Supplementary material

Details of case surveillance and selection methods

The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) was created for the purpose of collecting and sharing data across individual birth defects surveillance programs worldwide. When new research projects are initiated by the ICBDSR or proposed by its members, a specific study protocol is approved and each program is invited to participate by providing existing data for that specific analysis, if not available from regular monitoring of birth defects. We obtained aggregate-level data on hypospadias from 27 birth defect surveillance programs in the ICBDSR. Since each program had data for a potentially different study period, we chose the study period to be births from 1980 to 2010, years for which the majority of programs had more complete data. Surveillance methods and case definitions also vary between programs [1,2]. For example, for some programs, case identification is based on review of records by program staff for all births and terminations of pregnancy at all hospitals and delivery centers in the program's region, whereas surveillance for other programs relies on clinician reporting of cases to the program.

Programs identified cases based on infants with a recorded hypospadias diagnosis using the WHO International Classification of Diseases, ICD-9 (752.6) or ICD-10 (Q54) codes, in addition to reviewing the original birth defect descriptions. A British Pediatric Association (BPA) code extension for the ICD-9 code was used to differentiate hypospadias (752.60) from epispadias (752.61) and congenital chordee alone (752.62). The Royal College of Paediatrics and Child Health adaptation was used to identify the respective subtypes for ICD-10 codes. Thus, all systems could distinguish between hypospadias and epispadias or congenital chordee alone, which were not included in the study.

Cases among live births and stillbirths were included by all programs. ETOPFAs were included by programs where terminations were permitted, except the hospital-based Spanish program. (This should not have strongly impacted the results since the prenatal diagnosis of hypospadias is very rare, and ~90% of the cases are isolated.) For each program, data were available for the total number of cases with hypospadias (live births, stillbirths, and ETOPFA) during each year of surveillance and the total number of births (live births and still births) in the same surveillance region during each respective year.

When available, we also received data on the number of cases with hypospadias by the degree of severity (first-degree, second-degree, third-degree, or degree unspecified) during each respective year. To increase consistency, programs were asked to classify glandular or coronal forms of hypospadias as first-degree hypospadias; subcoronal, distal penile, midshaft or proximal penile forms as second-degree hypospadias; and meatus openings on the scrotum or below (including penoscrotal or perineal hypospadias) as third-degree hypospadias. In addition, we reviewed information with each program's leadership about their surveillance program, including the percentage of cases without available data on the degree of severity, the length of the ascertainment period after birth (e.g., inclusion of only diagnoses made before 1 year of age), whether the program used population-based (e.g., as opposed to hospital-based) case identification, and whether case diagnoses involved confirmation across multiple sources (e.g., diagnosis on more than one medical record).

To better interpret the observed results, we also queried the director of each program for insights into the prevalence and trend results for their program. We specifically asked: (1) How do you interpret your total prevalence of hypospadias being in the 1st / 2nd / 3rd/ 4th quartile? (2) How do you interpret the increase / decrease observed in the joinpoint regression analysis of your program? These responses were used to interpret the results and organize the discussion of this paper.

References

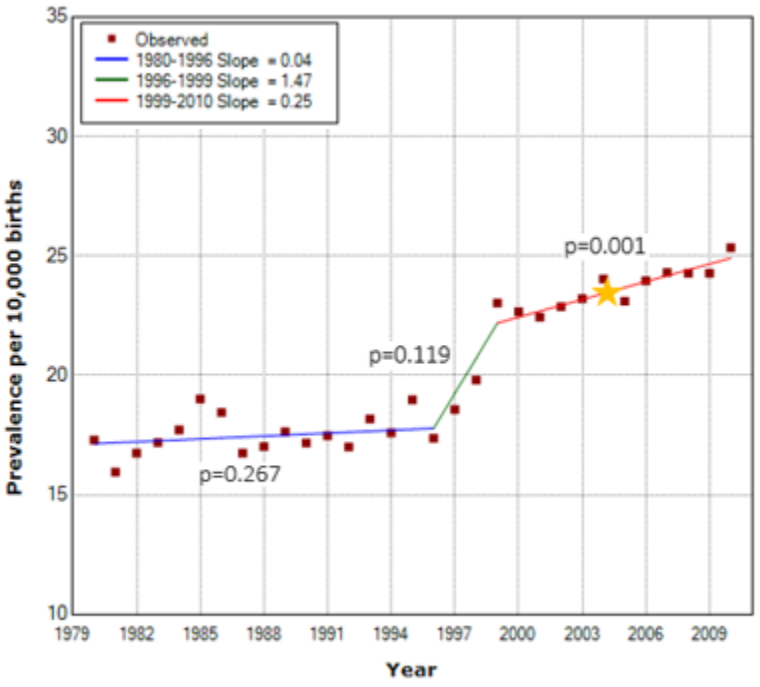
[1] Nassar N, Leoncini E, Amar E, et al. Prevalence of esophageal atresia among 18 international birth defects surveillance programs. Birth Defects Res A Clin Mol Teratol 2012;94:893–9.

