. EUROCAT Central Registry, "EUROCAT Guide 1.1: Instruction for the registration of Congenital Anomalies", Catholic University of Louvain (1990).

50. EUROCAT Central Registry, "EUROCAT Guide 1.2: Instructions for the Registration of Congenital Anomalies", University of Ulster (2002).

51. EUROCAT Working Group, "EUROCAT Report 6: Surveillance of Congenital Anomalies in Europe, 1980-1992", Brussels: Scientific Institute of Public Health - Louis Pasteur, (1995).

52. Swerdlow AJ, Melzer D, "The Value of England and Wales Congenital Malformation notification Scheme Data for Epidemiology: Male Genital Tract Malformations", *J Epid Comm Health* (1988), 42, pp 8-13.

53. Knox EG, Armstrong EH, Lancashire R, "The quality of notification of congenital malformations", *J Epid Commun Health* (1984), 38 (4), pp296-305.

54. Vrijheid M, Dolk H, Stone D, Abramksy L, Alberman E, Scott JES, "Socioeconomic Inequalities in Risk of Congenital Anomaly", *Archives of Disease in Childhood* (2000), 82, pp349-352.

55. Pattenden S, Dolk H, Vrijheid M, "Inequalities in Low Birthweight: Parental Social Class, Area Deprivation and 'Lone Mother' Status", *Journal of Epidemiology and Community Health* (1999), 53, pp355-358.

Appendix 1

Hypospadias Case Description Form

TRENDS IN HYPOSPADIAS PREVALENCE IN UK AND EUROPE:

AN ASSESSMENT AND ANALYSIS OF EXISTING SURVEILLANCE DATA

For information about the study and researchers, please see short protocol attached.

Hypospadias Case Description Questionnaire

EUROCAT Centre / Local ID number: _____

Date of Birth: _____

Age of the child at first operation (planned or performed): _____ year(s) and _____ months

Type of operation planned when first seen:
- ❑ One-Stage
- ❑ Two-Stage

Other members of family affected:
- ❑ None
- ❑ Father
- ❑ Brother/s
- ❑ Other : _____
- ❑ Not known

Please complete also the other side of this questionnaire

Comments :

✂----------

For local use only (to be cut off by EUROCAT registry before returning questionnaire to London) :

Name of child _____

Address _____

Name of Surgeon or Paediatric Surgeon Department _____

Hypospadias Description

Testes Position

Palpable in scrotum

Include testes which can be manipulated from groin into scrotum

- unilateral ☐
- bilateral ☐

Palpable in groin

Testes which cannot be manipulated into scrotum

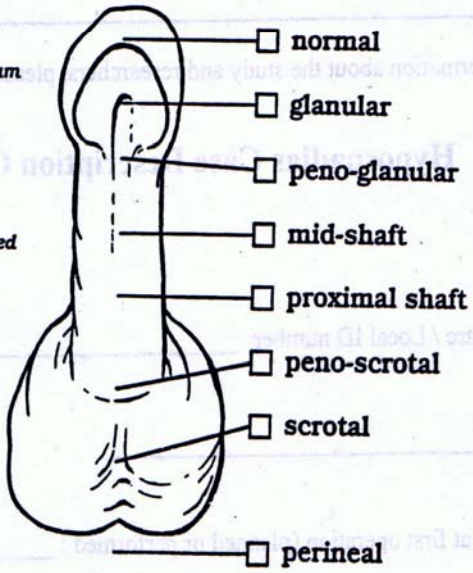
- unilateral ☐
- bilateral ☐

Impalpable

- unilateral ☐
- bilateral ☐

Urethral Meatus Position

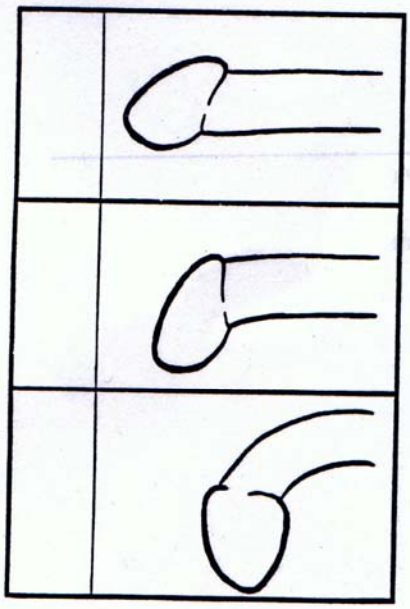
Please indicate on diagram position of urethral meatus



- ☐ normal
- ☐ glanular
- ☐ peno-glanular
- ☐ mid-shaft
- ☐ proximal shaft
- ☐ peno-scrotal
- ☐ scrotal
- ☐ perineal

Penile Chordee

Please indicate degree of curvature



Appendix 2

Questionnaire on registration practice Sent to EUROCAT Registries

TRENDS IN HYPOSPADIAS PREVALENCE IN UK AND EUROPE:

AN ASSESSMENT AND ANALYSIS OF EXISTING SURVEILLANCE DATA

For information about the study and researchers, please see short protocol attached.

Contact person: Martine Vrijheid, Environmental Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT. Tel +44 (0)171 927 2442; Fax +44 (0) 171 580 4524; e-mail m.vrijheid@lshtm.ac.uk.

QUESTIONNAIRE TO CONGENITAL ANOMALY REGISTERS

Please return by 30 June 1999

Name of register: _____

Name of person filling out this questionnaire: _____

Date: _____

1. **Is hypospadias currently recorded by your register :**

a) When isolated* and distal ("minor" , glandular/coronal) ?
- o Yes
- o Only if surgical correction was planned / performed
- o No

b) When isolated* and proximal ("major") ?
- o Yes
- o No

N.B. This question asks for your current "official policy". You can use the questions below to indicate the degree of underascertainment and case verification which occurs. Question 7b will ask you to record changes in your policy since 1980 or the start of you registry.

*** Isolated means when it is not associated with other major malformations**

If you have answered "no" to both of the above questions, please go directly to question 7b.

2. How are cases of hypospadias reported to your registry?

	Majority of cases	**Minority of cases**	**None**	**Proportion unknown**
Notifications sent to registry by midwives:	o	o	o	o
Found by systematically going to maternity units and looking at birth records:	o	o	o	o
Notifications sent to registry by paediatricians:	o	o	o	o
Found by systematically going to paediatric departments and looking at records :	o	o	o	o
Notifications sent to registry by paediatric surgeons:	o	o	o	o
Found by systematically going to paediatric surgery departments and looking at records:	o	o	o	o
Found from computerised hospital discharge records:	o	o	o	o

Other, please describe in full:

3. What age are cases when they are first reported to you?

	None	*Very Few*	*Up to half*	*Over half*	*Almost all*
< 10 days:	o	o	o	o	o
10 days – 3 months:	o	o	o	o	o
3 – 12 months:	o	o	o	o	o
1-3 years:	o	o	o	o	o
> 3 years:	o	o	o	o	o

Please comment:

4. **Answer this question only if your 'official' policy is to EXCLUDE isolated distal ("minor") hypospadias (otherwise go to question 5):**

a) Why do you exclude distal hypospadias ?

b) Do you use the EUROCAT list of minor anomalies for exclusion?
o Yes
o No

c) Do you ask notifiers not to report isolated distal ("minor") hypospadias cases to your registry (i.e. exclude at source) ?
o Yes
o No
Please describe how (e.g. in newsletters, by meeting with notifiers, instructions on back of notification form, etc.) :

d) If the type of hypospadias (i.e. distal or proximal) is not specified in the notification to your register, do you :
o Assume that it is proximal and include on the register
o Include on the register only after verification that it is proximal (please describe below how you verify the type of hypospadias)
o Exclude from the register

Please comment :

e) Despite your exclusion criterion, do you think that cases of isolated distal ("minor") hypospadias may be included on your register?
o No
o Yes, the occasional one
o Yes, quite a few
Please explain:

5. **Answer this question only if your 'official' policy is to INCLUDE isolated distal hypospadias on your register (otherwise go to question 6) :**

a) Do you have information at the registry on whether the hypospadias is distal or proximal for :
o All cases
o The majority
o The minority
o No cases

b) Are there any types of isolated hypospadias which you do exclude (e.g. incomplete or split prepuce) ?
o Yes
o No
If yes, please describe:

6. What are the main problems for your register in assuring complete ascertainment (i.e. finding all cases) of hypospadias ? (you can divide your answer into proximal and distal if relevant)

7.

a) What year did you first start systematically recording hypospadias on your register ? (if ascertainment was retrospective, state the year of birth, not the year of data collection)

19_____

b) Since then, have there been any changes over time in any of the answers to question 1 to 6 above ?
o Yes
o No
o Not known
If yes or not known, please explain giving dates where possible:

8. Are there any known differences between geographic areas (e.g. health districts) covered by your register in any of the answers to question 2 to 6 above ?
(e.g. in the way cases of hypospadias are reported to you, in the age at which cases are reported to you, in the way distal hypospadias is excluded and verified, in whether you have information on distal or proximal hypospadias, and in the completeness of ascertainment)

o Yes
o No
If yes, please describe:

9. Please list the paediatric surgeons, paediatric urologists and plastic surgeons or others who operate on hypospadias in your region (please give their names and addresses) :

(NB Names listed may be sent a questionnaire by Mr John Scott, consultant paediatric surgeon and urologist. If you do not want a questionnaire to be sent to them, or if you want the questionnaire to be sent via your registry, please indicate this clearly next to each name)

Paediatric Surgeons :

Paediatric Urologists :

Plastic Surgeons :

Others :

Appendix 3

EUROCAT: Brief Overall Description and Registry Descriptions

Funded by the Rare Diseases Programme of the European Commission

What is EUROCAT?

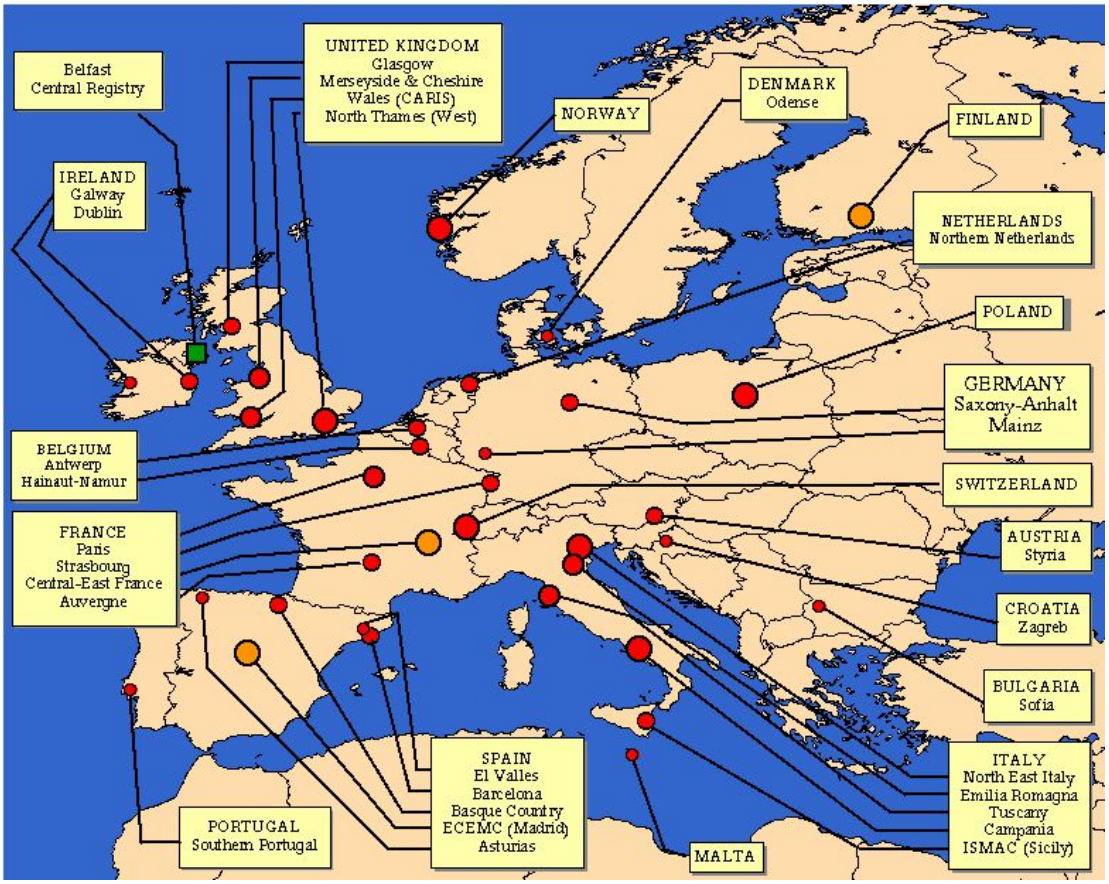
- European Network of population-based registries for the epidemiologic surveillance of congenital anomalies.
- Started in 1979.
- More than 1 million births per year in Europe surveyed by 37 registries in 18 countries of Europe.
- Standardised central database on more than 250,000 cases of congenital anomaly among livebirths, stillbirths and terminations of pregnancy, updated every year.

The Objectives of EUROCAT:

- To provide essential epidemiologic information on congenital anomalies in Europe.
- To facilitate the early warning of teratogenic exposures.
- To evaluate the effectiveness of primary prevention.
- To assess the impact of developments in prenatal screening.
- To act as an information and resource centre regarding clusters or exposures or risk factors of concern.
- To provide a ready collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children.
- To act as a catalyst for the setting up of registries throughout Europe collecting comparable, standardised data.

Contact EUROCAT:
Barbara Norton, EUROCAT Administrator, EUROCAT Central Registry
Room 15E12, Faculty of Life & Health Science, University of Ulster
Shore Road, Newtownabbey, Northern Ireland, BT37 0QB
Tel: +44 (0)28 90366639
Fax: +44 (0)28 90368341
Email: eurocat@ulster.ac.uk
Web: www.eurocat.ulst.ac.uk/

Map of EUROCAT registries



Styria (Austria)
Styrian Malformation Registry

History and funding: The registry was set up in 1986 following the Chernobyl disaster. It registers fetuses/babies with congenital anomalies born after January 1st 1985. The registry has been a member of EUROCAT since 1995. It is funded by research grants provided by the Styrian government on an annual basis.

Population coverage: The registry covers all births to residents of the province of Styria (Population-based I = All mothers resident in defined geographic area) which amounts to a total of approximately 11,000 births annually.

Sources of ascertainment: The registry operates as a research programme with voluntary participation of hospitals. Information is actively gathered from 49 sources and reports are requested once per year. Sources consist of 34 minor or major obstetric hospitals, 1 cytogenetic laboratory, 2 pathology services, 11 child health services, including specialised departments for diagnosis and treatment, and free practicing midwives. The main record forms are filled out by medical doctors at the reporting source and are sent to the registry. Six sources have to be visited for data collection by a member of the registry. 48% of cases are reported by more than one source. In the remaining 52% of cases, only one source provided data. Fetuses/babies with anomalies are registered if diagnosed before birth, at birth or during the first year of life.

Terminations of pregnancy: Terminations of pregnancy following prenatal diagnosis of congenital anomaly are registered. Termination of pregnancy is legal in all cases for Socioeconomic reasons up to 12 weeks and thereafter, if serious psychological or health problems for mother or the fetus were to be expected. If a nonlethal congenital anomaly is diagnosed, most obstetricians in Austria would follow the maternal wish for TOP only up to 24 WG+0. Non-viable forms of congenital anomalies may be terminated at any stage of gestation. The official policy regarding prenatal diagnosis is: pregnant women are offered 2 ultrasound scans (16-20 and 30-34 weeks' gestation) according to a booklet called 'Mother-child passport'. More scans are done in most cases.

Stillbirth and early fetal deaths: Stillbirths with congenital anomaly are registered. Stillbirth definition is: late fetal death from a Crown Foot Length>=35cm and from 01.01.95 a limit of >=500g has been introduced by law. There is no lower gestational age or weight limit for registration of congenital anomaly in early fetal deaths/spontaneous abortions. Autopsy rates in 1999 were are as follows: stillbirths 63, induced abortions 68%, early neonatal deaths (0-7 days) 70% (estimate), later deaths 1 week to 1 year 70% (estimate) and deaths with congenital anomaly 64%.

