



Platinum Priority – Pediatric Urology

Editorial by Anne-Françoise Spinoit on pp. 491–492 of this issue

Hypospadias Prevalence and Trends in International Birth Defect Surveillance Systems, 1980–2010

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Abstract

Background: Hypospadias is a common male birth defect that has shown widespread variation in reported prevalence estimates. Many countries have reported increasing trends over recent decades.

Objective: To analyze the prevalence and trends of hypospadias for 27 international programs over a 31-yr period.

Design, setting, and participants: The study population included live births, stillbirths, and elective terminations of pregnancy diagnosed with hypospadias during 1980–2010 from 27 surveillance programs around the world.

Outcome measurements and statistical analysis: We used joinpoint regression to analyze changes over time in international total prevalence of hypospadias across programs, prevalence for each specific program, and prevalence across different degrees of severity of hypospadias.

Results and limitations: The international total prevalence of hypospadias for all years was 20.9 (95% confidence interval: 19.2–22.6) per 10 000 births. The prevalence for each program ranged from 2.1 to 39.1 per 10 000 births. The international total prevalence increased 1.6 times during the study period, by 0.25 cases per 10 000 births per year ($p < 0.05$). When analyzed separately, there were increasing trends for first-, second-, and third-degree hypospadias during the early 1990s to mid-2000s. The majority of programs (61.9%) had a significantly increasing trend during many of the years evaluated. Limitations include known differences in data collection methods across programs.

Conclusions: Although there have been changes in clinical practice and registry ascertainment over time in some countries, the consistency in the observed increasing trends across many programs and by degrees of severity suggests that the total prevalence of hypospadias may be increasing in many countries. This observation is contrary to some previous reports that suggested that the total prevalence of hypospadias was no longer increasing in recent decades.

Patient summary: We report on the prevalence and trends of hypospadias among 27 birth defect surveillance systems, which indicate that the prevalence of hypospadias continues to increase internationally.

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1. Introduction

Hypospadias, which is caused by incomplete development of the urethra, is one of the most common congenital anomalies in male infants, with an estimated prevalence of 64.7 cases per 10 000 male live births in the USA [1]. Hypospadias can have different degrees of clinical severity, as defined by the location of the urethral opening [2]. Estimates of the prevalence of hypospadias vary across and within different geographical settings globally. The extent to which artifactual differences (eg, differences in clinical practice, registry ascertainment, or case definitions) contribute to the observed prevalence differences is unknown. Moreover, there have been reports of increases in the prevalence of hypospadias in many countries, especially in the last decades of the 20th century [2–9]. However, a number of countries have also reported that the prevalence has not increased in recent decades [3,7,9–17].

To better understand prevalence trends in recent years across the world, we evaluated hypospadias data in 27 birth defect surveillance programs participating in the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR).

2. Patients and methods

2.1. Data collection

The ICBDSR is a World Health Organization (WHO)-affiliated network of birth defects surveillance programs. The general methods of the ICBDSR are described elsewhere [18]. Each of the 27 surveillance programs identified hypospadias cases under their established protocol for births during 1980–2010 (case surveillance and selection methods are detailed in the [Supplementary material](#)).

2.2. Statistical analysis

We calculated an international total prevalence of hypospadias per 10 000 births, defined as the total number of cases of live births, stillbirths, and elective terminations of pregnancy for fetal anomaly (ETOPFAs) across all 27 programs divided by the total number of births (live births and stillbirths, regardless of sex) during the full study period (1980–2010). (We reported the total prevalence per male and female births for comparability with international prevalence reports of other birth defects.) As some programs did not have data between 1980 and 1999, we also calculated the international total prevalence of hypospadias per 10 000 births for a more recent period (2000–2010). Lastly, we calculated the total prevalence of hypospadias for each individual program during 1980–2010 and 2000–2010. The approximate 95% confidence interval (CI) was also calculated for all prevalence estimates. In addition, we determined the quartile (1, 2, 3, or 4) in which each

program's total prevalence was located (eg, programs in quartile 1 had a total prevalence within the lowest 25% of all the programs).

To visualize the data over time and to assess temporal changes in trends, we conducted analyses using joinpoint regression. Joinpoint regression is helpful for identifying linear trends in total prevalence over time that are restricted to subperiods, rather than testing for linear trends only across the entire time period [19]. This approach agnostically identifies joinpoints that parse the data into periods of varying sizes, based on the presence of similar linear trends within each period [19].

