HHS Public Access

Author manuscript

Am J Perinatol. Author manuscript; available in PMC 2023 November 29.

A Multicountry Analysis of Prevalence and Mortality among Neonates and Children with Bladder Exstrophy

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Conflict of Interest

VK has received Consulting fee related to her work on the project from Medizinische Fakultät Otto-von-Guericke-Universität Magdeburg, Germany.

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Abstract

Objective—Bladder exstrophy (BE) is a rare but severe birth defect affecting the lower abdominal wall and genitourinary system. The objective of the study is to examine the total prevalence, trends in prevalence, and age-specific mortality among individuals with BE.

Study Design—We conducted a retrospective cohort study. Data were analyzed from 20 birth defects surveillance programs, members of the International Clearinghouse for Birth Defects

Surveillance and Research in 16 countries. Live births, stillbirths, and elective terminations of pregnancy for fetal anomaly (ETOPFA) diagnosed with BE from 1974 to 2014. Pooled and program-specific prevalence of BE per 100,000 total births was calculated. The 95% confidence intervals (CI) for prevalence were estimated using Poisson approximation of binomial distribution. Time trends in prevalence of BE from 2000 to 2014 were examined using Poisson regression. Proportion of deaths among BE cases was calculated on the day of birth, day 2 to 6, day 7 to 27, day 28 to 364,1 to 4 years, and ≥5 years. Mortality analysis was stratified by isolated, multiple, and syndromic case status.

Results—The pooled total prevalence of BE was 2.58 per 100,000 total births (95% CI = 2.40, 2.78) for study years 1974 to 2014. Prevalence varied over time with a decreasing trend from 2000 to 2014. The first-week mortality proportion was 3.5, 17.3, and 14.6% among isolated, multiple, and syndromic BE cases, respectively. The majority of first-week mortality occurred on the first day of life among isolated, multiple, and syndromic BE cases. The proportion of first-week deaths was higher among cases reported from programs in Latin America where ETOPFA services were not available.

Conclusions—Prevalence of BE varied by program and showed a decreasing trend from 2000 to −2014. Mortality is a concern among multiple and syndromic cases, and a high proportion of deaths among cases occurred during the first week of life.

Keywords

birth defects; bladder exstrophy; epidemiology; mortality; prevalence; surveillance

Bladder exstrophy (BE) is a rare but severe congenital anomaly characterized by an absence of the anterior bladder wall and incomplete closure of the posterior wall.[1,2] BE is associated with eversion of the bladder, divergence of pubis, abnormal external genitalia, and inferiorly placed umbilicus.[3] BE results from the failure of mesenchymal cells to migrate between the ectoderm of the abdomen and the cloaca during the fourth week of gestation.[4–6] The prenatal diagnosis of BE is made based on a nonvisible fetal bladder, normal fetal kidneys, normal amniotic fluid volume, low insertion of the umbilical cord, a bulging mass protruding from the lower abdominal wall, a small penis, epispadias, and splayed iliac bones.[3,7] Current treatments for BE, which include Modern Staged Repair of BE, the Complete Primary Repair of BE, and Radical Soft-Tissue Mobilization, have improved survival outcomes among cases.[8–11] However, clinical management is complex with a potential for surgical complications and poor long-term health outcomes.[12–14]

The prevalence of BE is reported to range between 1.6 and 4 per 100,000 births, varying by region and surveillance methods.[15–21] About one-third of all cases occur in combination with other birth defects (i.e., multiple or syndromic cases).[16] A US multiregistry study reported a stillbirth prevalence of 11 per 1000 fetuses with BE[22]; stillbirths are also frequent in BE cases with co-occurring malformations.[17] Mortality among those affected by BE is not well explored. There are very few population-based registry studies on first-year mortality among individuals with BE.[19,23] Very little is known about mortality among children, adolescents, and adults with BE.

Data collected through national and regional birth defects surveillance systems provide a unique opportunity to study total prevalence of BE. Linking birth defects surveillance data to death certificates and other administrative datasets allows us to examine age-specific mortality among individuals affected by BE. The objectives of our study were to examine total prevalence, trends in prevalence, and age-specific mortality among individuals with BE, using data from multinational population- and hospital-based birth defects programs affiliated with the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). We examined trends in prevalence stratified by all, isolated, multiple, and syndromic case types, for a period of 15 years (2000–2014) during which most programs contributed data for the study.

Materials and Methods

Design, Setting, and Partidpants

Data were used from ICBDSR (http://www.icbdsr.org/), a consortium of 42 birth defects surveillance programs from around the world. These programs conduct either population- or hospital-based surveillance, and 27 of them contribute aggregated data on fetuses and children affected with at least one of 39 different birth defects annually. Each program collects data on the total annual number of live births and stillbirths in their source population that serve as population- or hospital-based total birth denominators for birth defect prevalence calculations.

For our analysis, we examined surveillance data from 20 ICBDSR surveillance programs, based in 16 countries (Table 1). We included live births, stillbirths, and elective terminations of pregnancy for fetal anomaly (ETOPFA), recorded between the year surveillance started (1974 or later), until 2014. Descriptions of individual surveillance programs that contributed aggregated data for the current analysis, including the name of the program, type of surveillance (population-based / hospital-based), coverage (national / regional / state-wide), ascertainment period (in years or until hospital discharge after birth), stillbirth definition (based on birth weight and/or gestational age), availability of services for ETOPFA (yes / no), and presence of prenatal screening services (yes / no) are presented in Table 1. Ethics approval was provided by each surveillance program locally. The current study did not require a separate ethics approval as we used aggregated totals without access to individual data or personal identifiers.

Case Definition

ICBDSR defined BE as “a complex malformation characterized by a defect in the closure of the infraumbilical abdominal wall and bladder. The bladder opens in the ventral wall of the abdomen between the umbilicus and the symphysis pubis. It is often associated with epispadias and structural anomalies of the pubic bones.” This case definition corresponds to *International Classification of Diseases,* Tenth Revision (ICD-10) code “Q64.1” and Ninth Revision (ICD-9) code “753.5.” Each surveillance program contributed the aggregated annual number of cases with BE, by live birth, stillbirth, or ETOPFA. BE cases with no other co-occurring unrelated major birth defects were classified as “isolated.” BE cases that had one or more co-occurring unrelated major anomalies were classified as “multiple.”

