A MULTI-COUNTRY STUDY OF PREVALENCE AND EARLY CHILDHOOD MORTALITY AMONG CHILDREN WITH OMPHALOCELE

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Abstract

Objective: Omphalocele is the second most common abdominal birth defect and often occurs with other structural and genetic defects. Little is known about rates, patterns and trends of mortality after the first year of life in diverse populations. The objective of this study was to determine the prevalence, time trends and mortality during early childhood for infants with omphalocele overall, by geographical region, and by presence of associated anomalies.

Methods: We conducted a retrospective study with 23 birth defect surveillance systems in 18 countries who are members of the International Clearinghouse for Birth Defects Surveillance and Research, which submitted data on cases ascertained between 2000 and 2012. Approximately 16 million pregnancies that ended in livebirths, stillbirths, or elective terminations for fetal anomalies (ETOPFA) were surveyed and cases with omphalocele were included. Overall prevalence and mortality rates for specific time periods were calculated (24 hours, neonatal, infant and early childhood). We used Kaplan-Meier estimates with 95% confidence intervals (CI) to calculate cumulative mortality and joinpoint regression for time trend analyses.

Results: Between 2000 and 2012, the prevalence of omphalocele was 2.6 per 10,000 births (95% CI: 2.5, 2.7). Prevalence decreased minimally during 2000-2012 (average annual percent change = −0.19%, P=0.52). The overall mortality rate for this period was 32.1% (95% CI: 30.2, 34.0). Most deaths occurred during the neonatal period and among children with multiple or syndromic omphalocele. Prevalence and mortality varied by registry type (e.g., hospital- vs. population-based) and inclusion or exclusion of ETOPFA.

Conclusions: The prevalence of omphalocele did not change over time during the study period. Approximately one-third of children with omphalocele did not survive early childhood with most deaths occurring in the neonatal period.

Precis:

In our multi-country study, we found that the prevalence of omphalocele did not change over the study period and about thirty percent of these children will not survive early childhood, with most deaths occurring in the neonatal period.

INTRODUCTION

Omphalocele is the second most commonly occurring abdominal birth defect, with prevalence estimates ranging between 1.0 and 3.8 per 10,000 births globally.[1-12] Characterized by a defect of the midline abdominal wall, a common feature is a thin membranous sac in which the organs (e.g., small intestine, liver, bladder, spleen, stomach, uterus, and ovaries) protrude into the base of the umbilical cord.[13] Omphaloceles range in severity and are classified as small (involving herniation of the bowel and stomach), giant (involving herniation of the bowel, stomach, and liver) and ruptured.[14-16]

The specific etiology of omphalocele remains largely unknown; however, an oft cited hypothesis is failure of the abdomen to completely close at the umbilical ring that results from a defect in lateral folding during embryogenesis.[17] Some risk factors have been identified, which include: advanced and very young maternal age,[7,18,19] maternal pre-pregnancy overweight or obesity,[18,20] nulliparity,[21] multiparity,[22] maternal prenatal alcohol use,[23] maternal cigarette smoking,[23,24] maternal asthma medication use,[25] maternal selective serotonin reuptake inhibitor (SSRI) use,[26] lack of periconceptional/prenatal multivitamin use,[18] abnormality in vitamin B12 production, transport and metabolism,[18] and the 677C–T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene.[18] Additionally, alterations in glycemic control,[18] maternal history of febrile illness,[18] multiple gestation pregnancies,[18,21,23,27-30] and *in vitro* fertilization (IVF) treatments also increase risk.[8,18,21,31,32] Folic acid fortification may decrease risk of omphalocele occurrence.[18] In contrast to other abdominal defects,[13,32] the occurrence of omphalocele has been reported as stable over time[8,13,33-35] in developed countries. Omphalocele seems to occur more frequently in males than females,[2,3,8,18,21,31,33,35,36] in Hispanic populations[21,31] more than non-Hispanic (NH) white, and least frequently among US NH blacks.[31]

Omphalocele can occur in isolation in approximately one-third of all cases, but more often is associated with other major defects.[8,9,37-39] Associated defects mainly occur in the heart, central nervous system, urogenital or musculoskeletal system.[8,9,18,37,38] In about half of non-isolated omphalocele cases, chromosomal anomalies (mainly trisomy 13 and 18) or genetic defects (e.g., Beckwith-Wiedemann syndrome) are found.[9,13,37,40]

The number and type of associated anomalies may also influence the survival of infants with omphalocele. Prior studies show that survival rates for children with omphalocele depend upon the severity of the associated anomalies.[8,41] Children born with isolated omphalocele usually have better survival than children born with omphalocele and other anomalies.[42-44]

A US-based study reported survival rates of 92% (overall) in liveborns; 100% in those with isolated omphalocele; 88% in those with non-isolated omphalocele,[39] but estimates were based on a very small number of prenatally diagnosed cases. Surprisingly, little is known about mortality during early childhood among children with omphalocele. Most studies conducted to date focused on clinical populations and in-patient mortality, with small numbers of omphalocele cases.[39,40,45-48] Few population-based studies have investigated early childhood mortality among children with omphalocele.[8,9,49,50] One US study pooled data from several birth defects registries and reported infant mortality rates.[8] Early and late neonatal mortality was studied in 493 omphalocele cases from Europe[51] and a study from China which used data from a single registry, reported perinatal mortality rates.[49] Thus, information about mortality beyond age one year or in countries outside the US is lacking. Therefore, the purpose of this study was to investigate (1) total and livebirth prevalence, (2) time trends, and (3) mortality related to omphalocele during early childhood (< age 5 years) overall, by country/geographical region and by presence of associated anomalies.