We conducted joinpoint regression for the total analytic group (all 27 programs) during the full study period. These analyses were repeated among a subset of 19 programs with three characteristics (hereafter referred to as the “main subgroup”): (1) population-based ascertainment, (2) ascertainment of cases ≥ 1 yr of age, and (3) ascertainment of cases from multiple sources. This subanalysis was repeated again, including only eight programs from the main subgroup with at least 30 yr of data available. For comparison, we plotted the total prevalence of these eight programs over time in the same figure.

We also conducted analyses separately for first-, second-, and third-degree hypospadias, including only the 12 programs for which the degree of severity was specified for $\geq 80\%$ of cases. These analyses were repeated among seven programs that were also in the main subgroup.

To better understand similarities and differences across programs, analyses were also performed during the full study period for each separate program. (Programs with < 11 yr of data or with intermediate years of missing data were not included in this analysis, in order to meet the software's minimal requirements [19].)

All statistical tests were two sided, and we interpreted statistical significance based on $p < 0.05$. Joinpoint regression analyses were performed using Joinpoint Trend Analysis Software (version 4.4.0.0) from the National Cancer Institute [20].

3. Results

3.1. Program characteristics

The characteristics of each program are summarized in Table 1. The majority of programs used population-based case identification (21 programs, 77.8%), registered cases up to 12 mo of age or beyond (22 programs, 81.5%), and received notification of cases from multiple sources (19 programs, 70.4%). Only 12 programs (44.4%) specified the degree of severity of hypospadias in $\geq 80\%$ of cases.

3.2. International prevalence of hypospadias

For all programs combined, there were 36 127 500 births and 74 814 cases with hypospadias. The international total prevalence of hypospadias was 20.9 (95% CI: 19.2–22.6) per 10 000 births among 27 programs of the ICBDSR during 1980–2010. For 2000–2010 specifically, the international total prevalence was 23.8 (95% CI: 22.1–25.5) per 10 000 births. Program-specific prevalences for 1980–2010 and 2000–2010 were tabulated (Table 2) and also presented in a histogram (Fig. 1). Arkansas, USA, had the highest total prevalence (39.1 cases per 10 000 births, 95% CI: 36.7–41.4), while Argentina had the lowest total prevalence (2.1 cases per 10 000 births, 95% CI: 1.1–4.8). Programs in Latin American countries (ie, Argentina, Chile, Colombia, Mexico, and Costa Rica) had relatively lower total

prevalence estimates than programs in other regions (Fig. 1). The total prevalence in Europe was highly variable, ranging from 10.6 (France) to 37.4 (Lombardia, Italy) cases per 10 000 births. Only four (Atlanta, GA, USA; Mexico; Spain; and Slovak Republic) out of 27 programs had a lower total prevalence in the recent period (2000–2010) than the whole period (1980–2010; Fig. 1).

Changes in the international total prevalence of hypospadias were visualized using joinpoint regression (Supplementary Fig. 1), with joinpoints identified at 1996 and 1999. Since 1999, the total prevalence increased significantly by 0.25 cases per year ($p = 0.001$). This analysis was repeated among the main subgroup (Fig. 2A). For these programs, there was an increasing trend during the entire period 1980–2010, and this increase was statistically significant ($p < 0.001$) during 1980–1996 (0.19 cases per year) and 1999–2010 (0.34 cases per year). The analysis was repeated using data from the eight programs with at least 30 yr of data (Fig. 2B). Among these programs, there was a 1.6-time increase in the total prevalence of hypospadias during the entire study period (from 1980 to 2010) by an average of 0.34 cases per year ($p < 0.001$). Among these programs (Fig. 2C), France had a relatively lower total prevalence during the entire period.

3.3. Prevalence of hypospadias by degree of severity

Fig. 3A–C shows the results from joinpoint regression analyses for first-, second-, and third-degree hypospadias, respectively. These analyses were restricted to programs with the degree of severity of hypospadias specified in $\geq 80\%$ of cases (12 programs). Across all three degrees of severity, increasing trends were observed from the mid-1990s to the mid-2000s (Fig. 3A–C). Similar trends were observed after repeating these analyses among seven programs that were also in the main subgroup (Supplementary Fig. 2A–C). Among these, 62.2% of cases had first-degree hypospadias, 20.1% had second-degree hypospadias, 4.5% had third-degree hypospadias, and 13.2% had an unspecified degree of severity (data not shown).

3.4. Program-specific prevalence of hypospadias

Supplementary Fig. 3 illustrates the results from the joinpoint regression for each program with at least 11 yr of data (the software's minimal requirements). Five of the 27 programs were excluded from these analyses because they had < 11 yr of data (Argentina, Colombia, Chile, Canada [National], and Iran). As the software required complete data for each year analyzed, New Zealand was also excluded due to missing data for some years. Table 3 summarizes the trends from these analyses. Different trend patterns were observed across programs, including patterns of increases in total prevalence during much or all of the study period for a number of programs. In fact, significant increases in the total prevalence of hypospadias were observed for 45.0% of the years of observation, whereas significant decreases in the total prevalence were observed for only 10.4% of the years of observation.