When BE was part of a genetic disorder or recognized syndrome, the case was classified as "syndromic."

Method of Mortality Tracking

In Table 2, we present the method of mortality tracking for BE cases by program. BE cases were followed up from birth until their discharge from the maternity or the birth hospital in several participating programs. Information on whether the follow-up was conducted by clinicians or program staff was recorded for each program. Linkage of birth defect cases to death certificates or other healthcare databases, and the period until which linkages were available, were recorded. The maximum period of follow-up in each program, recorded from the time of birth, was available for analysis. Follow-up periods varied widely across programs; most programs followed cases up to 27 days of life to record mortality. Mortality on or after 28 days of life was available in only a few programs that could link to death registration data or other administrative databases.

Statistical Analysis

Prevalence Analysis—We estimated total prevalence of BE as the total number of cases with BE (sum of live births, stillbirths, and ETOPFA) divided by the total number of births (sum of live births and stillbirths) for each participating program for the duration they contributed data. The term "total births" in the denominator of prevalence estimates will henceforth be an indicator for the sum of live births and stillbirths. Pooled total prevalence of BE was estimated by combining data from all participating programs across available years. We estimated 95% confidence intervals (CI) for BE prevalence using the Poisson approximation of the binomial distribution. For each program, we also calculated the proportion of live births, stillbirths, and ETOPFA among all cases of BE, along with 95% CI for the proportions using the Poisson approximation of the binomial distribution.

Prevalence Trend Analysis—Prevalence trends were examined by pooling the total number of BE cases and by live births, stillbirths, ETOPFA, isolated, multiple, and syndromic case status. Because BE is a rare birth defect, we aimed to prevent random variability in prevalence trends by smoothing and combining data through an overlapping sequence of three consecutive years. Based on the rare disease assumption, Poisson regression was used to quantify time trends in prevalence for data from 2000 to 2014, when most programs contributed data. Trend analyses for isolated, multiple, and syndromic BE cases were limited to programs that had Information on co-occurring birth defects.

Mortality Analysis—Mortality risk was estimated as a probability measure. We examined the number of deaths among BE cases divided by total number of live-born BE cases. Mortality proportion was calculated by age groups: day 1 / day 2 to 6 / day 7 to 27 / day 28 to 364 / year 1 to 4 / year ≥5. We also calculated mortality during the first week of life for deaths on day 1 and day 2 to 6 after birth, stratified by isolated, multiple, and syndromic case status from 15 of the 20 programs where Information on case classification by co-occurring birth defects was available.

Results

The overall surveillance period for BE cases varied by participating programs, between years 1974 and 2014. Of the 20 participating programs, seven provided data for more than 30 years of surveillance. Thirteen programs were population-based and seven were hospital-based. Of the population-based programs, three had national, seven regional, and three state-wide coverage for case identification. Two of the seven hospital-based programs had national coverage. Seventeen of the 20 programs operated in regions where ETOPFA was allowed. However, three of these 17 programs did not have adequate surveillance to include BE cases occurring in pregnancies resulting in ETOPFA. Except Mexico-RYVEMCE, all other programs offered prenatal screening services (Table 1).

A total of 16 programs conducted follow-up of the new-born until discharge from the birth hospital; follow-up was monitored by clinicians or surveillance program staff for special pediatric care in 8 of these 16 programs (Table 2). Only nine of the 20 programs were equipped to conduct linkages with death certificates (during varying periods) at the time data were collected for the current study. Most programs did not have a long follow-up period to capture mortality in cases beyond the first week of life (Table 2).

Prevalence of BE

There were a total of 731 cases of BE (including live births, stillbirths, and ETOPFA) during the study period (1974–2014), identified from 19 of the 20 participating programs. Colombia-Cali did not have any cases during their surveillance period (2011–2014). Of the 731 cases, 635 (87%) resulted in live births, 36 (5%) stillbirths, and 60 (8%) ETOPFA. During the same years, there were 28,301,491 live births and stillbirths in these 20 programs. Pooling data from all 20 programs, we estimated the total prevalence of BE to be 2.58 per 100,000 total births (95% CI = 2.40, 2.78). The total prevalence of BE in 13 out of 20 programs where ETOPFA are registered was estimated to be 2.80 per 100,000 total births (95% CI = 2.57, 3.04). Northern Netherlands (5.69 per 100,000 total births), Ukraine-OMNI-Net (5.44 per 100,000 total births), and United Kingdom-Wales (5.27 per 100,000 total births) had a high prevalence of BE compared with other programs (Table 3). Programs in Latin America where ETOPFA was not allowed or registered during the study period had over 80% of all cases recorded as livebirths. There was a high proportion of stillborn BE cases in Mexico-RYVEMCE (22.2%) and Argentina-RENAC (18.2%). Programs in Europe, including France-Paris, Germany-Saxony Anhalt, UK-Wales, and Italy-Tuscany, had the highest proportion of cases that resulted in ETOPFA, with 55.8, 41.2, 30.0, and 25.0%, respectively (Table 3).

Time Trends in Prevalence of BE

Time trends in BE prevalence were examined for years between 2000 and 2014 when most programs provided data. There was a statistically significant decreasing trend in the total prevalence of all ($p < 0.0001$), isolated ($p < 0.0001$), and multiple ($p = 0.0008$) BE cases; prevalence also decreased for syndromic BE cases but the decrease was not statistically significant ($p = 0.1036$). Prevalence trend graphs for total, isolated, multiple, and syndromic BE cases from 15 programs that had data on cases status are presented in Fig.

1A. Prevalence trends were also examined by live births, stillbirths, and ETOPFA outcomes. Between years 2000 and 2014, there was a significant decreasing time trend for livebirth (p = 0.0001), stillbirth (p = 0.0015), and ETOPFA prevalence of BE (p = 0.0001) (Fig. 1B).