[2] International Clearinghouse for Birth Defects Surveillance and Research. Facts about hypospadias. 2018. http://www.icbdsr.org

Supplementary Table 1. Examples of reported systematic changes during 1980-2010 among International Clearinghouse for Birth Defects Surveillance and Research programs

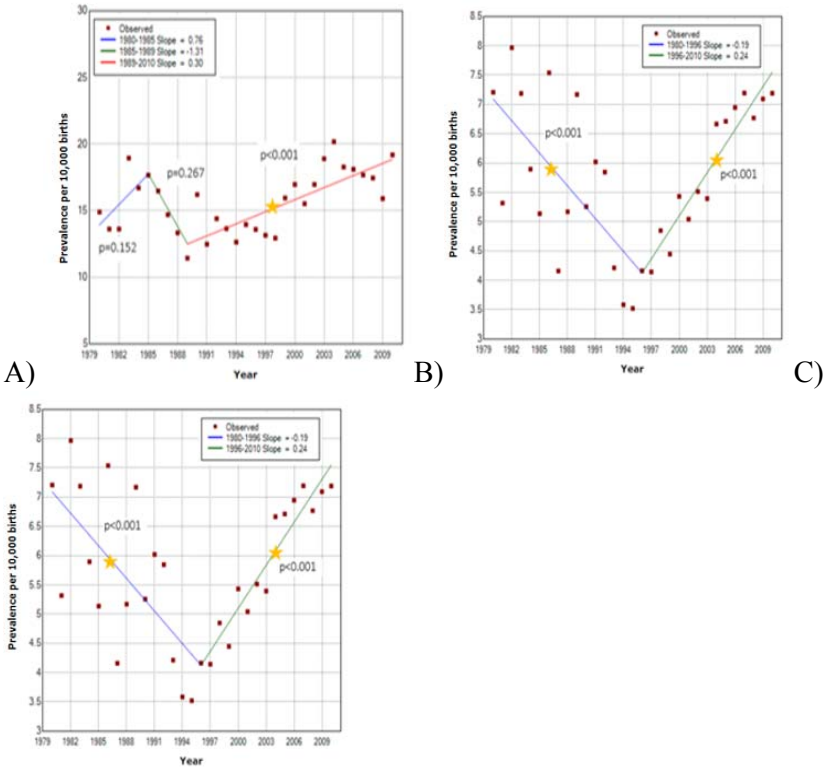
Program Location	Systematic change
Alberta, Canada	During the 1990s, case ascertainment dropped during a period of financial uncertainty.
Costa Rica	The age of ascertainment changed from ~3 days to 1 year in 2008.
Costa Rica	New training activities were implemented in the mid and late 2000's.
Czech Republic	Supplemental case ascertainment with additional newborn report records began in 2000.
Czech Republic	There were suspected changes in the awareness of hypospadias reporting requirements among neonatologists during the study period.
France	Data collection reportedly improved over time, as the number of data sources increased and other improvements in data quality were implemented.
Hungary	Reporting of documented birth defects became legally regulated and mandated in 1997, which resulted in higher numbers of most birth defects identified by early 2000.
Hungary	New procedures based on territorial representation were established in 2000, under which a different public health professional conducted the quality control of their respective county's data.
Many European programs	EUROCAT registry guidelines changed in 2005 to include isolated first degree hypospadias, which was previously excluded.
Many European programs	ICD classification and codes changed from ICD-9 752.6 to ICD-10 Q54.0-54.9 in many European countries around 1985, allowing for greater specification of severity classification.