Table 1 – Summary of program characteristics (International Clearinghouse for Birth Defects Surveillance and Research)

Program	Delivery years	Total births	Ascertainment to at least 1 yr	Population based	Ascertainment from multiple sources	Degree of severity specified in ≥80% of cases
Argentina ^a	2009–2010	42 136	No	No	No	No
Australia ^b	1980–2010	792 512	Yes	Yes	Yes	Yes
Canada (National) ^c	2005–2010	1 416 099	No	Yes	No	No
Alberta, Canada ^d	1980–2010	1 309 669	Yes	Yes	Yes	No
Chile–Maule ^e	2002–2010	119 900	No	No	No	Yes
Colombia	2001–2010	174 425	Yes	No	No	Yes
Costa Rica ^f	1987–2010	1 842 791	Yes ^g	Yes	No	No
Czech Republic	1980–2010	3 597 530	Yes	Yes	Yes	Yes
Finland	1993–2010	1 068 457	Yes	Yes	Yes	Yes
France ^h	1980–2010	2 819 326	Yes	Yes	Yes	No
Germany ⁱ	1987–2010	336 716	Yes	Yes	Yes	No
Hungary	1980–2010	3 507 915	Yes	Yes	Yes	No
Iran ^j	2005–2010	130 724	Yes	No	Yes	– ^k
Lombardia, Italy	1999–2010	179 484	Yes	Yes	Yes	No
Tuscany, Italy ^l	1992–2010	519 749	Yes	Yes	Yes	No
Malta ^m	1993–2010	77 261	Yes	Yes	Yes	Yes
Mexico ⁿ	1980–2010	1 093 745	No	No	No	Yes
New Zealand	1980–1993 1996–2010	1 638 216	Yes	Yes	Yes	– ^k
Northern Netherlands	1981–2010	496 810	Yes	Yes	Yes	Yes
Slovak Republic	1995–2010	902 372	Yes	Yes	No	Yes
Spain ^o	1980–2010	2 648 286	No	No	No	Yes
Sweden	1980–2010	3 166 009	Yes	Yes	Yes	No
Arkansas, USA ^p	1993–2010	684 001	Yes	Yes	Yes	Yes
Atlanta, GA, USA ^q	1980–2010	1 299 822	Yes	Yes	Yes	No
Texas, USA	1996–2010	5 216 949	Yes	Yes	Yes	No
Utah, USA ^r	1999–2010	615 886	Yes	Yes	Yes	Yes
Wales ^s	1998–2010	430 710	Yes	Yes	Yes	No

^a National Network of Congenital Anomalies of Argentina (RENAC).^b Western Australian Register of Developmental Anomalies.^c Canadian Congenital Anomalies Surveillance System.^d Alberta Congenital Anomalies Surveillance System.^e Registro de malformaciones congénitas del Servicio de Salud Maule (RRMC-SSM).^f Centro de Registro de Enfermedades Congénitas.^g For births during 2009 and later only.^h Registre des Malformations en Rhône-Alpes (REMERA).ⁱ Saxony-Anhalt.^j Tabriz Registry of Congenital Anomalies.^k No information on degree of severity.^l Tuscan Registry of congenital defects (RTDC).^m Malta Congenital Anomalies Register.ⁿ Registration and Epidemiologic Surveillance of External Congenital Malformations (RYVEMCE).^o Spanish Collaborative Study of Congenital Malformations (ECEMC).^p Arkansas Reproductive Health Monitoring System.^q Metropolitan Atlanta Congenital Defects Program.^r Utah Birth Defect Network.^s Congenital Anomaly Register & Information Service for Wales.

4. Discussion

Among 27 programs participating in the ICBDSR, the total prevalence of hypospadias was 20.9 per 10 000 births during 1980–2010, although it varied greatly by geographical region.

The international total prevalence of hypospadias increased during the entire study period, with significant increases from 2000 to 2010. When we restricted to programs among the main subgroup, the rates of increase were similar, although the time trend was significant over more years. The increasing trends were also consistent for most of the study period across all degrees of clinical severity of hypospadias.