METHODS

Study Design

We conducted a retrospective study using data from 23 birth defects surveillance systems that are members of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR; http://www.icbdsr.org). The ICBDSR was established in 1974 as a not-for-profit volunteer organization affiliated with the World Health Organization. Its purpose is to conduct worldwide surveillance and research into the occurrence and possible causes of birth defects for prevention and reduction of their consequences. As of 2018, 42 birth defects surveillance programs from 36 countries were members and 27 programs submit aggregated data annually on 39 birth defects for the ICBDSR annual report.

Twenty-three member programs of the ICBDSR from 18 countries in North and South America, Europe, and the Middle East submitted data for this project. Surveillance programs were eligible to participate if they ascertained cases of omphalocele and could provide information on vital status. Programs included data on the surveillance method used (hospital- or population-based), year the program began surveillance, years of ascertainment of omphalocele cases, follow-up period for ascertainment of death, method of ascertaining death, program's definition of stillbirth, program's definition of elective terminations, national policy on elective terminations of pregnancy for fetal anomalies (ETOPFA) and availability of prenatal screening and diagnostic services.

Study Population

Each of the 23 programs submitted information on the annual number of omphalocele cases and pregnancy outcomes (live birth, stillbirth, and ETOPFA) from the earliest time period available in each registry until December 31, 2014, the end of the study period (or the most current available data for the registry). Omphalocele (exomphalos) was defined as "a congenital malformation characterized by herniation of abdominal contents through the umbilical insertion and covered by a membrane which may or may not be intact. Excludes: gastroschisis (para-umbilical hernia), aplasia or hypoplasia of abdominal muscles, skin-

covered umbilical hernia"[52] which corresponds to the *International Classification of Disease* (ICD)-10-Clinical Modification (CM) code "Q79.2" and ICD-9-CM code "756.70". Omphalocele cases were classified based on clinical presentation (i.e., isolated, multiple congenital anomalies (MCA), and syndromic) by 16 programs with available data. South America - Latin American Collaborative Study of Congenital Malformations (ECLAMC) and Israel – Soroka Medical Center (SMC) had data on isolated and MCA cases and Czech Republic had data only on genetic cases. We defined isolated cases as pregnancies affected by an omphalocele with no other major malformation present based on the ICBDSR definition. We defined MCA cases as those having two or more major unrelated anomalies in different organ systems (e.g., a fetus/infant who had an omphalocele and craniosynostosis was defined as MCA). Syndromic cases were defined as omphalocele cases that have chromosomal or genetic abnormalities.

Ascertainment of Mortality

Surveillance programs ascertained the vital status of omphalocele cases using various methods, such as active or passive follow-up of cases by clinical or registry staff or linkage to death records (Supplementary Table 1 and 2); some programs used more than one mortality ascertainment method. Length of follow-up for vital status varied by program, e.g., from birth until hospital discharge, first week, first year or longer (Supplementary Table 2). We considered infants deceased if identified as such by the surveillance program through examination of medical files or reports from medical or government death records.

Statistical Analysis

We calculated descriptive statistics for the main study variables and covariates. Three-year rolling averages of overall, live birth, stillbirth and ETOPFA prevalence were calculated and graphed for all 23 programs and for the 17 programs that include data from 2000 to 2012. We examined the prevalence estimates and mortality rates from 2000 to 2012 since that was the time period that the majority of registries had the most complete data. We calculated total prevalence as the total number of omphalocele cases (all pregnancy outcomes combined) divided by the total number of live births and stillbirths per 10,000. The denominator of the prevalence formula did not include ETOPFA because of the lack of information on the total number of terminations for each program. We calculated the average annual percent change (AAPC) from Joinpoint regression analyses. Joinpoint regression analyses were used to assess statistically significant annual changes in prevalence and mortality for nonlinear time trends between 2000 and 2012.[53] Each regression model began with zero joinpoints and up to four joinpoints were allowed in the model if statistically significant changes in rates or direction were noted using a Monte Carlo permutation test until an optimal-fitted model were selected.[53] Among live birth cases with omphalocele, we calculated age-specific mortality as the number of deaths at different ages (day of birth, 1-6 days, 7-27 days, 28-364 days, 1-4 years, and 5 years of age), divided by the total number of live birth cases with omphalocele,. We also examined cumulative percent mortality with corresponding confidence intervals (CI) at specific ages using a modified Kaplan-Meier Product-Limit method for each program, registry type, and total to account for censoring. Survival probability was calculated by taking the cumulative proportion of cases that were still alive at different time periods after birth divided by the total number of live births with

omphalocele. We display cumulative survival graphs (which adjust for differential follow-up time) for North American and European programs, since they had the highest number of participating programs and most complete follow-up of live births through linkage with death certificates. We examined mortality by clinical presentation: isolated, omphalocele cases with MCA and syndromic omphalocele cases for the programs where data was available (18 programs; 78.0%). SAS version 9.4 (SAS Inc., Cary, NC) and Joinpoint Regression Program version 4.7.0.0 were used for the analyses.

Human Subjects

We conducted the research in accordance with the prevailing ethical principles and the Office of Research Integrity and Compliance, Institutional Review Board (IRB) at the University of Arkansas for Medical Science determined this study exempt from IRB review.