Supplementary Figure 1. Trends in the international total prevalence of hypospadias for 27 ICBDSR programs using joinpoint regression, 1980-2010.[a]



[a] Stars indicate joinpoints with statistically significant ($p<0.05$) trends.

Supplementary Figure 2. Trends in the international total prevalence of hypospadias by clinical degree of severity among 7 ICBDSR programs with select characteristics,[a] 1980-2010.[b]

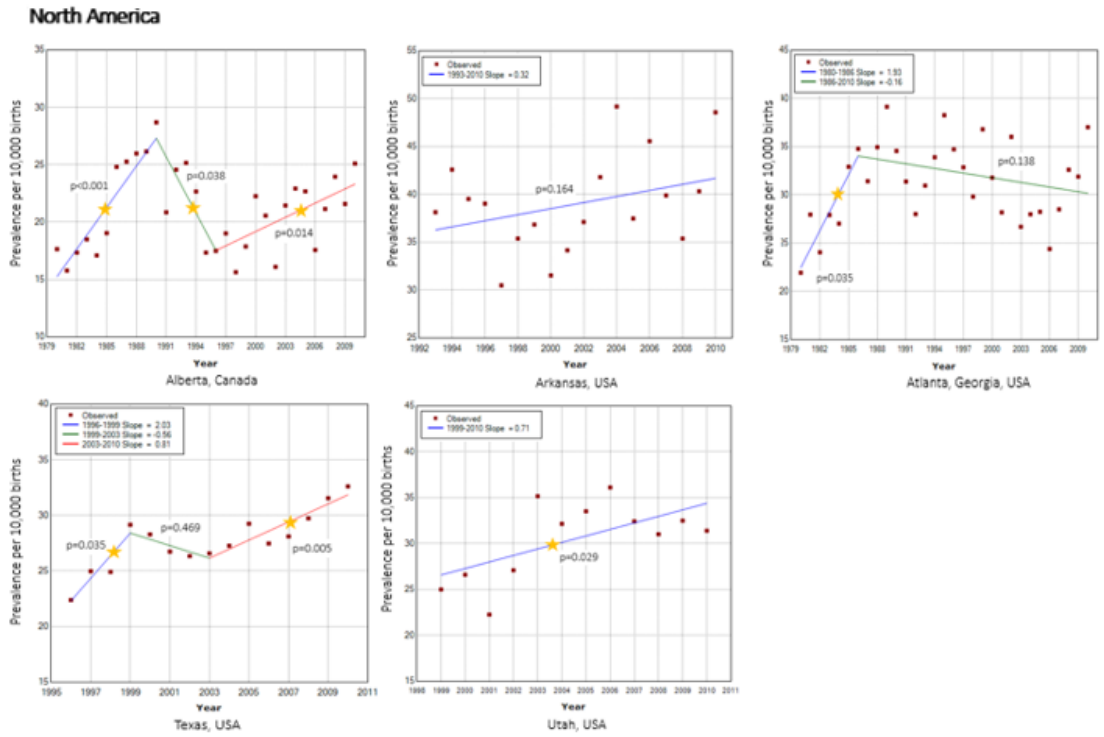


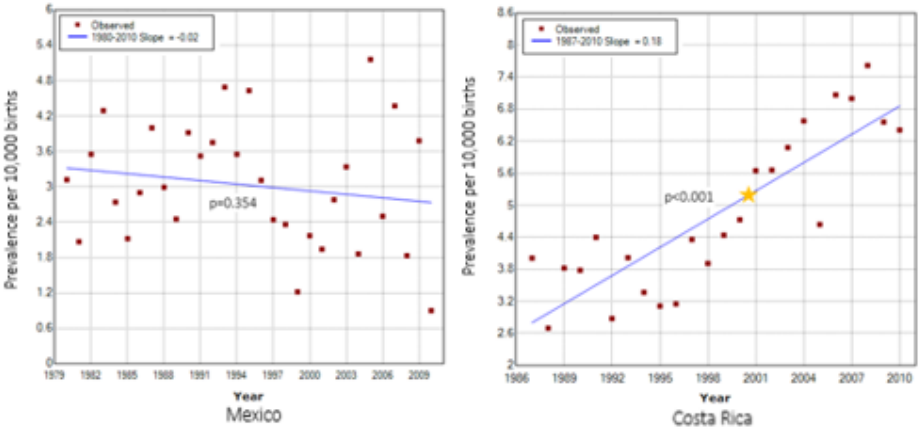
A) First-degree hypospadias, B) second-degree hypospadias, and C) third-degree hypospadias

[a] Programs with 1) the clinical degree of severity specified in ≥80% of cases, 2) population-based ascertainment, 3) age of ascertainment ≥1 year, and 4) ascertainment from multiple sources.