Mortality in BE

Overall, 635 (87%) of the 731 cases of BE occurring during the study period (1974–2014) were live births. Mortality was examined by pooling data from all programs and separately for each of the 20 participating programs (Table 4). Of the total 635 live-born cases of BE, 83 died within 1 year after birth. Age-specific distribution of deaths of these 83 deaths showed that 37 (5.8%) died on the day of birth, 22 (3.5%) died between days 2 and 6 after birth, which includes Argentina for deaths occurring any time before day 6, 10 (1.9%) died between days 7 and 27, and 14 (2.8%) between days 28 and 364. Ten programs had a follow-up beyond 1 year of age, and very few deaths were reported during this period, stratified at 1 to 4 years of age (n = 3; 0.7%) and ≥5 years of age (n = 2; 0.5%); there were 2 (0.5%) deaths during the follow-up period where the age death was unknown (Table 4) Most programs followed cases to 1 week after birth, and thus, the overall first-week mortality was 9.3% (95% CI = 7.0%, 11.5%). Among the deaths that occurred during the first week of life, a high proportion occurred on the first day of life. Latin American programs including Argentina-RENAC and South America-ECLAMC reported a high proportion of deaths in the first week of life (Table 4).

In the 15 programs that had Information on co-occurring birth defects among BE cases, mortality was stratified by isolated (n = 256), multiple (n = 176), and syndromic (n = 67) case status (Table 5). Out of 256 isolated BE cases, 233 were live born, and 8 of them died during the first week of life. Mortality in the first week of life was higher among multiple and syndromic cases compared with isolated cases, with 22% (29 / 133) first-week deaths in multiple cases, and 11% (6 / 55) in syndromic cases. Only 3% (8 / 233) of isolated cases died in the first week of life (Table 5).

Discussion

We conducted a multicountry analysis that examined prevalence, prevalence trends, and mortality for BE using data from 20 member programs of ICBDSR from 1974– 2014. The total prevalence of BE was 2.58 per 100,000 total births, while the total prevalence of BE among 13 programs that tracked ETOPFA was higher (2.80 per 100,000 total births). Prevalence of BE varied by program. We found that a considerable proportion of pregnancies affected by BE resulted in stillbirths and ETOPFA; these proportions varied depending on ETOPFA policies in the regions the programs operated. The highest proportion of cases that resulted in ETOPFA was observed in European registries. Prevalence trends, examined over a period spanning 15 years (2000–2014), showed a significant decrease in total, isolated, and multiple BE cases. Mortality is a concern among infants born with BE, as 6% died on the first day of life and 3.5% died between days 2 to 6 after birth. Stillbirths and mortality were higher in programs based in Latin America where ETOPFA was not available. A greater proportion of multiple or syndromic BE died within the first week of life compared with isolated cases.

The EUROCAT (European Surveillance of Congenital Anomalies) network reports prevalence of BE and/or epispadias as 6.6 per 100,000 births (birth years 1980–2018, all full member registries and genetic disorders included)[24]; however, the case definition of BE differs between EUROCAT and the current study including ICBDSR member programs. While some of the programs overlap between ICBDSR and EUROCAT networks (including Czech Republic, France-Paris, Germany-Saxony Anhalt, Italy-Tuscany, Malta-MCAR Northern Netherlands, Spain-ECEMC, Sweden, Ukraine-OMNI-Net, United Kingdom-Wales), ICBDSR included several programs that were not in the EUROCAT network (including Argentina-RENAC, Colombia-Bogotá, Colombia-Cali, Israel-SMC, Mexico-RYVEMCE, Slovak Republic, South America-ECLAMC, and USA-Arkansas, USA-Atlanta, USA-Texas, and USA-Utah). Thus, our analysis expands the geographic representativeness of the findings.

A previous study using data from 22 ICBDSR programs examined data from 1980 to 2006 and reported total prevalence of BE to be 2.07 per 100,000 total births (95% CI = 1.90, 2.25).[16] Our study was also based on the same ICBDSR member programs; however, our surveillance period included a larger time span (1974–2014). Another ICBDSR study from 10 programs (Australia, Denmark, France-Paris, France-Rhône-Alpes Auvergne, Italy, Mexico, Norway, Spain, Sweden, USA-Atlanta), with each program covering varying time periods from 1967–1985, reported a pooled prevalence of BE of 3.3 per 100,000 births (range: 2.1–4.7 per 100,000 births); 70% of cases were classified as isolated, and mortality among live births was not examined.[17]

Martínez-Frías et al reported the live birth prevalence of BE as 2.8 per 100,000 live births using data from the Spain-ECEMC between January 1980 and March 1999.[25] The current study includes data from Spain-ECEMC for years 1990 to 2014 and showed a live birth prevalence of 2.1 per 100,000 live and stillbirths. Older studies that examined live birth prevalence of BE reported a prevalence of 2.5 per 100,000 live births (1941–1953) and 10 per 100,000 live births (1954–1960) in hospitals that treated almost all infants with BE in the Liverpool region of the United Kingdom[26]; 2.1 per 100,000 live births in New York State population-based birth defects registry (1983–1999)[19]; 2.15 per 100,000 live births in a US Nationwide Inpatient Sample where cases included BE and cloacal exstrophy (comprising of ~10% of all cases) (1988–2000)[15]; and 3.2 per 100,000 live births in the US Healthcare Cost and Utilization Project with national hospital admissions data (1997–2001) and 3.2 per 100,000 live births in 12 population-based birth defects surveillance programs in the United States that do not survey ETOPFAs (1997–2001).[27] Swedish national data between years 1973 to 2011 reported a live birth prevalence of 3 per 100,000 births.[28] The live birth prevalence of 2.24 per 100,000 births (95% CI = 2.07, 2.43) in our study is comparable to some of the studies referenced above; inconsistencies in findings can be a result of differences in time periods and surveillance methods across the studies. More comparable to our study methods, Bird et al published the prevalence of BE in 14 US population-based state-wide birth defects surveillance systems (which include BE cases resulting in live births, stillbirths, and ETOPFA), and this prevalence was 2.80 per 100,000 live births, closer to the total prevalence estimate of 2.58 per 100,000 total births in the current study.