RESULTS

Approximately 16 million births occurred during the 2000-2012 study period in the areas monitored by the 23 surveillance programs in 18 countries. Most programs which participated in the study were population-based (n=15, 65%). Sixty-five percent monitored regions of countries or states; only 13% of the programs monitored entire states or provinces, and 22% monitored an entire country. Registries also varied in inclusion of stillbirths and terminations in their case ascertainment methods. Although 22 of the 23 registries included stillbirths in their case ascertainment methods, the definition of stillbirth varied between registries (Supplementary Table 1). Seventy percent (16/23) of registries included ETOPFA in their case ascertainment methods during the entire study period (Supplementary Table 1) and all but one registry were in areas that had access to prenatal screening services.

Prevalence of Omphalocele

During 2000-2012, 4,157 cases of omphalocele were identified from 15,955,640 births, for an overall prevalence of 2.6 per 10,000 births (95% CI: 2.5, 2.7) based on all programs (Table 1). Of the 4,157 cases, 63.0% were live births, 11.5% were stillbirths, 25.2% were ETOPFA and 0.3% had an unknown outcome. The highest ETOPFA proportions were seen in Spain, France (Paris) and Italy (Tuscany) (83%, 71% and 66%, respectively). ETOPFA was more often performed in syndromic omphalocele cases (67%) compared to MCA omphalocele (23%) and isolated omphalocele (20%) (Supplementary Table 3). Total and livebirth prevalence varied by case ascertainment method: hospital-based programs had a higher prevalence of omphalocele cases than population-based programs (3.1 vs. 2.4 and 2.4 vs. 1.4 per 10,000 births, respectively, Table 1). France (Paris) and the UK (United Kingdom, Wales) showed the highest omphalocele prevalences (5.8 and 4.1, respectively), whereas the lowest prevalence were seen in Slovak Republic and Israel (0.8 and 0.9, respectively). The three-year rolling average prevalence between 2000 and 2012 for omphalocele cases by pregnancy outcomes is displayed in Supplementary Figure 1a and the 3-year rolling average prevalence between 2000 and 2012 for omphalocele cases by pregnancy outcomes for surveillance systems which included ETOPFA is displayed in Supplementary Figure 1b. Joinpoint regression analyses showed a negligible decline in the

overall prevalence of omphalocele from 2000-2012 (AAPC = −0.19%; *P*=0.52) (data not shown). Time trends varied by registry type: population-based registries showed an overall modest linear decrease in prevalence over time (AAPC = −0.41%; *P*=0.31). In contrast, hospital-based registries showed a statistically significant increase in prevalence from 2000-2010 (AAPC = 3.19%) followed by a drastic decline from 2010-2012 (AAPC = −21.74%) (data not shown).

The prevalence of omphalocele cases during 2000-2012 by clinical presentation was 1.1 per 10,000 births (95% CI: 1.0, 1.2) for isolated cases, 1.2 per 10,000 births (95% CI: 1.1, 1.3) for omphalocele with MCA and 0.7 per 10,000 births (95% CI: 0.6, 0.8) for syndromic omphalocele (data not shown). Of the registries that reported clinical presentation (n=2,499), 37% were isolated, 42% had multiple congenital anomalies and 21% had chromosomal or genetic abnormalities (Supplementary Table 3).

Overall mortality

During 2000-2012, the overall mortality rate was 32.1% (95% CI: 30.2, 34.0) (Table 2); however, the rate varied by method of case ascertainment and age at death. For hospital-based surveillance systems, the overall mortality rate was 40.8% (95% CI: 37.4, 44.3), whereas for population-based surveillance systems the overall mortality rate was 27.8% (95% CI: 25.7, 30.0). The greatest percentage of deaths occurred within the first 24 hours of life (12.2% overall; 18.9% for hospital-based and 8.7% for population-based) followed by 1-6 days (8.7% overall; 11.5% for hospital-based and 7.5% for population-based). Overall, the largest proportion of deaths (25.9%; 39.7% for hospital-based and 19.9% for population-based) occurred during the neonatal period (0-27 days of life). About 6 percent of deaths occurred between 28 and 364 days of life. Our one-year mortality rate was 30.7%. Five-year mortality rates overall were higher for surveillance systems in countries that did not include ETOPFA/did not register ETOPFA than those that allowed ETOPFA (overall mortality: 42.4% vs. 27.3%) (Table 2).

Figure 1 shows Kaplan-Meier survival curves up to age five years for all liveborn cases with omphalocele in ten surveillance systems with linkage to death certificates in North America and Europe. Overall, survival is somewhat lower in North America compared to Europe. Survival was highest in Italy (Lombardy) (90%, based on 10 cases) and the Czech Republic (83.3%, based on 168 cases) and lowest in Malta (49.9%, based on 12 cases) and Arkansas (59.0%, based on 100 cases).

Time trend analyses for mortality rates between 2000 and 2012 showed an overall pattern of decline during the time period but was not constant. Between 2000 and 2004, mortality rates declined (AAPC = −5.51%; *P*=0.14) but then increased between 2004 and 2007 (AAPC = 8.59%; *P*=0.47) and then decreased again from 2007 to 2012 (AAPC = −10.47%; *P*=0.02). For population-based registries, no time trends in mortality rates were observed (AAPC = −0.01%; *P*=0.96) and hospital-based registries showed a very modest decline in mortality rates between 2000 and 2012 (AAPC = −2.15%; *P*=0.20) (data not shown).