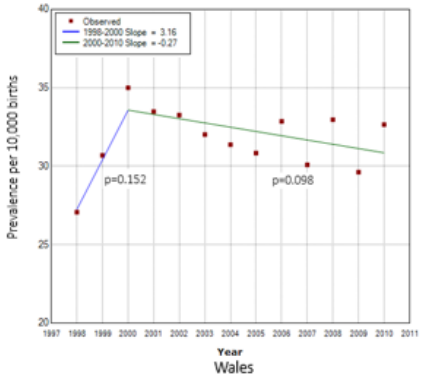
[b] Stars indicate joinpoints with statistically significant ($p<0.05$) trends.

Supplementary Figure 3. Trends in the total prevalence of hypospadias by ICBDSR program, 1980-2010.[a, b]

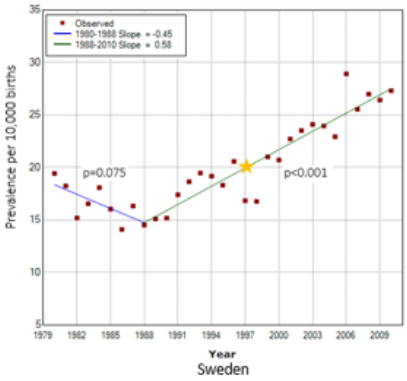




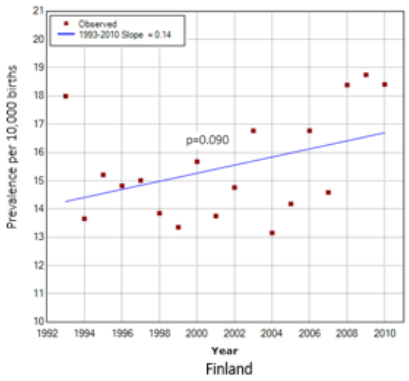
Northern Europe



Wales

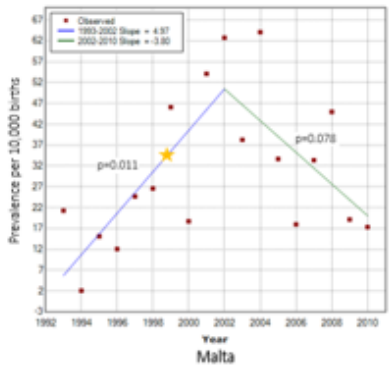


Sweden

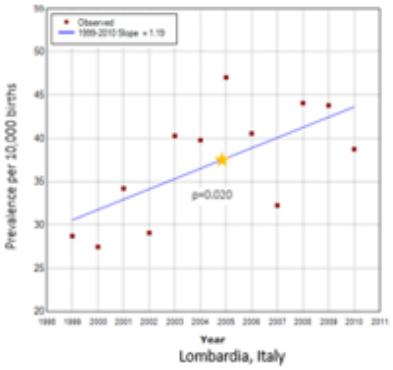


Finland