We found only one population-based study that used active-surveillance data from nine states in the United States (1997–2011) reporting a stillbirth proportion of ~1% among all BE cases.[22] In comparison, our study found an average of 5% stillbirths in the overall pooled data; regionally, stillbirth proportion varied by program, with highest proportions (10–20%) in Latin American programs (i.e., Argentina-RENAC, Mexico-RYVEMCE, and South America-ECLAMC).

Time trends in prevalence of BE were examined in three previous studies. The ICBDMS study, which included some of the ICBDSR programs from the current study, reported no significant trend in the prevalence of BE from 1970 to 1985.[17] The second study, by Caton et al, using population-based surveillance data from New York state, reported a downward linear trend in the prevalence of BE from 1983 to 1999. The trend reported in New York was consistent with our finding, but our study spans a later time period (2000–2014) with more heterogeneous data pooled from multiple countries. Lastly, a Swedish registry-based study, partly coinciding with our study period, reported no specific trend to indicate either an increase or decrease in BE prevalence from 1973 to 2011.[28]

Overall, 3.5, 20, and 14% of those born with isolated, multiple, and syndromic BE, respectively, died within the first 7 days of life in the current study. A previous study by ICBDSR programs (1967–1985) reported similar findings for first-week mortality among isolated BE cases (2/145; 2.1%); a high proportion of multiple cases died during the first week (15/63; 24%).[17] It was not mentioned in the ICBDMS study whether syndromic cases were categorized as multiple cases.

We found only one study that reported on neonatal mortality (defined as death within the first 28 days of life) among BE cases. This population-based study from Sweden of 120 BE cases born between 1973 and 2011 reported 0% neonatal mortality.[28] A few studies published findings on first year mortality in BE cases.[19,23,28] A population-based Hawaii Birth Defects Registry study on 8 BE cases born between 1986 and 1999 reported 0% first year mortality (95% CI = 0–37%).[23] Caton et al, using data from the population-based New York State Congenital Malformation Registry (1983–1999), reported that 4.2% infants with BE died during the first year of their life; a total of four deaths out of 77 cases, two deaths recorded on the day of birth, and two more deaths recorded in the first month of birth. Our literature search did not yield studies that examined mortality among BE cases after 1 year of age, or during early childhood, adolescence, or adulthood.

Most of the programs in our study had linkages to death certificates or other administrative data sources to identify deaths among BE cases on the day of birth and days 1 to 6 after birth. Programs located in Latin America had higher numbers of BE cases resulting in first-week mortality compared with programs in Europe and North America. Future research on this disparity may help identify preventable underlying factors, including prenatal screening, and availability, and access to medical and surgical care soon after birth in these regions.

There are several strengths to our study. ICBDSR allowed us to examine a large number of BE cases, including all pregnancy outcomes and spanning an extended time period over 30 years in some programs. We could examine total prevalence of BE as programs tracked

live births, stillbirths and ETOPFA. Prevalence trends, and mortality at selected ages, and by isolated, multiple and syndromic BE cases could be examined. Programs participating in ICBDSR track diverse populations from different countries providing global data. All ICBDSR member programs have quality control protocols. Case specificity for BE and other birth defects is established by trained surveillance personnel. Multiple data sources are used for completeness of surveillance data. The majority of surveillance programs had linkages to death certificates or other administrative data sources that provided information on mortality up to at least 1 week of age and some for up to 5 years of age.

Our study also has some limitations. Not all programs were population-based, but several hospital-based programs had national coverage. Surveillance periods differed making it difficult to compare findings across all programs. Data were available for each participating program as aggregate number of BE cases and denominators included aggregate number of live births and stillbirths that limited our ability to conduct individual-level analyses. It has been reported that classification of BE, especially for multiple and syndromic cases, can be difficult due to nonspecific coding.[19] Despite the fact that all programs tracked BE cases among stillbirths, the definition of stillbirth varied by program, impacting comparability. There may not be a high level of accuracy for mortality Information obtained from death certificates and administrative sources. Data linkage methods to establish mortality differed by program; linkage success and data quality could not be assessed. It is likely that some deaths were missed in our study due to linkage inconsistencies or migration of cases after birth. Lastly, our analysis of temporal trends in prevalence was limited to more recent years during that the majority of registries provided data.

Our analysis is one of the largest to date to report on the total prevalence of BE, prevalence trends, and mortality in BE cases. We were able to stratify our findings by isolated, multiple, and syndromic cases. The total prevalence of BE varied by region. Early neonatal mortality among cases is a concern and infants born with BE are highly encouraged to be monitored for mortality. Readers may consider the impact of different characteristics of participating programs when interpreting our study findings. Our findings can inform clinicians and caregivers about prevalence, trends in prevalence, and mortality associated with BE. Individual- and community-level factors impacting BE prevalence and mortality could be further explored in future research.

Acknowledgments

We would like to thank Prof. Paul A. Romitti and Dr. Anthony Rhodes (Iowa Registry for Congenital and Inherited Disorders, The University of Iowa, Iowa City, IA) for providing data management guidance at the inception of the study. We would like to acknowledge each ICBDSR member program staff for providing data and Information on the characteristics of their program.

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Key Points

- Total prevalence of BE was 2.58 per 100,000 births.
- Prevalence decreased from 2000 to 2014.
- The first-week mortality was 9.3%.