Mortality by Geographic Location

The highest mortality for omphalocele in 2000-2012 was seen for Malta (50%, 12 liveborn cases), Argentina (43.3%, 97 liveborn cases), South America (41.5%, 639 liveborn cases) and USA (Arkansas) (41.0%, 100 liveborn cases) (Table 2). The lowest mortality (0%) was seen for Colombia (Cali) (3 liveborn cases), Iran (33 liveborn cases) and Israel (15 liveborn cases).

Mortality by Clinical Presentation

Mortality rates varied by clinical presentation (**Supplementary Tables 4**). Overall, only 17.2% of children with isolated omphalocele died during the 2000-2012 period. For hospital-based surveillance systems the mortality rate for cases of isolated omphalocele was higher than the population-based programs (23.7% vs. 8.9%). Similar to the pattern observed for all cases of omphalocele, the majority of deaths of isolated omphalocele occurred within the first 24 hours, days 1-6 and days 7-27 (6.1%, 4.6% and 4.6%, respectively)(data not shown). Forty-eight percent of children with omphalocele with MCA died during the 2000-2012 period. Hospital-based surveillance systems also had higher mortality rates of omphalocele with MCA than population-based systems (56.7% vs. 28.5%). The pattern of mortality by age at death for omphalocele with MCA remained similar to the pattern observed for all cases and isolated cases of omphalocele with the majority of deaths occurring within the first 7 days of life and the neonatal period. Children with syndromic omphalocele had the highest mortality rates (55.8%). However, hospital-based programs had a lower mortality rate for syndromic omphalocele cases than population-based programs (46.4% vs. 54.7%, respectively). Unlike the pattern observed for age at death for other clinical presentations of omphalocele, a higher proportion of deaths in syndromic omphalocele occurred during days 1-6 (17.5%) rather than within the first 24 hours of birth (15.6%). In addition, rather than a steady decline in mortality rates as age increases, mortality rates in syndromic omphalocele almost doubled between the 7-27 days and 28-364 days period, from 6.7% to 13.2% (data not shown).

Mortality by clinical presentation and geographic location

The highest mortality in isolated omphalocele was seen in South America (23.4%, 282 liveborn cases) and Argentina (23.3%, 43 liveborn cases). In Italy (Lombardy) and Malta high mortality was observed (33.3%), but each reported only 3 liveborn cases. Also for omphalocele associated with MCA, the highest mortality was seen in Argentina (60.8%, 51 liveborn cases) and South America (55.7%, 357 liveborn cases). In Italy (Tuscany), mortality was 66.7%, but this was based on only 3 liveborn cases. In contrast, among syndromic cases highest mortality was registered in and Malta (100%, only 2 cases), the Czech Republic (78.6%, 14 cases), Italy (Tuscany) (75%, 4 liveborn cases) and Sweden (73.7%, 19 cases).

Figure 2 displays Kaplan-Meier curves up to age five years for isolated, MCA and syndromic omphalocele cases. Survival for omphalocele cases with isolated defects ranged from 66.7% (Italy-Lombardy) to 94.5% (Sweden). For omphalocele cases with MCA, survival ranged from 33.3% (Italy-Tuscany) to 86% (Sweden) and 100% (Italy-Lombardy) based on 66 MCA cases. Syndromic omphalocele cases had survival estimates which ranged

from 25.0% (Italy-Tuscany) to 70.8% (UK-Wales) and 100% (Italy-Lombardy, based on 1 case).

DISCUSSION

The prevalence of omphalocele in our multi-country retrospective study from 2000-2012 was 2.6 per 10,000 births. Approximately one-third of children born with omphalocele died before age 5 years. Most deaths occurred during the first 24 hours after delivery, followed by the first week of life. Once children survived to one year of age, few deaths occurred at older ages. Children born with omphalocele and chromosomal or genetic abnormalities had higher mortality rates than children born with omphalocele alone or those with MCA.

Our prevalence estimate of 2.6 per 10,000 births is consistent with the published literature which reports prevalence estimates that range from 2.8 to 3.8 per 10,000 for studies conducted in the US, United Kingdom and Australia.[7,9,10,54] Our livebirth prevalence of 1.6 per 10,000 births is also consistent with previous reports (1.3 to 1.92 per 10,000 live births).[7-9,31,54] In agreement with prior studies,[8,33,34] we observed no decline in the overall prevalence from 2000-2012 (AAPC = −0.19%; P=0.52). Forty-two percent of our omphalocele cases were MCA and 21% had chromosomal or other genetic abnormalities. Comparing our results to the published literature is somewhat challenging since the prevalence of MCA and chromosomal anomalies among infants with omphalocele varied greatly. Springett et al. observed that 31% of their cases had MCA and 32% were chromosomal.[9] A New York-based study reported that 8% of their infants had chromosomal anomalies.[7] In a US multi-state study, 16.7% of infants had a chromosomal anomaly and more than 50% had MCA.[8] Conner et al. (2018) found that 48% of cases had associated structural anomalies and 19% of cases had a genetic disorder. Agopian et al. reported that 17.4% of their cases had chromosomal anomalies.[21]

Our study demonstrated an overall five-year mortality rate of 32.1%, a one-year mortality rate of 30.7% and an overall mortality rate of 17.2% for isolated cases. We observed that children with omphalocele and chromosomal or genetic abnormalities had the highest mortality rates (55.8%). Most studies in the literature focused on infant mortality and thus only reported first-year mortality rates. Our first-year mortality rate is generally consistent with the published literature. A study based on 1992-1999 data from New York reported a 23% mortality rate.[7] A 2005-2011 study from six British Isles Network of Congenital Anomaly Regional (BINOCAR) registries in England and Wales reported an overall mortality rate of 16%.[9] Marshall et al[8] used 1995-2005 data from twelve state birth defect registries in the US National Birth Defects Prevention Network and reported a 28.7% first year mortality rate. An Australian study using 1980-1990 data reported a 15.6% first-year mortality rate.[54] Corey et al[40] conducted a hospital-based study that included data from 1997-2012 and reported a mortality rate of 18%.