Our international total prevalence estimates of hypospadias were similar to those from previous studies, with many previous reported estimates from individual ICBDSR programs, including the USA [5], Australia [2], Germany [21], Northern Netherlands [21], Hungary [21], Malta [21], Spain [21], and Tuscany [21]. For Latin American countries, our results were consistent with previous estimates from Argentina [22] and Mexico [23]. In fact, all Latin American programs had a relatively low prevalence that fell within the lowest quartile of all participating programs. As the magnitude of the difference was quite large and consistent across programs in Latin American countries, it is possible that the difference between Latin American countries and other countries may reflect true prevalence differences,

Table 2 – Total prevalence of hypospadias by program and time period (International Clearinghouse for Birth Defects Surveillance and Research)

Program	Delivery years	1980–2010				2000–2010			
		Total prevalence per 10 000	95% Confidence interval		Quartile ^a	Total prevalence per 10 000	95% Confidence interval		Quartile ^a
			Lower	Upper			Lower	Upper	
Argentina	2009–2010	2.14	1.11	4.83	Q1	2.14	1.11	4.83	Q1
Australia	1980–2010	33.68	31.58	35.34	Q4	36.21	34.26	38.32	Q4
Canada (National)	2005–2010	24.45	23.57	25.31	Q3	24.45	23.57	25.31	Q3
Alberta, Canada	1980–2010	21.13	19.77	22.31	Q3	21.51	19.84	22.94	Q2
Chile-Maule	2002–2010	8.26	6.62	9.85	Q1	8.26	6.62	9.85	Q1
Colombia	2001–2010	4.70	4.24	9.17	Q1	4.70	4.24	9.17	Q1
Costa Rica	1987–2010	4.77	4.24	5.42	Q1	6.17	5.62	6.74	Q1
Czech Republic	1980–2010	25.64	24.31	27.72	Q3	31.86	30.29	32.70	Q4
Finland	1993–2010	15.54	14.64	16.37	Q2	15.97	14.74	17.11	Q2
France	1980–2010	10.60	9.56	11.54	Q1	12.55	11.67	13.49	Q1
Germany	1987–2010	18.21	16.47	20.61	Q2	19.32	17.09	21.65	Q2
Hungary	1980–2010	22.30	21.17	23.92	Q3	25.78	23.28	28.35	Q3
Iran	2005–2010	13.69	8.70	18.41	Q2	13.69	8.70	18.41	Q2
Lombardia, Italy	1999–2010	37.38	33.42	40.92	Q4	38.11	34.17	41.70	Q4
Tuscany, Italy	1992–2010	19.22	17.15	21.16	Q2	20.17	18.07	22.34	Q2
Malta	1993–2010	29.64	22.46	38.88	Q4	36.45	26.22	47.28	Q4
Mexico	1980–2010	3.17	2.67	3.40	Q1	2.75	2.04	3.53	Q1
New Zealand	1980–1993	19.61	16.56	22.21	Q2	27.02	24.65	29.70	Q3
	1996–2010								
Northern Netherlands	1981–2010	15.06	12.80	17.05	Q2	20.04	17.39	22.98	Q2
Slovak Republic	1995–2010	21.98	20.30	23.81	Q3	21.35	19.09	23.93	Q2
Spain	1980–2010	14.75	14.12	16.34	Q2	12.11	11.47	12.73	Q1
Sweden	1980–2010	20.01	18.52	21.48	Q3	24.97	23.39	26.26	Q3
Arkansas, USA	1993–2010	39.11	36.67	41.43	Q4	40.13	36.67	43.50	Q4
Atlanta, GA, USA	1980–2010	31.28	29.66	32.70	Q4	30.21	27.99	32.61	Q3
Texas, USA	1996–2010	28.14	26.36	29.01	Q3	28.57	27.32	29.75	Q3
Utah, USA	1999–2010	30.59	28.03	32.84	Q4	31.05	28.52	33.34	Q3
Wales	1998–2010	31.65	30.57	32.80	Q4	32.15	31.25	33.13	Q4
Total	–	20.91	19.19	22.63	–	23.78	22.06	25.50	–

^a Q1 corresponds to the lowest quartile of total prevalence and Q4 corresponds to the highest quartile.

perhaps related to differences in both genetic and nongenetic hypospadias risk factors.

As previously reported, programs in the USA and northern Europe had higher prevalence estimates

[23]. There have been reports of increases in the prevalence of hypospadias in many countries, particularly during the late 1960s until around the early 1990s in the USA and Europe (reviewed in the work of Agopian [24]). Our results