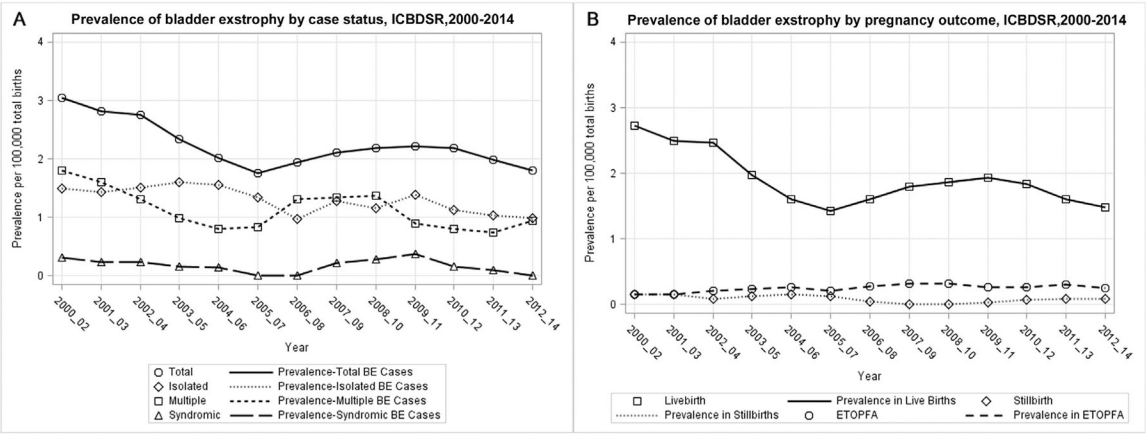

Fig. 1.

Three-year rolling averages of prevalence trends of (**A**) total, isolated, multiple and syndromic bladder exstrophy cases; (**B**) live births, stillbirths, and ETOPFA among bladder exstrophy cases, International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), 2000–2014. BE, bladder exstrophy; ETOPFA, elective termination of pregnancy for fetal anomalies.

Table 1

Description of birth defects surveillance programs contributing to the bladder exstrophy prevalence and mortality study, International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

Country program	Type of program	Coverage	Ascertainment period	Stillbirth definition	ETOPFA allowed	Prenatal screening services
Argentina-RENAC	Hospital-based	National	Hospital discharge	> 500 g	No	Yes, but no official program
Colombia-Bogotá	Hospital-based	Regional	1st day / hospital discharge	> 500 g	Yes, since 2006, but not registered	Yes
Colombia-Cali	Hospital-based	Regional	1st day / hospital discharge	> 500 g	Yes, since 2006, but not registered	Yes
Czech Republic	Population-based	National	15 years	22 weeks or > 500g	Yes	Yes
France-Paris	Population-based	Regional	28 days	22 weeks	Yes	Yes
Germany-Saxony Anhalt	Population-based	Regional	1 year	> 500 g	Yes	Yes, since 1990
Israel-SMC	Hospital-based	Regional[a]	Hospital discharge	Not included	Yes, but not registered	Yes
Italy-Tuscany	Population-based	Regional	1 year	20 weeks	Yes	Yes
Mexico-RYVEMCE	Hospital-based	Regional	3 days	20 weeks or > 500g	No	No
Netherlands-Northern	Population-based	Regional	10 years	24 weeks	Yes	Yes, since 2007
Slovak Republic-STIC	Population-based	National	Hospital discharge	> 500 g	Yes	Yes
South America-ECLAMC	Hospital-based	Regional[b]	Hospital discharge	> 500 g	No[e]	Yes
Spain-ECEMC	Hospital-based	National[c]	3 days	24 weeks or 500 g[d]	Yes, since 1985	Yes
Sweden	Population-based	National	Until 1986: 1 month, since 1987: 1 year	Until 2006: 28 weeks, since 2007: 22 weeks	Yes, since 1999	Yes, since early 1980s
United Kingdom-Wales	Population-based	Regional	18 years	24 weeks	Yes	Yes, since 2003
Ukraine-OMNI-Net	Population-based	Regional	1 year	Until 2005: 28 weeks, since 2006: 22 weeks	Yes	Yes
USA-Arkansas	Population-based	State-wide	2 years	20 weeks	Yes, till 20 weeks	Yes
USA-Atlanta	Population-based	Regional	6 years	20 weeks	Yes[f]	Yes
USA-Texas	Population-based	State-wide	1 year	20 weeks	Yes	Yes
USA-Utah	Population-based	State-wide	2 years	20 weeks	Yes	Yes

Abbreviations: ECEMC, Registry of the Spanish Collaborative Study of Congenital Malformations; ECLAMC, Latin American Collaborative Study of Congenital Malformations; ETOPFA, Elective termination of pregnancy for fetal anomalies; OMNI-Net, Ukraine Birth Defects Prevention Program; RENAC, National Network of Congenital Anomalies of Argentina; RYVEMCE, Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; SMC, Soroka Medical Center; USA, United States of America.

Am J Perinatol. Author manuscript; available in PMC 2023 November 29.

[a] Referral area of one hospital.

[b] Several regions in South America (Argentina, Brazil, Uruguay, Bolivia, Chile. Ecuador, Peru, Colombia, Venezuela).

[c] Data from all regions in Spain in the study period, currently covering 18% of total births in the country

[d] If gestational age of death is not determined (since 1980).

[e] Except for anencephaly.

[f] ETOPFA were ascertained from prenatal diagnostic sites beginning in 1994, prior to that they were only rarely ascertained from hospital records.

Table 2

Description of follow-up method for live births from birth defects surveillance programs contributing to the bladder exstrophy prevalence and mortality study, International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