We also demonstrated that in most cases, hospital-based surveillance systems had higher prevalence and mortality among omphalocele cases compared to population-based surveillance systems. Furthermore, surveillance systems in countries which do not include ETOPFA also had higher prevalence and mortality of omphalocele cases. A possible

explanation could be that the most severe omphalocele cases (with MCA or syndromic cases) in these countries are not terminated during pregnancy, leading to a higher mortality in liveborns, compared to countries where ETOPFA is included.

One of the main strengths of our study is its large study population. It is the largest study to date of omphalocele prevalence and mortality with more than 16 million births and over 4,000 cases. Another strength is its ethnic diversity; it includes cases from 18 countries in Europe, North and South America, and the Middle East. Another major strength of the study is that cases were ascertained from hospital- and population–based surveillance systems, which allowed us to examine differences between types of surveillance systems in their prevalence and mortality estimates. Livebirths, stillbirths and terminations of pregnancy for fetal anomalies were included, which allowed us to assess the impact of ETOPFA on prevalence and mortality estimates. In addition, for most registries data was available on the clinical presentation, allowing us to compare mortality between isolated, MCA and syndromic cases of omphalocele.

Notwithstanding, our study has potential limitations that should be considered. The main limitation of our study is the lack of individual level information on patient characteristics, clinical presentation of the defect (e.g., size of the omphalocele), sociodemographic factors and co-morbidities. Another limitation is the varying methodologies that were used by the different programs, especially for ascertainment of mortality. For example, the length of follow up that differed between registries, with six registries only having information on first week mortality and nine registries having follow-up available through age five years. Moreover, our 5-year mortality rates were based on nine registries, one in Israel, five in Europe and three in the US and is therefore not representative for the worldwide mortality of omphalocele. The other registries did have longer follow up, but not all had linked to death certificates and it remains possible that some deaths will have been missed, leading to an underestimation of the mortality. The overall cumulative mortality percentages are based on different follow-up times and should, therefore, be interpreted as the minimum cumulative mortality (with longer follow-up times, the mortality is expected to increase). Also, we did not have information on the exact cause of death, on risk factors for a poor prognosis, on time of diagnosis (pre- or postnatal), or on type of treatment. Variability in the data is present due to limitations with the consistency in data collection for many registries in multiple countries. However, our results are similar to previously published studies and we have described the characteristics of each registry in detail.

Based on a very large multi-country sample of pregnancies and children affected by omphalocele, one-third of livebirths will not survive the first five years of life, with most deaths occurring in the neonatal period. Mortality varied by region of the world, ascertainment method and inclusion or exclusion of ETOPFA. Considerations for future studies may include clinical factors to elucidate the factors associated with mortality and how they might vary by region. It seems clear that omphalocele is quantitatively and qualitatively important and deserves attention. This study provides valuable information for clinicians and public health professionals around the world in planning and providing obstetric and pediatric services. It also makes data available for use in future comparisons in the follow-up of mortality linked to omphalocele.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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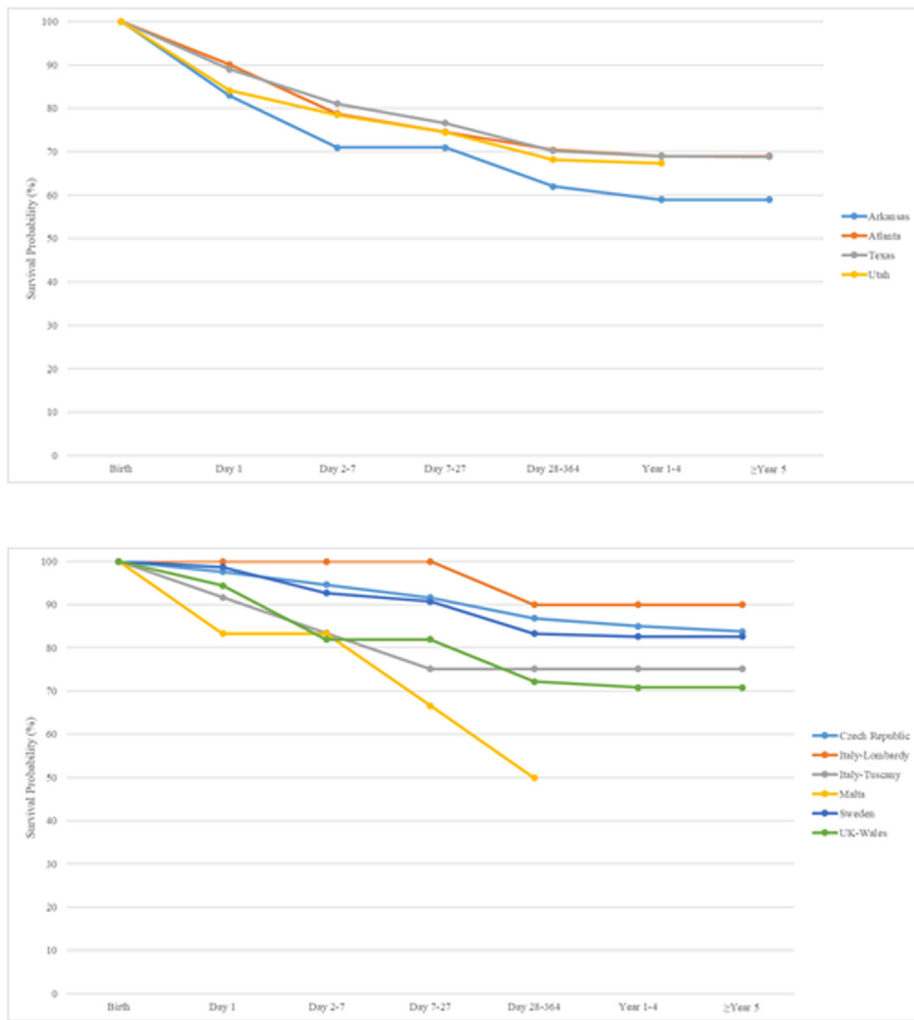
Figure 1.