Exposure data availability: Exposure information (e.g. maternal occupation, intake of drugs or illnesses during pregnancy) is not available. Data about techniques of prenatal screening (ultrasound, serum markers) and prenatal diagnosis are not systematically collected. Maternal residency is recorded and can be used for evaluating the subregional pattern of birth defects.

Denominators and controls information: Information on all births is available from birth certificates, gathered by Statistics Austria.

Address for further information:
Prof Martin HAEUSLER, Registry Leader, Dept of Obstetrics and Gynecology, Karl-Franzens University, Graz
Auenbruggerplatz 14, A-8036 Graz, Austria
Tel: +43 31 6 38581079 Fax: +43 31 6 3853199
Email: martin.haeusler@uni-graz.at

Prof Andrea BERGHOLD, Institute for Medical Informatics, Statistics and Documentation, Karl-Franzens University, Graz, Engelgasse 13, A-8010 Graz, Austria
Tel: +43 31 6 3854162 Fax: +43 31 6 3853590
Email: andrea.berghold@uni-graz.at

Antwerp (Belgium)

History and funding: The registry began with a pilot study on procedures for registration of congenital anomalies in 1989. In 1990 the registry formally started in a region in Antwerp. Since 1997, the whole province of Antwerp has been covered. The registry is developed in collaboration with the provincial government and the university of Antwerp. The program is funded by the provincial government of Antwerp. The Registry has been a member of EUROCAT since1990.

Population coverage: The registry covers about 18,000 births annually, these are all births in the province of Antwerp (about 15% of the births in Belgium, Population-based I = All mothers resident in defined geographic area).

Sources of ascertainment: Reports are actively collected from maternity, Pediatric, and neonatologic units by registry staff who visit each maternity and neonatal unit in the covered region. There are a total of 23 participating hospitals. The midwife gives the basic information of children born with congenital anomalies. Further information is gathered from the Gynecologist and Pediatrician. Information about the parents is obtained from the general practitioners. The Gynecologist also reports cases to the registry if an anomaly is prenatally detected. If an anomaly is detected after the stay in the maternity hospital the Pediatrician reports it to the head nurse of the Pediatric ward. A check is made to ascertain whether the case has already been notified. Clinical geneticists, surgeons, pathologists and the Pediatrician of the centre of metabolic diseases are also contacted for more information. In 1996, the Child Welfare centres, an important notifier underwent reorganisation and computerisation, leading to a deficit of notifications that year. All cases of congenital anomaly diagnosed prenatally or in the first year of birth are registered. Reporting by hospitals and health workers is voluntary.

Termination of pregnancy: Termination of pregnancy is registered. Termination of pregnancy is legal under 13 weeks. If congenital anomaly is diagnosed, the upper gestational age for termination is 23 to 24 weeks.

Stillbirth definition and early fetal deaths: The stillbirth definition for denominators is: a baby which is not viable with a gestational age of >180 days. Stillbirths are registered. Early fetal deaths/spontaneous abortions are registered. Autopsy rates are as follows: stillbirths 75% (estimate), induced abortions 61%, neonatal deaths (0-7 days) unknown, later deaths 1 week to 1 year unknown and deaths with congenital anomaly 48%.

Exposure data availability: Exposure information: includes: maternal drug use maternal smoking and alcohol abuse, maternal and paternal diseases and family history, parental occupation.

Denominators and controls information: Background data on births are retrieved from the population databases of the local authorities and from the study centre for perinatal epidemiology in the Flanders region. Controls are not included in the registry, but data can be ascertained for specific studies.

Address for further information:
Dr Vera Nelen, Provinciaal Instituut voor Hygiëne, Kronenburgstraat 45, 2000 Antwerpen, Belgium
Phone: +32 3 2591270 Fax: +32 3 2591201
E-mail: vera.nelen@pih.provant.be

Hainaut (Belgium)

History and funding: The registry of Hainaut-Namur was initiated in 1978 and it started in 1979. It has been a member of EUROCAT since the beginning. From 1979 to 1990, it was located at the School of Public Health of the Catholic University of Louvain (Brussels). Since 1990, it was integrated into the Centre of Human Genetics of the Institute of Pathology and Genetics of the Institute of Pathology and Genetics (Loverval – Belgium). As a part of the Institute of Pathology and Genetics of Loverval, it is supported by an annual grant front the Institute of Research in Pathology and Genetics of Loverval. From 2001 it is also partly supported by the Ministry of Public Health of Wallonia.

Population coverage: The registry annually covers approximately 12,000 births in the provinces of Hainaut (south) and Namur (Population-based II = All mothers delivering within defined geographic area, irrespective of place of residence), which represents about 11% of all births in Belgium.

Sources of ascertainment: Delivery units, neonatal and Pediatric departments divided into 13 hospitals. All cytogenetic, genetic and pathological data including the examination of aborted fetuses are regionally concentrated in the Institute of Pathology and Genetics of Loverval. Children with malformations are registered up to one year of age.

Termination of pregnancy: Termination of pregnancy is legal up to 12 weeks of gestation. If a congenital anomaly is diagnosed, the upper gestational age limit for termination is approximately 24 weeks. Theoretical access to information is available on all cases of termination of pregnancy as they are registered, however, in practice ascertainment is slow to process.

Stillbirth definition and early fetal deaths: Stillbirth definition is: 28 weeks (or 180 days). Stillbirths are registered. Early fetal deaths/spontaneous abortions are included if the gestational age is greater than or equal to 20 weeks (weight is not a factor). Early fetal deaths/spontaneous abortions are registered. Autopsy rates are as follows: stillbirths 52% for all cases (95% of cases of malformations), induced abortions virtually 100%, early neonatal deaths (0-7 days) 52% for all cases (95% of cases of malformations), later deaths 1 week to 1 year unknown and deaths with congenital anomaly 48% in 1992-94 compared with 25% in 1982.

Exposure data availability: Exposure information: All that concerns information of maternal diseases during pregnancy, maternal drugs, occupations and genetic data is available.

Denominators and controls information: Background data on births are available from national and regional institutes of statistics. It is also based on our own statistics in collaboration with the ONE (Office de la Naissance et de l'Enfance).

Address for further information:
Prof Yves Gillerot, Institut de Morphologie Pathologique, Departement Genetique, Allée des Templiers 41, B-6270 Loverval, Belgium
Tel: +32.71 473047 Fax : +32.71.47.15.20
E-mail: yves.gillerot@ipg.be

Croatia

History and funding: The project started as a pilot investigation in 1982 and began formally as a registry in 1983 when it also joined EUROCAT. Until the end of 2000 we did not have any local funding, collection and transmission of data were on voluntary basis. From the year 2000 we have received funding from Ministry of Science and Technology and as a public health project we are in process of applying for funding from the Ministry of Health.

Population coverage: The registry is population based (Population-based I: All mothers resident in defined geographic area) and covers approximately 6000 annual births, up to 12% of births in Croatia (cities Rijeka, Varazdin, Koprivnica and region Pula).

Sources of ascertainment: Data are actively collected from four Delivery Units in the cities of Rijeka, Varazdin, Koprivnica and region Pula by neonatologists and Gynecologists. Birth certificates include notification of congenital anomaly and are used as a source. Death certificates also allow for notification of congenital anomaly and are used as a source. Children can be registered up to the first week of life.

Termination of pregnancy: Termination of pregnancy is legal and the upper gestational age limit set for termination is 24 weeks for all reasons. Terminations of pregnancy with congenital anomaly are not completely ascertained, but ascertainment has improved since 1996.

Stillbirth definition and early fetal deaths: Stillbirth definition is: 22 completed gestational weeks/500g weight. Stillbirths and early fetal deaths/spontaneous abortions are registered. Autopsy rates are as follows: stillbirths 90-100%, induced abortions 100%, early neonatal deaths (0-7) days 90-100%, later deaths 1 week to 1 year 90-100% and deaths with congenital anomaly 100%.

Exposure data availability: Exposure information: information on maternal drug use, maternal and paternal diseases and occupations, outcome of previous pregnancies is available for almost all malformed cases.

Denominators and controls information: Information on all births is available from the birth certificates.