Country-program	Follow-up until discharge from the maternity hospital	Follow-up by a clinician or program staff	Linkage with death certificates	Maximum follow-up period reported in the study
Argentina-RENAC	Yes	Only until discharge from maternity hospital	No	2–6 days
Colombia-Bogotá	Yes	Yes	No	1 day
Colombia-Cali	Yes	Yes	No	No cases with BE
Czech Republic	No	No	Yes	≥ 5 years
France-Paris	Yes	Yes	No	7–27 days
Germany-Saxony Anhalt	Yes	Yes[b]	No	No mortality reported for live births with BE
Israel-SMC	Yes	Only until discharge from maternity hospital	Yes, 2000 up to 2014	1 day
Italy-Tuscany	No	No	Yes, 1992 up to 2015	No mortality reported for live births with BE
Mexico-RYVEMCE	Yes	Only until discharge from maternity hospital	No	2–6 days
Netherlands-Northern	Yes	Yes	No	7–27 days
Slovak Republic	Yes	Only until discharge from maternity hospital	No	No mortality reported for live births with BE
South America-ECLAMC	Yes	Yes	No	7–27 days
Spain-ECEMC	Yes[a]	Only until discharge from maternity hospital	No	2–6 days
Sweden	No	No	Yes, 1974 up to April 2016	Until 1998: ≥ 5 years, since 1999: 28 days - 11 months
United Kingdom-Wales	Yes	Only until discharge from maternity hospital	Yes, to CP system, until age 18	≥ 5 years
Ukraine-OMNI net	Yes	Yes	No	28 days-11 months
USA-Arkansas	Yes	Only until discharge from maternity hospital	Yes, 1993 up to 2015	≥ 5 years
USA-Atlanta	Yes	Yes	Yes, 1979 up to 2008	≥ 5 years
USA-Texas	Yes	Only until discharge from maternity hospital	Yes, 1996 up to 2013	≥ 5 years
USA-Utah	Yes	Only until discharge from maternity hospital	Yes, until age 2	≥ 5 years

Abbreviations: ECEMC, Registry of the Spanish Collaborative Study of Congenital Malformations; ECLAMC, Latin American Collaborative Study of Congenital Malformations; OMNI-Net, Ukraine Birth Defects Prevention Program; RENAC, National Network of Congenital Anomalies of Argentina; RYVEMCE, Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; SMC, Soroka Medical Center; USA, United States of America.

[a]The participating physicians in the program are especially trained on the ascertainment of birth defects.

[b]Until age 18 years.

Table 3

Total prevalence of bladder exstrophy per 100,000 total births, and proportion of live birth, stillbirths, and ETOPFA among total cases of bladder exstrophy from programs contributing to the bladder exstrophy prevalence and mortality study, International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), 1974–2014

Country-program	Type of registry	Surveillance period	Total births	Total cases of bladder exstrophy	Total prevalence per 100,000 total births (95% CI)	Live birth % (95% CI)	Stillbirth % (95% CI)	ETOPFA % (95% CI)
Argentina-RENAC[a]	H	2009–2014	1,023,108	11	1.08 (0.54, 1.93)	81.8 (52.3, 94.9)	18.2 (5.1,47.7)	–
Colombia-Bogota[b]	H	2001–2014	407,199	2	0.49 (0.05, 1.79)	100 (34.2, 100)	0 (0, 65.8)	–
Colombia-Cali[b]	H	2011–2014	27,294	0	0.00 (2.58, 14.07)	–	–	–
Czech Republic	P	1993–2014	2,269,002	57	2.51 (1.90, 3.25)	93.0 (83.3, 97.2)	0 (0, 6.3)	7.0 (2.8, 16.7)
France-Paris	P	1981–2014	875,241	43	4.91 (3.56, 6.62)	41.9 (28.4, 56.7)	2.3 (0.4, 12.1)	55.8 (41.1, 69.6)
Germany-Saxony Anhalt	P	1980–2014	526,289	17	3.23 (1.88, 5.17)	47.1 (26.2, 69.0)	11.8 (3.3, 34.3)	41.2 (21.6, 64.0)
lsrael-SMC[c]	H	2000–2014	200,660	1	0.50 (0.00, 2.82)	100 (20.7, 100)	–	–
Italy-Tuscany	P	1992–2014	636,562	16	2.51 (1.44,4.08)	68.8 (44.4, 85.8)	6.3 (1.1, 28.3)	25.0 (10.2,49.5)
Mexico-RYVEMCE	H	1978–2013	1,198,579	45	3.75 (2.74, 5.02)	77.8 (63.7, 87.5)	22.2 (12.5, 36.3)	–
Netherlands-Northern	P	1981–2014	562,462	32	5.69 (3.89, 8.03)	87.5 (71.9, 95.0)	0 (0, 10.7)	12.5 (5.0, 28.1)
Slovak Republic	P	2000–2014	778,344	10	1.28 (0.61, 2.37)	100 (72.2, 100)	0 (0, 27.8)	0 (0, 27.8)
South America-ECLAMC[a]	H	1995–2014	2,927,555	61	2.08 (1.59, 2.68)	86.9 (76.2, 93.2)	13.1 (6.8, 23.8)	–
Spain-ECEMC[d]	H	1980–2014	2,891,337	62	2.14 (1.64, 2.75)	98.4 (91.4, 99.7)	1.6 (0.3, 8.6)	–
Sweden[e]	P	1974–2014	4,195,523	148	3.53 (2.98, 4.14)	95.9 (91.4, 98.1)	0.7 (0.1, 3.7)	3.4 (1.5, 7.7)
Ukraine-OMNI-Net	P	2000–2014	404,172	22	5.44 (3.41, 8.24)	95.5 (78.2, 99.2)	0 (0, 14.9)	4.5 (0.8, 21.8)
United Kingdom-Wales	P	1998–2014	569,341	30	5.27 (3.56, 7.52)	63.3 (45.5, 78.1)	6.7 (1.8, 21.3)	30.0 (16.7, 47.9)
USA-Arkansas	P	1993–2012	760,777	22	2.89 (1.81,4.38)	90.9 (72.2, 97.5)	9.1 (2.5, 27.8)	0 (0, 14.9)
USA-Atlanta	P	1974–2008	1,348,237	21	1.56 (0.96, 2.38)	95.2 (77.3, 99.2)	4.8 (0.8, 22.7)	0 (0, 15.5)
USA-Texas	P	1996–2012	5,980,798	116	1.94 (1.60, 2.33)	94.8 (89.2, 97.6)	4.3 (1.9, 9.7)	0.9 (0.2, 4.7)
USA-Utah	P	1999–2012	719,011	15	2.09 (1.17, 3.44)	93.3 (70.2, 98.8)	0 (0, 20.4)	6.7 (1.2, 29.8)
Total pooled results		1974–2014	28,301,491	731	2.58 (2.40, 2.78)			

Abbreviations: CI, confidence Interval; ECEMC, Registry of the Spanish Collaborative Study of Congenital Malformations; ECLAMC, Latin American Collaborative Study of Congenital Malformations; ETOPFA, Elective Termination of Pregnancy for Fetal Anomalies; H, hospital-based program; MCAR, Malta Congenital Anomalies Registry; OMNI-Net, Ukraine Birth Defects Prevention Program; P, population-based program; RENAC, National Network of Congenital Anomalies of Argentina; RYVEMCE, Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; SMC, Soroka Medical Center; TROCA, Tabriz Registry of Congenital Anomalies; USA, United States of America

[a] ETOPFA not allowed.