Kaplan-Meier survival curves up to age five years for all liveborn cases with omphalocele in ten birth defects surveillance systems with linkage to death certificates by continent, 2000-2012

1a: North America

1b Europe: Czech, Italy Lombardy, Italy Tuscany, Malta, Sweden, UK Wales

Figure 2.

Kaplan-Meier survival curves up to age five for isolated, multiple congenital anomalies (MCA) and syndromic omphalocele in six surveillance systems with available data, 2000-2012

2a Isolated Cases: Italy Lombardy, Italy Tuscany, Sweden, UK Wales, USA Utah

2b Omphalocele with Multiple Congenital Anomalies: Italy Lombardy, Italy Tuscany, Sweden, UK Wales, USA Utah

2c. Syndromic omphalocele: Czech Republic[1], Italy Lombardy, Italy Tuscany, Sweden, UK Wales, USA Utah

[1]Czech Republic only provided data on syndromic cases

Table 1.

Total number of births, total number of omphalocele cases, prevalence per 10,000 births and pregnancy outcome proportions by registry type, 23 birth defects surveillance systems in 18 countries for surveillance period 2000-2012

Country - registry	Surveillance period	Total births	Number of cases	Total prevalence[3] per 10,000 births (95% CI)	Livebirth prevalence (95% CI)	Livebirth % (95% CI)	Stillbirth % (95% CI)	ETOPFA[4] % (95% CI)
Hospital-based registries								
Argentina – RENAC[1]	2009-2012	422,173	113	2.7 (2.2, 3.2)	2.3 (1.9, 2.8)	85.8% (78.0, 91.7)	14.2% (8.3, 22.0)	-
Colombia – Bogotá[1]	2000-2012	356,649	53	1.5 (1.1, 1.9)	1.4 (1.0, 1.8)	94.3% (84.3, 98.8)	5.7% (1.2, 15.7)	-
Colombia – Cali[1]	2011-2012	12,762	3	2.4 (0.5, 6.9)	2.4 (0.5, 6.9)	100 (29.2, 100)	0.0% (0.0, 70.8)	-
South America – ECLAMC[1]	2000-2012	2,035,032	794	3.9 (3.6, 4.2)	3.1 (2.9, 3.4)	80.5% (77.6, 83.2)	19.5% (16.8, 22.5)	-
Spain - ECEMC	2000-2012	275,813	88	3.2 (2.6, 3.9)	0.5 (0.3, 0.9)	15.9% (9.0, 25.3)	1.1% (0.03, 6.2)	83.0% (73.5, 90.1)
Mexico – RYVEMCE[1]	2000-2012	287,674	58	2.0 (1.5, 2.5)	1.7 (1.2, 2.2)	84.5% (72.6, 92.7)	15.5% (7.3, 27.4)	-
Iran – TROCA	2004-2012	160,755	37	2.3 (1.6, 3.2)	2.1 (1.4, 2.9)	89.2% (74.6, 97.0)	5.4% (0.7, 18.2)	5.4% (0.7, 18.2)
Israel – SMC[2]	2000-2012	169,973	15	0.9 (0.5, 1.5)	0.9 (0.5, 1.5)	100 (78.2, 100)	-	-
Total	**2000-2012**	**3,720,831**	**1,161**	**3.1 (3.0, 3.3)**	**2.4 (2.3, 2.6)**	**77.5% (75.0, 79.9)**	**16.0% (14.0, 18.3)**	**6.5% (5.2, 8.0)**
Population-based registries								
Czech Republic	2000-2012	1,364,555	310	2.3 (2.0, 2.5)	1.2 (1.1, 1.4)	54.2% (48.5, 59.8)	0.6% (0.1, 2.3)	45.2% (39.5, 50.9)
France - Paris	2000-2012	346,109	202	5.8 (5.1, 6.7)	1.5 (1.1, 1.9)	25.2% (19.4, 31.8)	4.0% (1.7, 7.7)	70.8% (64.0, 77.0)
Germany - Saxony Anhalt	2000-2012	226,907	70	3.1 (2.4, 3.9)	1.0 (0.6, 1.5)	31.4% (20.9, 43.6)	10.0% (4.1, 19.5)	58.6% (46.2, 70.2)
Italy - Lombardy	2003–2012	133,182	24	1.8 (1.2, 2.7)	0.8 (0.4, 1.4)	41.7% (22.1, 63.4)	8.3% (1.0, 27.0)	50.0% (29.1, 70.9)
Italy - Tuscany	2000-2012	379,464	76	2.0 (1.6, 2.5)	0.6 (0.4, 0.9)	31.6% (21.4, 43.3)	2.6% (0.3, 9.2)	65.8% (54.0, 76.3)
Malta – MCAR[1]	2000-2012	52,474	14	2.7 (1.5, 4.5)	2.3 (1.2, 4.0)	85.7% (57.2, 98.2)	14.3% (1.8, 42.8)	-
Netherlands - North	2000-2012	242,341	59	2.4 (1.9, 3.1)	1.2 (0.8, 1.7)	49.2% (35.9, 62.5)	6.7% (1.9, 16.5)	44.1% (31.2, 57.6)
Slovak Republic	2001-2012	667,992	55	0.8 (0.6, 1.1)	0.8 (0.6, 1.0)	92.7% (82.4, 98.0)	1.8% (0.1, 9.7)	5.5% (1.1, 15.1)
Sweden	2000-2012	1,319,370	361	2.7 (2.5, 3.0)	1.1 (1.0, 1.3)	41.3% (36.2, 56.6)	2.2% (1.0, 4.3)	56.5% (51.2, 67.7)
UK - Wales	2000-2012	435,834	179	4.1 (3.5, 4.8)	1.7 (1.3, 2.1)	40.2% (33.0, 47.8)	3.9% (1.6, 7.9)	55.9% (48.3, 63.3)
Ukraine - OMNI-Net[5]	2000-2012	372,434	136	3.7 (3.1, 4.3)	1.3 (1.0, 1.7)	35.3% (27.3, 44.0)	6.6% (3.1, 12.2)	52.9% (44.2, 61.6)
USA - Arkansas[5]	2000-2012	508,654	130	2.6 (2.1, 3.0)	2.0 (1.6, 2.4)	76.9% (68.7, 83.9)	16.9% (10.9, 24.5)	3.8% (1.3, 8.8)