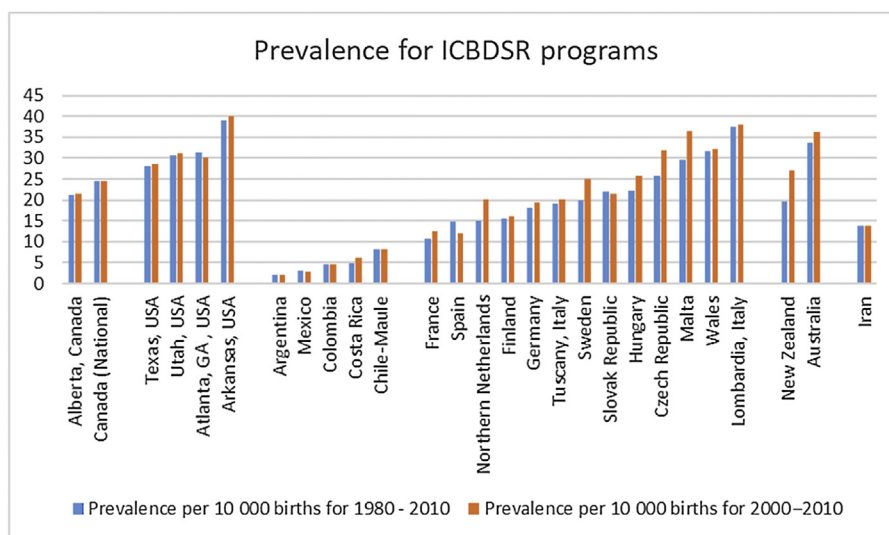


Fig. 1 – Total prevalence of hypospadias (per 10 000) for International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) programs, grouped by world region, 1980–2010 and 2000–2010.