Address for further information:
Dr Ingeborg Barisic, Registry Leader and Medical Geneticist,, Children's University Hospital Zagreb, Department of Pediatrics, Klaiceva 16, 10 000 Zagreb, Croatia
Tel: +385 1 4600141 Fax: +385 1 4600160
Email: ibarisic@kdb.hr / romanagjergja@yahoo.com

Odense (Denmark)
Registry of Funen County

History and funding: The registry started in 1979 and joined the EUROCAT network from the beginning of EUROCAT. The registry has been approved by the "Data Tilsynet" as a private registry for the purpose of research. There is no specific funding except private funding for computer equipment.

Population coverage: The registry covers Funen County (island of Funen with surrounding small islands) situated in the middle of Denmark (Population-based I = All mothers resident in defined geographic area). The total number of births per year in Funen County is around 6,000.

Sources of ascertainment: The registry is based on active case finding. Data for the registry includes hospital records from obstetric and Pediatric departments, birth notifications, deaths certificates, post-mortem examinations and data from the cytogenetic laboratory. For livebirths, late diagnosed cases are included up to the age of seven years.

Terminations of pregnancy: Termination of pregnancy is legal and the upper gestational age limit is 12 weeks without special permission. After 12 weeks of gestation induced abortion can be performed after permission from a local committee. If a congenital anomaly is diagnosed, the upper gestational age for termination is usually 24 weeks (24 to 28 weeks possible if survival is impossible). Terminations of pregnancy for fetal malformations are registered.

Stillbirth definition and early fetal deaths: Stillbirths include fetal deaths with gestational age ≥ 28 weeks. Stillbirths and fetal deaths/spontaneous abortions from 20 weeks are registered. The autopsy rate in stillbirths is 70% but is declining over the years.

Exposure data availability: Exposure information: Parental occupation, maternal smoking and medication during first trimester, maternal illness before and during pregnancy.

Denominators and controls information: Data on births per year and maternal age distribution covering Funen county is available from National Danish Statistics.

Address for further information:
Dr Ester Garne, EUROCAT Registry of Congenital Malformations, Epidemiology,, University of Southern Denmark, Sdr Boulevard 23A, DK – 5000 Odense C, Denmark
Tel : +45 76362000 Fax : +45 76363474
E-mail: egarne@health.sdu.dk

Paris (France)

History and funding: The programme was initiated in 1975, but the registry began formally in 1981. It has also been a member of EUROCAT since 1982. The registry is part of a research unit of INSERM (National Institute of Health and Medical Research). The registry has been officially recognised by the French National Committee of Registries, and is renewed for four years (2001-2004) and partially supported by an annual grant from INSERM and Institut de la Veille Sanitaire (Institute for Health Surveillance).

Population coverage: The registry is population-based III (includes all mothers delivering in defined geographic area excluding non-residents of that area) and covers 38,000 annual births (about 5% of all births in France), that is, all births (live and stillbirths of 22 weeks or more) and terminations of pregnancy in the population of Greater Paris delivering in Paris maternity units. The estimation of the coverage of the registry is around 95%. The percentage of non-residents delivering within the registry area was 9.5% in 1998.

Sources of ascertainment: Notification to the registry is voluntary. Reports are actively collected from delivery units, Pediatric departments, cytogenetic laboratories, and pathology departments. Terminations of pregnancy are included. Case information is also received from the health certificates of the first week of life and this is the maximum age at diagnosis. Birth certificates include notification of congenital anomaly and are used as a source of notification.

Termination of pregnancy: Termination of pregnancy is legal and there is no upper gestational age limit for termination after diagnosis of congenital anomaly.

Stillbirth definition and early fetal deaths: Stillbirths of 22 weeks after the last menstrual period or more are registered. Early fetal deaths/spontaneous abortions are registered and included when the gestational age is 16 weeks. Autopsy rates in 1998 were as follows: 86% in stillbirths, 90% in induced abortions, 70% in early neonatal deaths (0-7 days) and no data are available for later deaths except from specific studies. All autopsies are carried out by fetopathologists.

Exposure data availability: Information on maternal drug use, maternal and paternal diseases and occupations, outcome of previous pregnancies, is available for the malformed cases.

Denominators and controls information: Background data on births are available from the National Institute of Statistics (INSEE).

Address for further information:
Dr Catherine de Vigan, INSERM U149, 16 Av P Vaillant-Couturier, 94807 Villejuif Cedex, France.
Tel: +33 1 45595009 Fax: +33 1 45595089
E-mail: devigan@vjf.inserm.fr

Strasbourg (France)
Strasbourg Prospective Study of Congenital Malformations.

History and funding: The registry was started in 1979 and became a member of EUROCAT in 1982. The programme is a research program, recognised by the local health authorities and funded by Social Security, Ministry of Health and INSERM.

Population coverage: The registry is population-based III and includes all mothers delivering in the covering area excluding non-residents. 3.5% of non-residents gave birth in the covered hospitals and 2% of the residents delivery outside the area. The geographic area covered by the Registry is the "departement du Bas-Rhin", Northeastern France, including Strasbourg, an urban area, and rural areas around Strasbourg. The registry covers about 13,500 births which represents approximately 2% of all births in France.

Sources of ascertainment: Registration is active. Sources of information are multiple including reports obtained from Pediatricians examining the newborn infants, hospital discharge records, maternity records, fetal ultrasound screening, laboratory records (cytogenetic, molecular, pathology) and specialised departments. Birth certificates include notification of congenital anomaly and are also used as a source of notification. The maximum age at diagnosis is between 2 and 5 years of age.

Termination of pregnancy: Termination of pregnancy is legal and there is no upper gestational age limit set for either social terminations or terminations as a result of diagnosis of a congenital anomaly. Terminations of pregnancy are registered.

Stillbirth definition and early fetal deaths:
Before 1993 stillbirths were defined as 180 days and since 1993 the definition has been set at 22 weeks of gestation. There is no limit, with regard to either gestational age or weight which impedes notification of a fetal death/spontaneous abortion to the register. Both stillbirths and fetal death/spontaneous abortions are registered. Autopsy is refused by about 10% of parents in cases not involving a congenital anomaly. Rates were as follows in 1994: in stillbirths 94%, in induced abortions 94%, in early neonatal deaths (0-7 days) 94%, in later deaths 1 week to 1 year 94% and 80% in deaths with congenital anomaly.

Exposure data availability: Detailed information on various exposures is obtained by interview of the mothers of the malformed infants and their controls. The children are followed to the age of one year.

Denominators and controls information: General demographic information is obtained from the National Institute of Statistics. Further information is obtained from Social Security Records and Health Sheets. A control infant is selected for each malformed one: the next infant of the same sex as the proband born at that hospital.

Address for further information:
Prof Claude Stoll, Service de Génétique Médicale, Hôpital de Hautepierre, Avenue Molière, 67098 Strasbourg Cedex, France
Tel: +33 3 88128120 Fax : +33 3 88128125
Email : claude.stoll@chru-strasbourg.fr

Mainz (Germany)

History and funding: The Mainz Model was launched in 1990. The aim of this screening project was to determine prevalences and etiological causes of congenital birth defects. The registry and its associated research is funded by the Ministry of Health of the Federal Republic of Germany from 1990-1995 and by the Ministry of Labour, Social Affairs and Health of Rhineland-Palatine from 1990 until now. The Registry joined EUROCAT in 1992.

Population coverage: The registry covers births in three maternity hospitals which serve the Mainz district of Rhineland-Palatinate in SW Germany with approximately 3,300 births per year. Births to non-residents of the area are excluded (population-based III).

Sources of ascertainment: The registry employs three Pediatricians specially trained in clinical genetics, neonatalology and pediatric ultrasonography who examine each baby born in the participating hospitals twice within the first week of life. Routine sonography of hips and kidneys are performed. For particular indications (e.g. microcephaly or heart murmur) further ultrasound examinations of heart, brain and other investigations are made. Both major and minor anomalies are recorded according to a standard examination protocol, but only major anomalies are transmitted to the EUROCAT Central Registry. Information concerning stillbirths is obtained from pathology reports. Information concerning terminations of pregnancy is obtained from pathology reports and from the one centre in the district doing the final prenatal diagnosis. Cases of Microcephaly are not transmitted to EUROCAT Central Registry.

Termination of pregnancy: Terminations of pregnancy following prenatal diagnosis are registered. Induced abortion for social reasons is legal but not done in the Mainz region. Terminations of pregnancy for fetal malformation are performed in one of the hospitals. It is relatively common for prenatal diagnosis of major malformation not to result in a decision to terminate the pregnancy. 60% of terminations have an autopsy examination.