[b] ETOPFA not registered.

[c] Data on live born children with bladder exstrophy from one hospital.

[d] Spain included Information on ETOPFA from 1995–2014. ETOPFA not routinely registered in all the participating hospitals.

[e] Sweden included Information on ETOPFA from 1999 to 2014.

Table 4

Mortality among bladder exstrophy-affected births from programs contributing to the prevalence and mortality of bladder exstrophy study, International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), 1974–2014

Country-program	Surveillance period	Number of live births with bladder exstrophy	Live birth prevalence per 100,000 total births (95% CI)	Age at death[e]						
				Day 1	Day 2–6	Day 7–27	Day 28–364	Year 1–4	Year ≥5	Death time unknown
				n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Argentina-RENAC[a]	2009–2014	9	0.88 (0.40, 1.67)	5 (55.6)		–	–	–	–	–
Colombia-Bogotá[b]	2001–2014	2	0.49 (0.05, 1.79)	1 (50.0)	–	–	–	–	–	–
Colombia-Cali[b]	2011–2014	0	0.00 (2.58, 14.07)	–	–	–	–	–	–	–
Czech Republic	1993–2014	53	2.34 (1.75, 3.06)	2 (3.8)	0 (0)	0 (0)	1 (1.9)	1 (1.9)	0 (0)	–
France-Paris	1981–2014	18	2.06 (1.22, 3.25)	0 (0)	2 (11.1)	0 (0)	–	–	–	0 (0)
Germany-Saxony Anhalt	1980–2014	8	1.52 (0.65, 3.00)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Israel-SMC[c]	2000–2014	1	0.50 (0.00, 2.82)	1 (100)	–	–	–	–	–	–
Italy-Tuscany	1992–2014	11	1.73 (0.86, 3.09)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mexico-RYVEMCE	1978–2013	35	2.92 (2.03, 4.06)	4 (11.4)	3 (8.6)	–	–	–	–	1 (2.9)
Netherlands-Northern	1981–2014	28	4.98 (3.31, 7.19)	3 (10.7)	2 (7.1)	3 (10.7)	0 (0)	0 (0)	0 (0)	0 (0)
Slovak Republic	2000–2014	10	1.28 (0.61, 2.37)	0 (0)	0 (0)	–	–	–	–	–
South America-ECLAMC[a]	1995–2014	53	1.81 (1.36, 2.37)	13 (24.5)	3 (5.7)	2 (3.8)	0 (0)	–	–	1 (1.9)
Spain-ECEMC[d]	1980–2014	61	2.11 (1.61, 2.71)	2 (3.3)	0 (0)	–	–	–	–	–
Sweden	1974–2014	142	3.38 (2.85, 3.99)	0 (0)	4 (2.8)	1 (0.7)	5 (3.5)	0 (0)	1 (0.7)	0 (0)
United Kingdom-Wales	2000–2014	19	3.34 (2.01, 5.21)	0 (0)	0 (0)	2 (10.5)	0 (0)	0 (0)	0 (0)	–
Ukraine-OMNI-Net	1998–2014	21	5.20 (3.22, 7.94)	0 (0)	0 (0)	0 (0)	3 (14.3)	–	–	0 (0)
USA-Arkansas	1993–2012	20	2.63 (1.61, 4.06)	0 (0)	1 (5.0)	0 (0)	1 (5.0)	0 (0)	0 (0)	0 (0)
USA-Atlanta	1974–2008	20	1.48 (0.91, 2.29)	3 (15.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
USA-Texas	1996–2012	110	1.84 (1.51, 2.22)	8 (7.3)	2 (1.8)	2 (1.8)	4 (3.6)	1 (0.9)	1 (0.9)	0 (0)
USA-Utah	1999–2012	14	1.95 (1.06, 3.27)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.6)	0 (0)	0 (0)
Total pooled results	1974–2014	635	2.24 (2.07, 2.43)	37 (5.8[f])	22 (3.5[f,g])	10 (1.9[f])	14 (2.8[f])	3 (0.7[f])	2 (0.5[f])	2 (0.5[f])

Am J Perinatol. Author manuscript; available in PMC 2023 November 29.

Abbreviations: CI, confidence interval; ECEMC, Registry of the Spanish Collaborative Study of Congenital Malformations; ECLAMC, Latin American Collaborative Study of Congenital Malformations; OMNI-Net, Ukraine Birth Defects Prevention Program; RENAC, National Network of Congenital Anomalies of Argentina; RYVEMCE, Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; SMC, Soroka Medical Center; USA, United States of America.

[a] ETOPFA not allowed.

[b] ETOPFA not registered.

[c] Data on live-born infants with bladder exstrophy from one hospital.

[d] Spain included Information on ETOPFA from 1995 to 2014. ETOPFA not routinely registered in all the participating hospitals.

[e] A hyphen (−) means that the registry did not report follow-up data for that time period.

[f] Excludes programs that have no data on mortality for selected age groups.

[g] Frequency and percentage refer to first-week mortality.