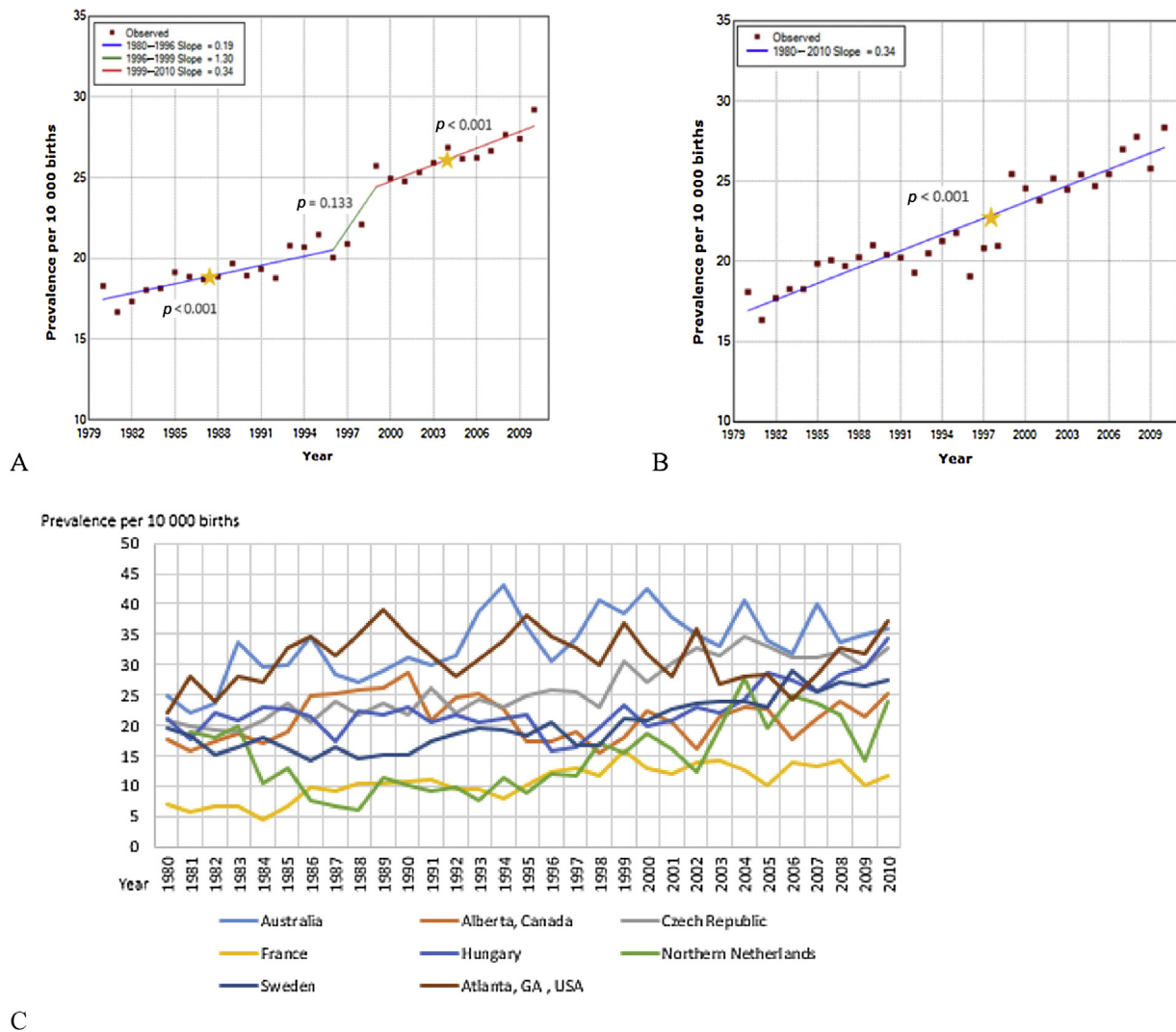


Fig. 2 – Trends in the international total prevalence of hypospadias among ICBDSR programs with select characteristics using joinpoint regression, 1980–2010. ^a (A) Among 19 programs with (1) population-based ascertainment, (2) age of ascertainment ≥ 1 yr, and (3) ascertainment from multiple sources. (B) Among eight programs with (1) population-based ascertainment, (2) age of ascertainment ≥ 1 yr, (3) ascertainment from multiple sources, and (4) at least 30 yr of data. (C) Results by program, among eight programs with (1) population-based ascertainment, (2) age of ascertainment ≥ 1 yr, (3) ascertainment from multiple sources, and (4) at least 30 yr of data. ICBDSR = International Clearinghouse for Birth Defects Surveillance and Research. ^a Stars indicate joinpoints with statistically significant ($p < 0.05$) trends.

for the period from 1980 to early 1990s seem consistent with these reported increases.

However, this increase was reported to stabilize or even decrease in more recent years in many, though not all, studies [3,7,21], whereas we detected an increase throughout this time. For example, separate reports from Washington State, USA (1987–2002 births) [17], New York State, USA (1983–1995 births) [13], Scotland (1988–1997 births) [11], Italy (2001–2004 births) [14], Finland (1970–1994 births) [12], and Europe (1980–1999 births from the EUROCAT network) [7] did not indicate increases in the prevalence in more recent years. Furthermore, individual reports from Spain (1996–2002 births) [16], Northern England (1993–2000 births) [10], and Japan (1985–1997 births) [15] suggested that the prevalence may have been decreasing in recent years. As expected, among the countries represented in our study (ie, Finland, Italy, Spain, and other

European regions), much of the corresponding data within these same time windows appeared to be similar in our data (ie, not increasing). However, our results among all programs indicated an increase in the total prevalence during recent years. This difference was probably related to the inclusion of a very large number of programs throughout a long (and in many instances, more recent) analysis period (1980–2010), as well as our use of joinpoint regression. However, it is noteworthy that these increases were not observed during the entire period for each program, and it is important to remember that our findings were most influenced by the programs with larger sample sizes.

Although our study likely reflects a better estimate of global trends than smaller studies, it is likely that some of the observed prevalence increases in our study were artifactual, and reflect changes over time in how cases