Stillbirth definition and early fetal deaths: The official stillbirth definition in Germany is a baby born with no signs of life weighing >=500g. The registry records information on all fetal deaths (including both stillbirths and spontaneous abortions) from 16 weeks gestation. Autopsy rates were as follows in 1995: in stillbirths 70%, in induced abortions 70%, in early neonatal deaths (0-7 days) 55%, in later deaths 1 week to 1 year - not applicable and in deaths with congenital anomaly – not known.

Exposure data availability: Exposure information on the EUROCAT form is obtained for both malformed and non-malformed babies from the pregnancy pass filled out throughout pregnancy and data collected by midwives 6-8 weeks before birth. Additional exposure data is held which is not transmitted to EUROCAT. Drugs are ATC coded.

Denominators and controls information: There is comparable information on all non-malformed babies in the population from the same process of Pediatric examination and information gathering. The number of births is taken from this database. Information on the total number of fetal deaths from 16 weeks is available and included in “stillbirth” statistics.

Address for further information:
Dr Annette Queisser-Luft, Universitatskinderklinik Mainz, Langenbeckstrasse 1, Postfach 3960, D-55101 Mainz, Germany
Tel: +49 6131 172773 Fax: +49 6131 176608
Email: queisser@kinder.klinik.uni-mainz.de

Saxony-Anhalt (Germany)

History and Funding: The registry started in 1980. The years 1980-89 were funded by Ministry of Health of former German Democratic Republic. The years 1990-92 were funded by the Academy of Medicine, Magdeburg whereas the period between 1993 and 1995 was sponsored by the Ministry of Health, Federal Republic of Germany. Since 1995, the registry has been funded by the Ministry of Labour, Women, Health and Social Security of the Federal State of Saxony-Anhalt. The registry joined EUROCAT in 1992.

Population Coverage: The registry started in 1980 in the city of Magdeburg with about 4,000 annual births. After it there was a successive enlargement of the registry from 1981 to 1986. In 1981 we expanded to include some counties around the city of Magdeburg and this process continued until 1987 when we registered the whole district (about 17,000 births per year). Then we had a stable system from 1987 to 1989 and in 1990 there was a dramatic political change. Since the reunification there has been a two-third decrease in the number of births in the so-called new federal states. After the reunification, a similar process of territorial enlargement took place. In year 2000, registration expanded to the entire Federal State of Saxony-Anhalt, with about 19,000 annual births, 21 counties and three major cities.
By comparison to 1987, currently we survey a much larger area in our registry with approximately twice as many inhabitants (2.7 million) but the births rate is the same as the 1980s. Registration concerns deliveries within surveyed region excluding non-residents (Population-based III).

Sources of ascertainment: About 80 health institutions in 2000 including obstetric clinics, maternity hospitals, neonatal and pathological departments, prenatal diagnostic departments, children's hospitals report fetuses/infants with malformations. Until 1990, registration extended to diagnoses made in the first year of life. Subsequently, the time period for registration was restricted to the first week of life.

Terminations of pregnancy: Terminations of pregnancy ("medical indication") have no time limitation by law in Germany. We have had complete information about terminations of pregnancy after prenatal diagnosis of fetal malformations since 1987.

Stillbirth definition and early fetal deaths: Stillbirths and spontaneous abortions with malformations from 16 weeks gestation are registered. The stillbirth definition has been >=500 g from 1.4.94 and >= 1000g before 1994.

Exposure data availability: Maternal and paternal occupation, drugs in pregnancy (ATC coded), alcohol, nicotine, drug abuse.

Denominators and controls information: Statistics on the total number of births comes from Statistical Office Saxony-Anhalt. There is the opportunity to exclude non-residents mothers with assistance of the postal code. A woman who gives births outside of Saxony-Anhalt but is a resident here is included in the statistics. The denominators include only livebirths and stillbirths. Information about maternal age for all births is available only at the level of the entire state of Saxony-Anhalt.
Information is also reported about two control infants per malformed child. The two control infants, theoretically, are those born directly before and directly after the malformed child. The information about the control children is the same as malformed because a standardised documentation sheet is used.

Address for further information:
Prof Volker Steinbicker, Program Director (Pediatrician, Geneticist), Malformation Monitoring Saxony-Anhalt, Faculty of Medicine, Otto-von-Guericke University, Halberstadter Straße 44, D-39112 Magdeburg, Germany
Tel: +49 391 6717231 Fax: +49 391 6714176
E-mail: volker.steinbicker@medizin.unimagdeburg.de
Web site: http://www.med.uni-magdeburg.de/fme/zkh/mz/

Dublin (Ireland)
Dublin EUROCAT Registry

History and funding: Register began in September 1979 and joined EUROCAT in 1980. The Registry is located within the Public Health Department of Eastern Regional Health Authority. Staffing includes a full time nurse/researcher and a part time secretary plus a part-time public health specialist and a part-time epidemiologist. Funding is provided by the Department of Health through the Eastern Regional Health Authority. There is a Steering Committee comprising specialists from each of Maternity and Pediatric Hospitals in the catchment plus a representative from the Department of Health.

Population coverage: The Registry is population-based I which includes all mothers resident in the Eastern Regional Health Authority of Ireland covering the counties of Dublin, Wicklow and Kildare. In 1999, less than 3% of resident mothers delivered outside the registry area. About one third (21,000 births) of all births in Ireland occur in this area.

Sources of ascertainment: All live and stillbirths are covered. Information collected by developmental screening clinics, child health centres, social allowances and health visitors are used as sources of notification. Birth certificates and death certificates do not include notification of congenital anomaly. Children with congenital anomaly are included in the registry when diagnosed up to the age of 5 years.

Termination of pregnancy: Abortion is illegal in Ireland.

Stillbirth definition and early fetal deaths: Babies born without signs of life with a gestational age of >=24 weeks or a weight of >=500g are registered. Early fetal deaths/spontaneous abortions are not registered. *National* autopsy rates only were available for 1999 for the following: stillbirths 50-60% and early neonatal deaths (0-7 days) 50-60%. There has been a decrease in the proportions having an autopsy due to controversy arising from the issue of consent – from about 70-80% in 1997 to 50-60% in 1999.

Exposure data availability: For each malformed infant reported, limited information is given on certain exposures.

Denominators and controls information: Denominator data are supplied by the government body - the Central Statistics Office. No information is available on controls.

Address for further information:
Dr Bob McDonnell, Department of Public Health, Eastern Regional Health Authority, Dr Steeven's Hospital, Dublin, Ireland.
Tel: +353 1 6352753 Fax: +353 1 6352745
E-mail: bob.mcdonnell@erha.ie

Galway (Ireland)

History and funding: Funding for the registry is provided nationally by the Department of Health and the Western Health Board. The Registry joined EUROCAT in 1981.

Population coverage: The registry is population-based I and includes all mothers resident in the County of Galway. The registry covers a total of about 3,000 births per year which represents 5% of all births in the Republic of Ireland.

Sources of ascertainment: Death certificates allow for the notification of a congenital anomaly, however, birth certificates do not. Notifications of children who are diagnosed up to the age of 5 years are included in the registry database.

Termination of pregnancy: Termination of pregnancy is illegal in the Republic of Ireland.

Stillbirth definition and early fetal deaths: The official definition of stillbirth is: a baby who shows no sign of life with a gestational age of >=24 weeks or weight of >= 500g. All stillbirths are registered. Early fetal deaths/spontaneous abortions are considered as such at a gestational age of 24 weeks and are included in the register if the birthweight is 500g. Autopsy rates for 1994 were: 90% in stillbirths, 70% in early neonatal deaths (0-7 days), 70% in later deaths 1 week to 1 year, 70% in deaths with congenital anomaly.

Additional exclusions and exposure data availability: No information was supplied on this section for the report.

Denominators and controls information: No information was supplied on this section for the report.

Address for further information:
Dr David Lillis, University College Hospital, Dept of Pediatrics, Galway, Ireland
Tel: +353 91 524111 Fax: +353 91 526588
Email: d.lillis@whb.ie

Emilia Romagna (Italy)
Emilia-Romagna Registry of Congenital of Malformations

History and funding: The registry started in 1978 in a few hospitals, has increased in size, and now includes 35 delivery units (2001). The programme is recognised and financed by the Emilia Romagna region and the Ministry of Scientific Research. The Registry joined EUROCAT in 1980.