Country - registry	Surveillance period	Total births	Number of cases	Total prevalence[3] per 10,000 births (95% CI)	Livebirth prevalence (95% CI)	Livebirth % (95% CI)	Stillbirth % (95% CI)	ETOPFA[4] % (95% CI)
USA - Atlanta[5]	2000-2008	479,379	137	2.9 (2.4, 3.4)	1.5 (1.2, 1.9)	51.8% (43.1, 60.4)	20.4% (14.0, 28.2)	26.3% (19.1, 34.5)
USA - Texas	2000-2012	5,033,546	1,044	2.1 (2.0, 2.2)	1.6 (1.4, 1.7)	74.9% (72.2, 77.5)	15.7% (13.6, 18.1)	9.4% (7.7, 11.3)
USA - Utah	2000-2012	672,568	199	3.0 (2.6, 3.4)	1.9 (1.6, 2.2)	63.3% (56.2, 70.0)	14.1% (9.6, 19.7)	22.6% (17.0, 29.1)
Total[5]	2000-2012	12,234,809	2,996	2.4 (2.3, 2.5)	1.4 (1.3, 1.5)	57.2% (55.5, 59.0)	9.8% (8.8, 10.9)	32.5% (30.9, 34.3)
All registries[5]	2000-2012	15,955,640	4,157	2.6 (2.5, 2.7)	1.6 (1.5, 1.7)	63.0% (61.6, 64.5)	11.5% (10.6, 12.5)	25.2% (23.9, 26.5)

[1] ETOPFA (elective termination of pregnancy for fetal anomalies) not allowed during (part of) surveillance period

[2] data on live born children with congenital omphalocele from one hospital

[3] denominator includes livebirths and stillbirths

[4] ETOPFA= elective termination of pregnancy for fetal anomalies

[5] percentages of live birth, stillbirth, and ETOFA do not add up to 100% due to unknown pregnancy outcome of some cases

ECEMC= Spanish Collaborative Study of Congenital Malformations; ECLAMC=Latin American Collaborative Study of Congenital Malformations; GP=General Practitioner; MCAR=Malta Congenital Anomalies Registry; OMNI-Net=Ukraine Birth Defects Prevention Program; RENAC=National Network of Congenital Anomalies of Argentina; RYVEMCE= Mexican Registry and Epidemiological Surveillance of Congenital Malformations; TROCA=Tabriz Registry of Congenital Anomalies; SMC=Soroka Medical Center; UK=United Kingdom; USA=United States of America

Table 2.

Mortality rates and Kaplan-Meier Product-Limit estimates with 95% confidence intervals by age at death and registry type for infants born with omphalocele in 18 countries from 23 birth defects surveillance systems, 2000–2012