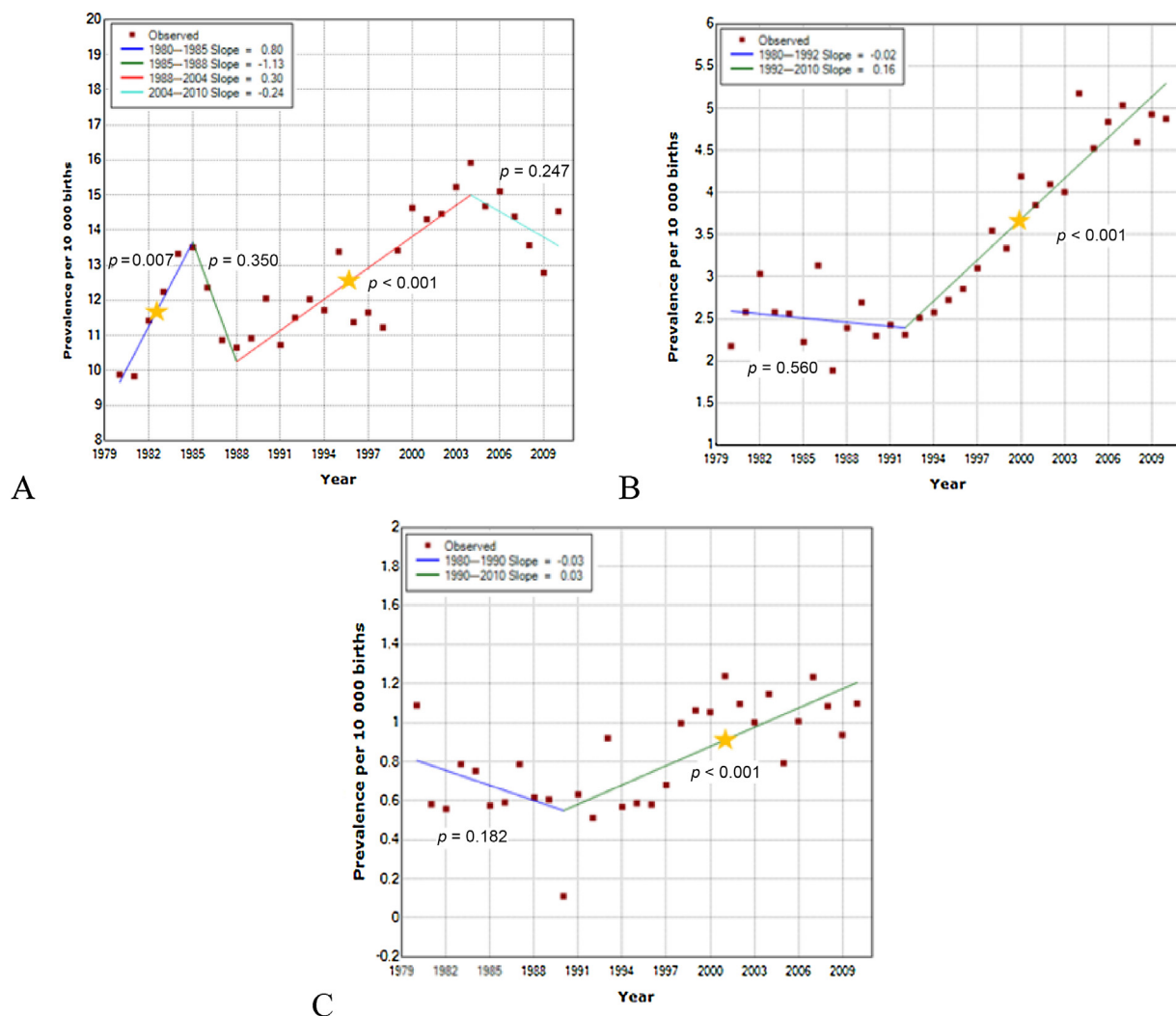


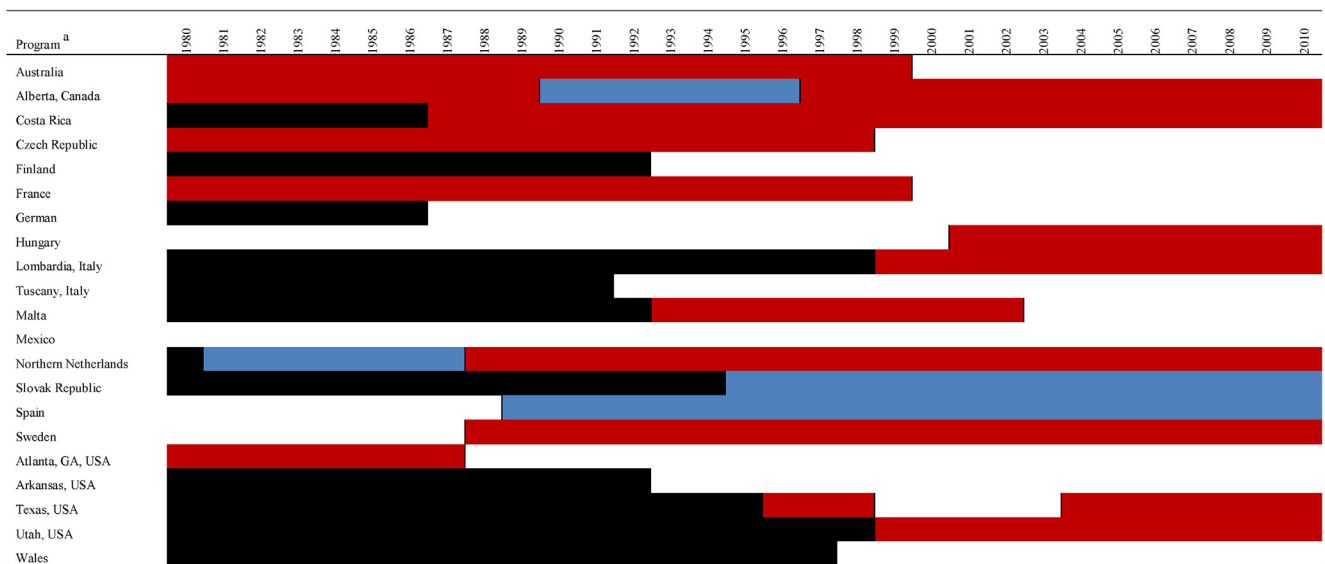
Fig. 3 – Trends in the international total prevalence of hypospadias for 12 ICBDSR programs by clinical degree of severity, 1980–2010^{a,b}: (A) First-degree hypospadias, (B) second-degree hypospadias, and (C) third-degree hypospadias. ICBDSR = International Clearinghouse for Birth Defects Surveillance and Research. ^a Stars indicate joinpoints with statistically significant ($p < 0.05$) trends. ^b Programs for which the degree of severity was unspecified in $\geq 80\%$ of cases were excluded.