Population coverage: The programme is population-based II and includes all mothers delivering within the region of Emilia Romagna, irrespective of place of residence (about 95% of all births in the Emilia-Romagna region) and covers approximately 24,000 annual births per year. Approximately 10% of non resident mothers are thought to deliver within the defined geographic region.

Sources of ascertainment: Hospital participation is voluntary. Reporting is carried out by both neonatologists and Pediatricians during the first week of the infant's life. Notification of congenital anomaly is recorded up to 1 week (after 1 week for selected malformations e.g. Downs Syndrome, cardiovascular defects, cleft palate). Selected malformations are followed up. An information exchange between Cytogenetic Laboratories, Pathology Services and Health Services has been established.

Termination of pregnancy: Termination of pregnancy became legal in Italy in 1978. At present the usual upper gestational age limit is 12 weeks and 23-24 weeks if a congenital anomaly is diagnosed. A psychiatric report is required for termination in the latter category. Data on induced abortions was not available to the IMER Registry until 1989. Between 1989 and 1993, recording was very incomplete due to difficulties in obtaining the data from the centres. Since 1994, ascertainment of IA has improved, but the data were still under revision of closure of the database of this Report.

Stillbirth definition and early fetal deaths: Stillbirths of 28 weeks or more gestation are included. The lower gestational age limit for inclusion of fetal deaths/spontaneous abortions is: less than 28 weeks of gestation (with no lower weight limit exclusion criteria). The autopsy rates for 1999 were: <10% in stillbirths, <5% in induced abortions, ~90% in early neonatal deaths (0-7 days), ~90% in later deaths 1 week to 1 year and ~90% in deaths with congenital anomaly.

Exposure data availability: Detailed exposure information is obtained by interviews of the mothers of malformed infants.

Denominators and controls information: Some general demographic information is known for all births in the area (e.g. mean maternal and paternal ages, percentage of mothers 35 years or older). For each participating hospital, the number of livebirths and stillbirths are known. A good information exchange has been established with regional health services. For each malformed infant, a control is chosen (the baby born before or after the malformed case in the same hospital) and its mother is interviewed in a similar way to the mothers with a registered baby.

Address for further information:
Prof Elisa Calzolari, Istituto di Genetica Medica, Via L. Borsari 46, I-44100 Ferrara, Italy
Tel: +39 05 32291385 Fax: +39 05 32291380
Email: cls@dns.unife.it
Website: www.unife.it/imer

North-East (Italy)
North East Italy Registry of Congenital Malformations

History and funding: The Registry was established in 1980 to include Veneto and Friuli Venezia Giulia regions. Trentino Alto Adige region was added in 1990. The Registry became a member of EUROCAT in 1985. The programme is partly run by privately funded research organisations and partly by Regional Health Authorities.

Population coverage: The registry is population-based II and so it includes all mothers delivering within the Veneto, Friui-Venezia, Giulia and Trentino-Alto Adige Regions, irrespective of place of residence. Reports are obtained from 78 participating hospitals, with a total of approximately 54,000 annual births. The estimated proportion of non-resident mothers giving birth in the covered hospitals is 1.8% (calculated using controls).

Sources of ascertainment: Reporting is voluntary and they are obtained on specific forms from delivery units, induced abortion units, Pediatric, cardiology, ophthalmology and pathology departments, regional induced abortion database and cytogenetic laboratories. Thirty-two selected malformations are recorded within 7 days from birth (as of 1st July 1991 postnatal registration up to 3 years of age is limited to cardiovascular and ophthalmologic anomalies only). In terminated fetuses all anomalies are recorded. From 1st January 2000 we are now registering all congenital anomalies adopting the EUROCAT list of exclusions (revised 1985). Up to 1999 we did not register cases of: microcephaly, arhinencephaly/ holoprosencephaly, cystic kidney disease, indeterminate sex, diaphraghmatic hernia, Patau syndrome (Trisomy 13), Edward syndrome (Trisomy 18). The following anomalies were not coded according to EUROCAT standard and therefore are included in total case counts but not tabulated separately: common arterial truncus, transposition of the great vesssels (complete), congenital absence, atresia and/or stenosis of duodenum, congenital absence, atresia and/or stenosis of other specified parts of the small intestine.

Termination of pregnancy: Termination of pregnancy is legal under normal circumstances up to 12 weeks of gestation and up to 26 weeks if a fetal anomaly is diagnosed. Most terminations in the latter category, however, are carried out before 22 weeks. The recording of induced abortions for embryo-fetal anomaly was established on 1st July 1988. A form is completed in the hospital where the pregnancy is terminated by a Gynecologist.

Stillbirth definition and early fetal deaths: The official stillbirth definition: is a gestational age of >=28 weeks. Death certificates do not always allow for notification of congenital anomaly as a cause of death and they are not used as a source of information for registration. Autopsy rates quoted for 1994 were: 44% in stillbirths, 74% in induced abortions, 60% in early neonatal deaths, (0-7 days) with congenital anomaly. If no information was found on the death certificate then it was assumed that an autopsy was not performed.

Exposure data availability: Detailed information on various exposures, including maternal or paternal occupation, diseases and drug use is obtained by interview of the mothers at the birth of the malformed infants and their controls.

Denominators and controls information: Some epidemiological background data of all births are available. For each participating hospital the number of livebirths and stillbirths by sex and number of twin pairs are known. Information on controls are available – two control infants are selected for each malformed one.

Address for further information:
Prof Romano Tenconi, Clinical and Epidemiological Genetic Service, Pediatric Department, Via Giustiniani 3, 35128 Padova, Italy
Tel: +39 049 8213513 Fax: +39 049 8211425
Email: romano.tenconi@unipd.it
Web: www.genetica.pedi.unipd.it

South East Sicily (Italy)
Sicilian Registry of Congenital Malformations

History and funding: The Registry started in 1991 and became a member of EUROCAT in 1997. The registry collaborates with other Italian Registries under supervision of the Italian National Institute of Health in Rome. The programme is supported at local level by A.S.MA.C, the Sicilian association for congenital malformation prevention.

Population coverage: It is hospital based and includes all mothers delivering in selected hospitals, irrespective of place of residence. The registry collaborates with four southeast provinces of the nine Sicilian provinces, (with a covering rate higher than 75% per year) which represented about one third of all births in Sicily with approximately 17,000 births per year.

Sources of ascertainment: Reports are obtained from delivery units, Pediatric units and other specialist departments. Congenital anomaly is registered up to and after 1 year of birth. The following anomalies are not coded according to EUROCAT standard and therefore not tabulated separately: cleft lip with or without palate, cleft palate, bilateral renal agenesis.

Termination of pregnancy: Termination of pregnancy is legal and the upper limit is usually 12 weeks, rising to 24 weeks if a congenital anomaly is diagnosed. Terminations of pregnancy following prenatal diagnosis are registered when notified, but ascertainment is currently still very incomplete. Registered terminations have been excluded from this Report.

Stillbirth definition and early fetal deaths: Stillbirths are registered as such if the gestational age is >180 days. Early fetal deaths/spontaneous abortions are not included. Although deaths due to congenital anomaly can be recorded on a death certificate, this information is not used as a source of notification. Autopsy rates were not reported.

Exposure data availability: For each malformed reported (livebirth, stillbirth and voluntary abortion), information is given on certain exposures, including maternal drug usage and parental occupation.

Denominators and controls information: Up to now no information on controls is available.

Address for further information:
Dr Sebastiano Bianca, Registro ISMAC, Via XXXI Maggio 51, I-92123 Catania, Italy
Tel: +39 095 26433 Fax: +39 095 26433
Email: sebastiano.bianca@tiscalinet.it

Tuscany (Italy)
Tuscany Registry of Congenital Defects

History and funding: The registry started in 1979 in the province of Florence and from 1992 in the whole Tuscany region. The Registry is a surveillance programme included in the Regional Statistics System; it is formally recognised and supported by the Tuscany Region Health Authority. The Registry joined EUROCAT in 1979.

Population coverage: The programme is population-based I which includes all mothers resident in the Region of Tuscany. It involves all the regional hospitals and the coverage is around 95% of all births in the Tuscany region (approximately 3.5 million inhabitants and 26,000 births per year). Exchanges between regional informative systems indicate that approximately 0.2% of resident mothers gave birth in a hospital outside Tuscany in 1999.