Country - registry	Surveillance period	Number Livebirths	Kaplan Meier Mortality Estimates for Age at Death[3]								
			< 1 day	1-6 days	7-27 days	0-27 days	28 - 364 days	1-year	1 - 4 years	5 years	5-year (95% CI)[3]
Hospital-based registries											
Argentina – RENAC[1]	2009-2012	97	43.3%		-	43.3%	-	43.3%	-	-	43.3% (33.4, 53.2)
Colombia – Bogotá[1]	2000-2012	50	20.0%	0.0%	-	20.0%	-	20.0%	-	-	20.0% (8.9, 31.1)
Colombia – Cali[1]	2011-2012	3	0.0%	0.0%	-	0.0%	-	0.0%	-	-	0.0% (0.0, 0.0)
South America – ECLAMC[1]	2000-2012	639	23.2%	8.0%	9.2%[5]	40.4%	1.1%[5]	41.5%	-	-	41.5% (37.7, 45.3)
Spain - ECEMC	2000-2012	14	0.0%	7.1%	-	7.1%	-	7.1%	-	-	7.1% (0.0, 20.6)[4]
Mexico – RYVEMCE[1]	2000-2012	49	18.4%	4.1%	-	22.5%	-	22.5%	-	-	22.5% (10.8, 34.1)
Iran - TROCA	2004-2012	33	0.0%	0.0%	-	0.0%	-	0.0%	-	-	0.0% (0.0, 0.0)
Israel – SMC[2]	2000-2012	15	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0% (0.0, 0.0)
Total	**2000-2012**	**900**	**18.9%**	**11.5%**	**9.3%**	**39.7%**	**1.1%**	**40.8%**	**0.0%**	**0.0%**	**40.8% (37.4, 44.3)**
Population-based registries											
Czech Republic	2000-2012	168	2.4%	3.0%	3.0%	8.3%	4.8%	13.1%	1.8%	1.2%	16.1% (10.5, 21.6)
France - Paris	2000-2012	51	5.9%	2.0%	0.0%	7.8%	-	7.8%	-	-	7.8% (0.5, 15.2)
Germany - Saxony Anhalt	2000-2012	22	0.0%	0.0%	4.5%	4.5%	0.0%	4.5%	-	-	4.5% (0.0, 13.2)[4]
Italy - Lombardy	2003-2012	10	0.0%	0.0%	0.0%	0.0%	10.0%	10.0%	0.0%	0.0%	10.0% (0.0, 28.6)[4]
Italy - Tuscany	2000-2012	24	8.3%	8.3%	8.3%	25.0%	0.0%	25.0%	0.0%	0.0%	25.0% (7.7, 42.3)
Malta – MCAR[1]	2000-2012	12	16.7%	0.0%	16.6%	33.3%	16.7%	50.0%	-	-	50.0% (37.3, 62.7)
Netherlands - North	2000-2012	29	3.4%	13.8%	6.9%	24.2%	3.4%	27.6%	-	-	27.6% (11.3, 43.9)
Slovak Republic	2001-2012	51	0.0%	13.7%	2.0%	15.7%	-	15.7%	-	-	15.7% (5.7, 25.7)
Sweden	2000-2012	149	1.3%	6.0%	2.0%	9.3%	7.4%	16.7%	0.7%	0.0%	17.4% (11.4, 23.5)
UK - Wales	2000-2012	72	5.6%	12.5%	0.0%	18.1%	9.7%	27.8%	1.4%	0.0%	29.2% (18.7, 39.7)
Ukraine - OMNI-Net	2000-2012	48	6.3%	6.2%	6.2%	18.7%	2.1%	20.8%	-	-	20.8% (9.3, 32.3)

Country - registry	Surveillance period	Number Livebirths	<1 day	1-6 days	7-27 days	0-27 days	28 - 364 days	1-year	1 - 4 years	5 years	5-year (95% CI)[3]
								Kaplan Meier Mortality Estimates for Age at Death[3]			
USA - Arkansas	2000–2012	100	17.0%	12.0%	0.0%	29.0%	9.0%	38.0%	3.0%	0.0%	41.0% (31.4, 50.6)
USA - Atlanta	2000-2008	71	9.9%	11.3%	4.2%	25.4%	4.2%	29.6%	1.4%	0.0%	31.0% (20.2, 41.7)
USA - Texas	2000-2012	782	11.0%	7.9%	4.5%	23.4%	6.4%	29.8%	1.2%	0.1%	31.1% (27.8, 34.3)
USA - Utah	2000-2012	126	15.9%	5.6%	4.0%	25.4%	6.3%	31.7%	1.6%	-	33.3% (25.1, 41.6)
Total	**2000-2012**	**1,715**	**8.7%**	**7.5%**	**3.6%**	**19.9%**	**6.4%**	**26.3%**	**1.3%**	**0.3%**	**27.8% (25.7, 30.0)**
All registries	**2000-2012**	**2,615**	**12.2%**	**8.7%**	**5.0%**	**25.9%**	**4.8%**	**30.7%**	**1.2%**	**0.2%**	**32.1% (30.2, 34.0)**
ETOPFA not allowed or registered versus ETOPFA allowed											
Not allowed/registered	**2000-2012**	**865**	**19.8%**	**12.0%**	**9.3%**	**41.1%**	**1.3%**	**42.4%**	**0.0%**	**0.0%**	**42.4% (38.9, 45.9)**
Allowed	**2000-2012**	**1,750**	**8.5%**	**7.4%**	**3.6%**	**19.5%**	**6.3%**	**25.8%**	**1.3%**	**0.2%**	**27.3% (25.2, 29.5)**

[1] ETOPFA (elective termination of pregnancy for fetal anomalies) not allowed during (part of) surveillance period

[2] data on live born children with congenital omphalocele from one hospital

[3] cumulative percent mortality was calculated using a modified Kaplan-Meier Product-Limit method to account for censoring and differential length of follow-up

[4] Lower limit confidence intervals fitted to zero

[5] incomplete follow-up, but deaths reported

ECEMC= Spanish Collaborative Study of Congenital Malformations; ECLAMC=Latin American Collaborative Study of Congenital Malformations; GP=General Practitioner; MCAR=Malta Congenital Anomalies Registry; OMNI-Net=Ukraine Birth Defects Prevention Program; RENAC=National Network of Congenital Anomalies of Argentina; RYVEMCE= Mexican Registry and Epidemiological Surveillance of Congenital Malformations; TROCA=Tabriz Registry of Congenital Anomalies; SMC=Soroka Medical Center; UK=United Kingdom; USA=United States of America