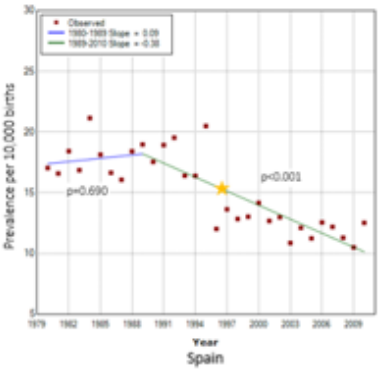
Southern Europe



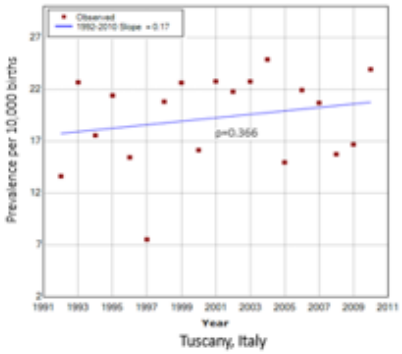
Malta



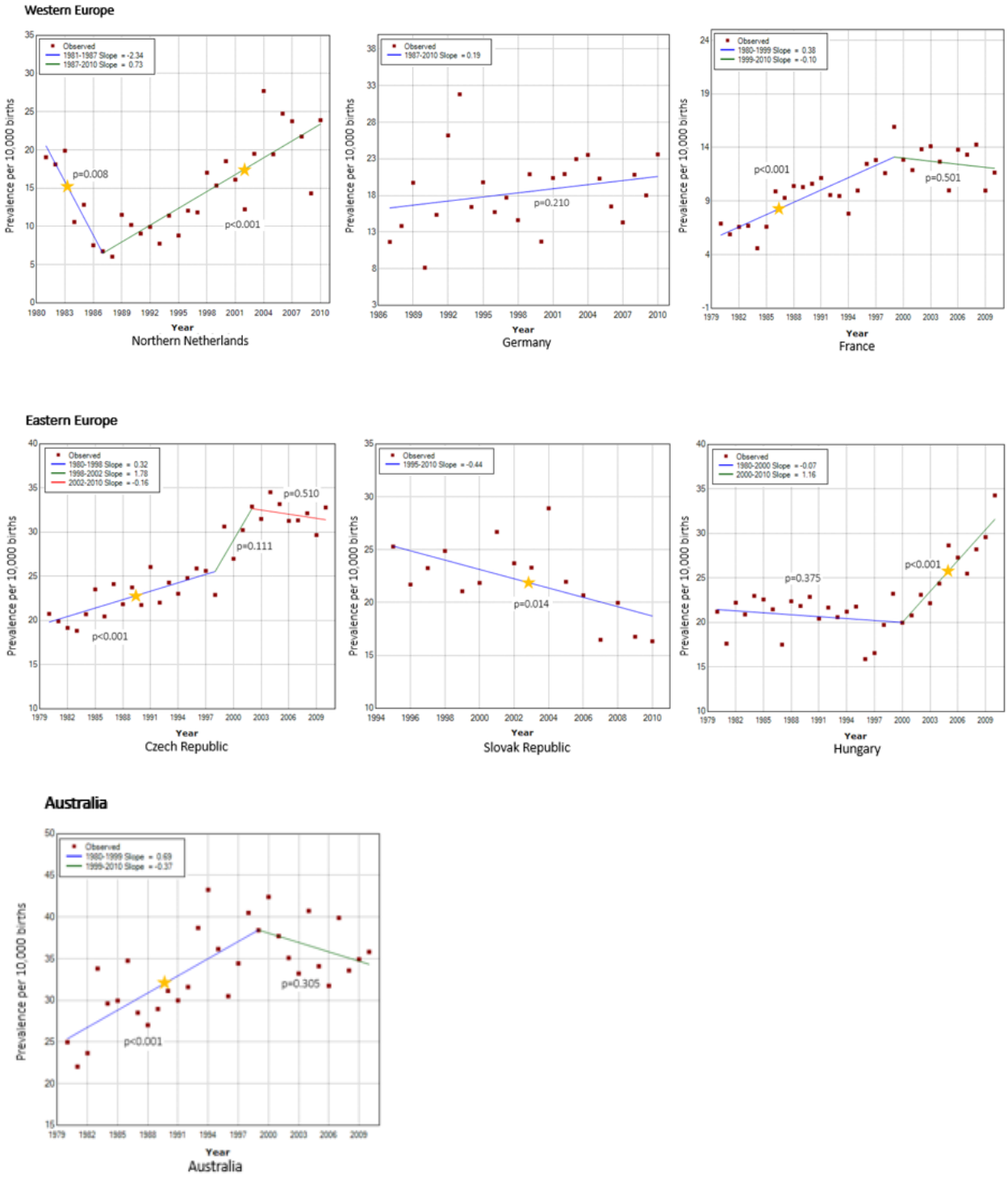
Lombardia, Italy



Spain



Tuscany, Italy



[a] Stars indicate joinpoints with statistically significant ($p<0.05$) trends.

[b] Joinpoint regression was not performed for programs with <11 years of data (Argentina, Colombia, Chile, Canada [National], Iran) or any years of missing data during the period analyzed (New Zealand).