Sources and ascertainment: Multiple sources are used to ascertain malformed infants; records are obtained from all obstetrical and maternity units, Pediatric departments, neonatal and Pediatric surgery units, prenatal diagnostic centres and pathology services. Mothers are interviewed by using a standardised questionnaire. Malformed babies diagnosed within the first year of life are also registered.

Termination of pregnancy: Termination of pregnancy became legal in Italy in 1978. Termination of pregnancy is legal when there is no possibility of autonomous life for the fetus. The Italian law (L.N. 194/78) lays down that termination is allowed in the case of diagnosis of serious fetal pathology which may detrimentally affect the woman's physical or psychological health. Induced abortions after prenatal diagnosis of birth defects are systematically included. Data for induced abortions first became available in 1982. Early ascertainment, however, was incomplete.

Stillbirth definition and early fetal deaths: The official definition of stillbirth in this registry is: 180 gestational days. Fetal deaths of 20 weeks or more gestation are systematically included if the weight is >=500g. Autopsy rates in 1999 were: ~60% in stillbirths, ~30% in induced abortions, ~50% in early neonatal deaths (0-7 days), ~30% in later deaths 1 week to 1 year and ~50% in deaths with congenital anomaly.

Exposure data availability: Maternal and paternal occupation, life-style, and Socioeconomic characteristics are obtained by interviews of mothers of malformed infants.

Denominators and controls information: Vital statistics and other epidemiological information is obtained by the birth medical records collected by the Regional Bureau of Statistics. Selected information is obtained from the control material collected.

Address for further information:
Dr Fabrizio Bianchi, Unit of Epidemiology, CNR Institute of Clinical Pysiology, Via Trieste 41, I-56126 Pisa, Italy.
Tel: +39 050 3152100 Fax: +39 050 3152095
Email: fabriepi@ifc.cnr.it

Malta
Malta Congenital Anomalies Register

History and funding: The register started in 1985 as a research project of the University of Malta. It started as a hospital-based register collecting data regarding congenital anomalies diagnosed in babies born at the main general hospital. It became a member of EUROCAT in 1986. Funding for the research project was stopped in 1995 and in 1997 the Department of Health Information resumed the functions of the registry increasing coverage to all hospitals on the islands making it a population-based register. The registry is now run and funded by the Government Department of Health Information. The aim of the Registry is to provide accurate epidemiological information regarding the occurrence of congenital anomalies in Malta and Gozo.

Population coverage: The registry is population-based I: covering all resident mothers in Malta, Gozo and Comino and presently covers about 4,300 births per year. The number of resident mothers giving birth in a hospital outside the area is considered to be negligible as Malta is an island and population movement is limited. It is unlikely that mothers will go abroad to give birth. It is precisely for this reason that the registry is thought to cover close to 100% of births.

Sources of ascertainment: Reporting is voluntary. Several new sources of information have been used since 1997 and the registry has back-dated its information to include these sources of information from 1993. For this reason data since 1993 may be considered most complete and reliable. The registry now employs active data collection from multiple sources including: labour, postnatal and nursery wards, cardiac laboratory records, genetics clinic records, National Mortality Register, National Obstetric Systems database, Hospital Activity Analysis database, National Cancer Register and the hypothyroid screening programme. Voluntary reporting by doctors is also available. These sources cover the whole population of the Maltese Islands. Babies with a congenital anomaly may be diagnosed and registered up to 1 year of age. Minor anomalies (as defined by EUROCAT) are not registered unless occurring in combination with other major defects.

Termination of pregnancy: Termination of pregnancy is illegal in Malta.

Stillbirth definition and early fetal deaths: The official definition of stillbirth is: a baby born with no signs of life at gestational age of 22 weeks or more, of a birth weight equal to or greater than 500g. Stillbirths are registered. All early fetal deaths of 20 weeks gestation and over which have been diagnosed as having a congenital anomaly are included. Autopsy rates for 1999 were as follows: 55% in stillbirths, 6% in early neonatal deaths (0-7 days), 20% in later deaths 1 week to 1 year and 50% in deaths with a congenital anomaly aged 0-1 years of age.

Exposure data availability: Information regarding maternal disease and exposure to medicinal drugs, smoking, alcohol and drug abuse as well as parental occupation are collected for all malformed infants.

Denominators and controls information: Epidemiological background data on all births are available from the National Obstetric Information Systems (NOIS) database and the National Statistics Office (NSO).

Address for further information:
Dr Miriam Gatt, Malta Congenital Anomalies Registry, Department of Health Information, 95 Guardamangia Hill,
Guardamangia MSD 08, Malta
Tel: +356 21234915 Fax: +356 21235910
Email: miriam.gatt@gov.mt
Website: http://www.health.gov.mt/ministry/dhi/mcar.htm

Northern Netherlands
EUROCAT Registration Northern Netherlands

History and funding: The programme started in 1981, and became a member of EUROCAT in that year. The programme is funded by the Dutch Ministry of Public Health, Welfare and Sports. The registry is carried out in the Department of Medical Genetics of the University of Groningen.

Population coverage: The registry is population-based I which includes all mothers resident in the Provinces of Groningen, Friesland and Drenthe. In the beginning the programme covered 7,500 births annually when it covered the province of Groningen and the northern part of the province of Drenthe. Coverage was gradually increased to 19,000 births annually in the provinces from 1989 onwards. Home deliveries (30% of births per year) are included and it is estimated that only a few percent of resident mothers would give birth outside the defined registry area.

Sources of ascertainment: Obstetricians, Pediatricians, clinical geneticists, surgeons, general practitioners, midwives, well-baby clinics, pathologists and the national obstetric registry send information to the registry on a voluntary basis. Registry personnel are actively involved in data collection. There are no age limits are applied regarding maximum age at diagnosis and if new information becomes available on infants born in 1981 or later, the files are updated.

Termination of pregnancy: Termination of pregnancy is legal. There is no specified upper gestational age limit for termination written in law –viability is the criterion. In practice 22 weeks is the usual upper limit unless a child has a lethal (or almost lethal) condition. In the case of diagnosis of congenital anomaly, there is no upper limit.

Stillbirth definition and early fetal deaths: Stillbirths are registered and the official stillbirth definition is: a gestational age of >=24 weeks. There are no age or weight limits for inclusion of early fetal deaths/spontaneous abortions. Autopsy rates in year were not given.

Exposure data availability: Since 1997 parents have been asked to fill out a questionnaire including questions on occupational activities, smoking, alcohol and drug use. In addition, data from community pharmacies are used to collect maternal drug exposure data.

Denominators and controls information: General statistics are available from the Dutch Central Bureau of Statistics (CBS).

Address for further information:
Dr Hermien de Walle, Department of Medical Genetics, University of Groningen, Ant. Deusinglaan 4, NL-9713 AW Groningen, The Netherlands.
Tel: +31 50 3632952 Fax: +31 50 3187268
Email: h.e.k.de.walle@medgen.azg.nl

Basque Country (Spain)
Registry of Congenital Anomalies of the Basque Country (RACAV)

History and funding: Registration of congenital anomalies in the Basque Country started on January 1st 1990. The Registry became a EUROCAT member in September 1990. The registry is financially supported by the Health Department of the Basque Government.

Population coverage: The registry is located in the Basque Country region, in northern Spain, covering a geographic area of 7260 Km^2, and a population of 2,250,000 inhabitants. It is a population-based III registry which therefore includes all mothers delivering in the Basque Country excluding any non-residents. The total number of annual births is about 16,000. It is estimated that 1-2% of outside resident mothers deliver in the covered hospitals.

Sources of ascertainment: Reporting is voluntary. There is an active search for cases (livebirths, stillbirths and induced abortions) through multiples sources of information: Neonatal Units, Specialist Pediatrics Departments, Cytogenetics and Pathology laboratories, Hospital discharge records and private maternity hospitals. The maximum age at diagnosis routinely reported to the registry is one year of age.

Termination of pregnancy: Termination of pregnancy is legal for certain indications, including prenatal diagnosis of severe anomaly with an official upper gestational age limit of 22 weeks. In practice there is no upper limit in the main public maternity hospitals, although in some the cases are officially registered as stillbirths. The private maternity hospitals send such mothers to the public hospitals or abroad (to the UK). Data about techniques of prenatal screening and diagnosis are systematically collected.