with hypospadias were identified and documented at the medical facility and/or were ascertained by the surveillance system (eg, underascertainment in earlier years). While quality metrics for systematic assessment of birth defect surveillance have recently been proposed [25], many programs have not yet reported on these metrics [26,27]. Some ICBDSR systems implemented systematic surveillance changes during the study period (Supplementary Table 1), including a stronger focus on ascertaining less severe hypospadias cases in more recent years [21] and improvements in data collection over time.

Nevertheless, we still observed increasing prevalence time trends in the main subgroup, which represented 47.0% of total births across all ICBDSR programs. The data from these programs may have been less subject to bias compared with those from other sites, and these trends within this subgroup were similar to the trends observed in the full analytic group. This consistency suggests that much of the increasing trends in the prevalence of

hypospadias may represent a true (nonartifactual) increase. However, consistent trends were not seen across every program.

It has been proposed that the observed prevalence increase might reflect increases in exposure to hypospadias risk factors over time [9]. However, given the broad range of potentially relevant environmental and occupational exposures that could be responsible for the observed increase, as well as issues related to exposure dosage, timing, and other factors, it has been challenging to identify the main culprits. It is also possible that changes over time in the distribution of other parental factors associated with hypospadias risk (eg, parity, body mass index, maternal age, and fertility treatments) may have influenced the prevalence over time, but data were not available to assess this possibility in our analyses [24]. Further study of potential hypospadias risk factors, including genetic factors, endocrine disruptors, and other maternal and paternal exposures and characteristics may shed light on this possibility.

Table 3 – Annual trends in the total prevalence of hypospadias by program, 1980–2010

Key: red boxes represent years with a significantly increasing trend in total prevalence of hypospadias ($p < 0.05$); blue boxes, years with a significantly decreasing trend ($p < 0.05$); white boxes, years with no significant trend ($p \geq 0.05$); and black boxes, years with no observations.

^a Joinpoint regression was not performed for programs with <11 yr of data (Argentina, Colombia, Chile, Canada [National], and Iran) or any years of missing data during the period analyzed (New Zealand) due to the software's minimum data requirements.

This study had some known limitations. First, it lacked uniformity in data collection across programs, which may have led to heterogeneity among cases across programs. Initiatives related to standardizing these methodologies across programs would be helpful to future work. Second, as individual-level data were not available, we could not adjust for differences in the distributions of hypospadias risk factors across countries, and this unmeasured confounding may also have partially accounted for the differences in hypospadias prevalence across programs. Third, the joinpoint regression modeled the data based on an assumption of linear trends across subperiods, although it did not account for completely nonlinear (eg, exponential) trends. Nevertheless, this statistical approach had more flexibility than a traditional assessment of a continuous prevalence estimate under the assumption of a linear change over an entire study period, which would not have been able to agnostically identify changes limited to study subperiods. We also did not have data related to co-occurring congenital malformations (~88.5% of hypospadias is expected to be isolated in European countries [21]) or on hypospadias treatment; while we had data on hypospadias severity for some programs, these data were not available for the majority of programs.

Despite these limitations, this study has several important strengths. We analyzed data from surveillance programs across the world, representing one of the largest case samples among published studies. Further, our data allowed us to look at trends over a 31-yr period. We also investigated the trends by differing degrees of severity and considered differences in characteristics of surveillance programs.

5. Conclusions

Our results suggest that the international total prevalence of hypospadias increased during 1980–2010 and that these trends were probably not entirely artifactual. Considering these trends, it seems clear that further surveillance around hypospadias is critical.

Author contributions: A.J. Agopian had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Nassar, Mastroiacovo, Canfield, Groisman, Bermejo-Sánchez, Ritvanen, Kiuru-Kuhlefelt, Benavides, Sipek, Pierini, Bianchi, Källén, Gatt, Morgan, Tucker, Canessa, Gajardo, Mutchinick, Szabova, Csáky-Szunyogh, Tagliabue, Cragan, Nembhard, Rissmann, Goetz, Bower, Baynam, Lowry, Leon, Luo, Rouleau, Zarante, Fernandez, Amar, Dastgiri, Contiero, Martínez-de-Villarreal, Borman, Bergman, de Walle, Hobbs, Nance.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.eururo.2019.06.027>.

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