Table 5

First-week mortality by case-status among bladder exstrophy-affected births from programs with available Information on case-status and contributing to the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), 1974–2014

Country-program	Isolated bladder exstrophy[e]						Multiple bladder exstrophy[e]						Syndromic bladder exstrophy[e]					
	Total cases	Type of birth outcome			Mortality		Total Cases	Type of birth outcome			Mortality		Total Cases	Type of birth outcome			Mortality	
		ETOPFA	SB	LB	Day 1	Day 2–6		ETOPFA	SB	LB	Day 1	Day 2–6		ETOPFA	SB	LB	Day 1	Day 2–6
n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Argentina-RENAC[a]	10 (90.9)	–	2 (20.0)	8 (80.0)	4 (50.0[f])		1 (9.1)	–	0 (0)	1 (100)	1 (100[f])		0 (0)	–	–	–	–	
Colombia-Bogotá[b]	0 (0)	–	–	–	–	–	1 (50.0)	–	0 (0)	1 (100)	1 (100.0)	–	1 (50.0)	–	–	1 (100)	–	–
Colombia-Cali[b]	0 (0)	–	–	–	–	–	0 (0)	–	–	–	–	–	0 (0)	–	–	–	–	–
France-Paris	14 (32.6)	7 (50.0)	1 (7.1)	6 (42.9)	0 (0)	0 (0)	22 (51.2)	11 (50.0)	0 (0)	11 (50.0)	0 (0)	2 (18.2)	7 (16.3)	6 (85.7)	0 (0)	1 (14.3)	0 (0)	0 (0)
Germany-Saxony Anhalt	5 (29.4)	1 (20.0)	0 (0)	4 (80.0)	0 (0)	0 (0)	12 (70.6)	6 (50.0)	2 (16.7)	4 (33.3)	0 (0)	0 (0)	0 (0)	–	–	–	–	–
Israel-SMC[c]	0 (0)	–	–	–	–	–	1 (100)	–	–	1 (100)	1 (100)	–	0 (0)	–	–	–	–	–
Mexico-RYVEMCE	21 (46.7)	–	7 (33.3)	14 (66.7)	0 (0)	0 (0)	5 (11.1)	–	0 (0)	5 (100)	1 (20.0)	0 (0)	19 (42.2)	–	3 (15.8)	16 (84.2)	3 (18.8)	3 (18.8)
Netherlands-Northern	15 (46.9)	0 (0)	0 (0)	15 (100)	1 (6.7)	0 (0)	16 (50.0)	3 (18.8)	0 (0)	13 (81.3)	2 (15.4)	2 (15.4)	1 (3.1)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Slovak Republic	9 (90.0)	0 (0)	0 (0)	9 (100)	0 (0)	0 (0)	1 (10.0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	–	–	–	–	–
South America-ECLAMC	16 (26.2)	–	2 (12.5)	14 (87.5)	0 (0)	0 (0)	45 (73.8)	–	6 (13.3)	39 (86.7)	13 (33.3)	3 (7.7)	0 (0)	–	–	–	–	–
Spain-ECEMC[d]	56 (90.3)	–	0 (0)	56 (100)	2 (3.6)	0 (0)	5 (8.1)	–	0 (0)	5 (100)	0 (0)	0 (0)	1 (1.6)	–	1 (100)	0 (0)	0 (0)	0 (0)
Sweden	73 (49.3)	1 (3.4)	0 (0)	72 (98.6)	0 (0)	1 (1.4)	39 (26.4)	4 (10.3)	0 (0)	35 (89.7)	0 (0)	3 (8.6)	36 (24.3)	0 (0)	1 (2.8)	35 (97.2)	0 (0)	0 (0)
Ukraine-OMNI-Net	18 (81.8)	1 (5.6)	0 (0)	17 (94.4)	0 (0)	0 (0)	4 (18.2)	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)	0 (0)	–	–	–	–	–

Country-program	Isolated bladder exstrophy[e]						Multiple bladder exstrophy[e]						Syndromic bladder exstrophy[e]					
	Total cases	Type of birth outcome			Mortality		Total Cases	Type of birth outcome			Mortality		Total Cases	Type of birth outcome			Mortality	
		ETOPFA	SB	LB	Day 1	Day 2–6		ETOPFA	SB	LB	Day 1	Day 2–6		ETOPFA	SB	LB	Day 1	Day 2–6
n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
United Kingdom-Wales	9 (30.0)	0 (0)	0 (0)	9 (100)	0 (0)	0 (0)	20 (66.7)	9 (45.0)	2 (10.0)	9 (45.0)	0 (0)	0 (0)	1 (3.3)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
USA-Utah	10 (66.7)	1 (10.0)	0 (0)	9 (90.0)	0 (0)	0 (0)	4 (26.7)	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)	1 (6.7)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
Total pooled results	256 (51.3)	11 (7.2[g])	12 (4.7)	233 (91.0)	3 (1.3[h])	5 (2.1[h,i])	176 (35.3)	33 (28.0[g])	10 (5.7)	133 (75.6)	18 (13.5[h])	11 (8.3[h,i])	67 (13.4)	7 (15.2[g])	5 (7.5)	55 (82.1)	3 (5.5[h])	3 (5.6[h])

Abbreviations: ECEMC, Registry of the Spanish Collaborative Study of Congenital Malformations: ECLAMC, Latin American Collaborative Study of Congenital Malformations: ETOPFA, Elective Termination of Pregnancy for Fetal Anomalies: LB, Live birth; OMNI-Net, Ukraine Birth Defects Prevention Program; RENAC, National Network of Congenital Anomalies of Argentina; RYVEMCE, Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; SB, Stillbirth; SMC, Soroka Medical Center; USA, United States of America.

Note: Czech-Republic, Italy-Tuscany, USA-Arkansas, USA-Atlanta, USA-Texas not included in the analysis due to lack of Information on case-status of BE.

[a]ETOPFA not allowed.

[b]ETOPFA not registered.

[c]Data on liveborn infants with bladder exstrophy from one hospital.

[d]Spain included Information on ETOPFA from 1995 to 2014. ETOPFA not routinely registered in all the participating hospitals.

[e]A hyphen (−) means that the registry did not report follow-up data for that time period.

[f]Frequency and percentage refer to first-week mortality.

[g]Excludes programs where ETOPFA is unavailable, or does not report on ETOPFA.

[h]Exdudes programs that have no data no mortality for selected age at death.

[i]Argentina is included under day 2–6.