Stillbirth definition and early fetal deaths: The official definition of stillbirth in the Basque Country is: a gestational age of 22 weeks or a birthweight of 500g. Postmortem examination rates are highly variable in the region. About 90% of autopsies in stillbirths and neonatal deaths were performed in the public maternity hospitals (the remaining 10% of parents did not give permission). Autopsy following induced abortion usually depends upon the condition of the fetus.

Exposure data availability: Information on maternal drug use, maternal and paternal diseases, outcome of previous pregnancies and assisted conception is available.

Denominators and controls information: Statistics are provided by the Basque Statistics Institute (EUSTAT).

Address for further information:
Dr Blanca Gener, RACAV, Hospital de Cruces, Departamento de Pediatría, Pediatria 5a planta, 48903 Baracaldo. Vizcaya, Spain
Tel: +34 94 6006073 Fax: +34 94 6006073
Email: bgener@prbb.org

Vaud (Switzerland)
Registry of Switzerland

History and funding: The registry of Switzerland was originally set up in 1988, and also became member of EUROCAT in 1988. Different cantonal registries sent their data to the central registry in Lausanne. The aim at the beginning was to cover the whole country (80,000 births/year). In the first years of activity, 30% - 81% of births were surveyed. For financial reasons, many cantons had to stop this activity and in 1993, the Swiss registry covered 50% of all births in Switzerland. In 1998, the following cantons were included in the programme: Zurich, Fribourg, Argovie, Tessin, Vaud, Valais, Neuchâtel and Jura. The registry is located in the Division of Medical Genetics of the University hospital in Lausanne. The registry has formerly been associated with members from the Swiss Academy of Medical Sciences and from the Swiss Society of Pediatrics. The system is financed by the Swiss Federal Agency for Statistics for the central registry and by the cantonal health department for some cantonal registries. As the level of ascertainment was quite heterogeneous between the local cantonal registries and their activities fluctuating according to the years (cf prevalence rate <200 per 10,000), it was decided in January 2002 to restrict the registration in canton of Vaud only and to change the name of the Registry: Registry of Vaud (Switzerland).

Population coverage: The registry is population-based I and as such it covers all mothers resident in the canton of Vaud. The percentage of mothers delivering in a hospital outside the registry area is not known precisely although it is thought to be very low. The registry covers about 9% of all births in Switzerland (approximately 7,500 births annually). The changing coverage is detailed above.

Sources of ascertainment: Reporting is voluntary. Active case finding and multiple sources of information are used: delivery units; Pediatric departments; cytogenetic and genetic counseling and pathology unit. Data about different methods of prenatal diagnosis are collected (ultrasound, serum markers, cytogenetic and molecular). There is no upper age limit for registration of a child with a malformation.

Termination of pregnancy: Termination of pregnancy is legal up to 12 weeks gestation under most circumstances but this limit is extended to 24 gestational weeks if a congenital anomaly is diagnosed. In the latter circumstance, additional permission must be granted by two further physicians. Induced abortions following prenatal diagnosis are included in the register.

Stillbirth definition and early fetal deaths: The official stillbirth definition is: a gestational age of >= 27 weeks or length >=30cm and these are included in the register. Early fetal deaths/spontaneous abortions are included if they are 20 gestational weeks or more with no weight restrictions. Autopsy statistics were not available.

Exposure data availability: Information on maternal occupations and diseases, maternal drug use, outcome of previous pregnancies is available for the malformed infants.

Denominators and controls information: Background data on births are available from the Swiss Federal Agency for Statistics and from Service Cantonal de Recherche et d'Information Statistique (SCRIS).

Address for further information:
Dr Marie-Claude Addor, Registre Vaudois des Anomalies Congénitales and Swiss Registry for EUROCAT, Division of Medical Genetics, Maternité, CH-1011 CHUV-Lausanne, Switzerland
Tel: +41 21 3143391 Fax: +41 21 3143392
Email : marieclaude.addor@chuv.hospvd.ch
Website: www.hospvd.ch/public/chuv/genmol/eurocat/euro-home.htm
Username: eurocat, password: tropic

Glasgow (UK: Scotland)

Greater Glasgow NHS Board Congenital Anomalies Register

History and funding: The Glasgow Register of Congenital Malformations was founded in 1972 under the auspices of the Social Pediatric and Obstetric Research Unit and jointly administered by the University of Glasgow and the Corporation of Glasgow. It became a member of EUROCAT in 1978. The first full year for which standardised notifications were made was 1979. Greater Glasgow NHS Board (formerly Greater Glasgow Health Board) funds the Register. The Register had three initial objectives: the detection of epidemics, the calculation of prevalence rates and the epidemiological investigation of selected malformations. The objectives were broadened after joining EUROCAT to include the evaluation of preventive and therapeutic measures.

Population coverage: Population based I: the reference population is defined as all births (live and still) to women resident in the Greater Glasgow NHS Board area irrespective of the place of birth. Livebirths, stillbirths of 24 weeks gestation or more, spontaneous and induced abortions are included. In 2000, 3% of Greater Glasgow NHS livebirths were delivered outwith the study area and 18% of Scottish births resided in Greater Glasgow NHS Board area (Source: General Register Office for Scotland). From 1972 to March 1974 the Registry population and geographic area was defined by the boundaries of the former City of Glasgow. Following the reorganisation of the National Health Service in 1974, the Greater Glasgow Health Board assumed responsibility for the Register. Consequently the population under observation was enlarged by 35% to accommodate those areas formerly outside the boundaries of the City of Glasgow which were included within the area of the newly created Greater Glasgow Health Board. Annual number of births within Greater Glasgow has dropped from 13,500 in 1979 to 9,500 in 2000.

Sources of ascertainment: Notification is voluntary. Sources available are: Hospital discharge data, Health visitor immunisation consent forms, Inborn errors of metabolism screening programme, Child health surveillance programme, Death & stillbirth registration, Regional medical genetics department, Regional pathology department. Maternal and Pediatric hospital case records are viewed to confirm each case. Two useful sources are no longer available: Pediatric discharge letters are no longer sent to registry staff due to the closure of participating Pediatric units and perinatal summaries - an important early source for terminations for fetal abnormality – were sent by one maternity hospital for a number of years but this has ceased. The timedelay in ascertainment is a growing problem. This is partly due to the above-mentioned loss of earlier notifications but also due to time constraints on medical records staff who pull hospital case records for the registry worker to view. Due to reorganization of medical records in some hospitals, a delay in obtaining 1998 and 1999 data was experienced, leading to deficits in the prevalence rates for those years in this Report. Around 20% of cases in 2000 were reported by more than one source of information. There is no time limit for registration or for updating diagnostic detail. Cases with antenatal false positive screening results that do not have a congenital anomaly are not recorded.

Terminations: Termination of pregnancy became legal in the United Kingdom in 1967 (Abortion Act). Termination for fetal malformation is legal up to 24 weeks gestation. Information on terminations is now mainly obtained by viewing post mortem reports in regional medical genetics department.

Stillbirth definition and early fetal deaths: The official stillbirth definition is: fetal death after 24 completed weeks. Stillbirths and infant deaths are routinely notified to the register where at least one cause of stillbirth/death is a congenital anomaly. There is no lower gestational age or weight limit. Autopsy rates are not known.

Exposure data availability: No information available.

Denominators and controls information: Data on births is available from the Registrar General for Scotland. Mid-year estimates are published by the middle of the year following. The number of births (live and still) is available by maternal age and by month of birth for the population from1983. These figures are produced by analysing birth and child record files from a quarterly download based on current status of residence and not initial status at birth. As a result the denominator data will therefore vary from quarter to quarter and will never correspond to the Registrar General's figures. Demographic/exposure information on controls is not collected.

Address for further information:
Dr David H Stone, Pediatric Epidemiology & Community Health (PEACH) Unit, Yorkhill Hospital, Glasgow G3 8SJ, Scotland
Tel : +44 141 2010178 Fax : +44 141 2010837
Email: d.h.stone@clinmed.gla.ac.uk
Hilary Jordan, Information Services Unit, Greater Glasgow NHS Board, Dalian House, PO Box 15328, 350 St Vincent Street, Glasgow, G3 8YY, Scotland