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RESEARCH ARTICLE

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A multi-country study of prevalence and early childhood mortality among children with omphalocele

Wendy N. Nembhard[1,2] | Jorieke E. H. Bergman[3] | Maria D. Politis[4] | Jazmín Arteaga-Vázquez[5] | Eva Bermejo-Sánchez[6] | Mark A. Canfield[7] | Janet D. Cragan[8] | Saeed Dastgiri[9] | Hermien E. K. de Walle[3] | Marcia L. Feldkamp[10] | Amy Nance[11] | Miriam Gatt[12] | Boris Groisman[13] | Paula Hurtado-Villa[14] | Kärin Kallén[15] | Danielle Landau[16] | Nathalie Lelong[17] | Jorge Lopez-Camelo[18] | Laura Martinez[19] | Margery Morgan[20] | Anna Pierini[21] | Anke Rissmann[22] | Antonin Šípek[23] | Elena Szabova[24] | Giovanna Tagliabue[25] | Wladimir Wertelecki[26] | Ignacio Zarante[27] | Marian K. Bakker[3] | Vijaya Kancherla[28] | Pierpaolo Mastroiacovo[29]

[1]Arkansas Center for Birth Defects Research and Prevention, Fay W. Boozman College of Public Health, Department of Epidemiology, University of Arkansas for Medical Sciences, Little Rock, Little Rock, Arkansas

[2]Arkansas Reproductive Health Monitoring System, Arkansas Children's Hospital, Little Rock, Arkansas

[3]Department of Genetics, EUROCAT Northern Netherlands, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[4]Arkansas Center for Birth Defects Research and Prevention, Fay W. Boozman College of Public Health, Department of Epidemiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

[5]RYVEMCE (Mexican Registry and Epidemiological Surveillance of Congenital Malformations), Department of Genetics, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

[6]ECEMC (Spanish Collaborative Study of Congenital Malformations) and ECEMC's Clinical Network, Research Unit on Congenital Anomalies, Institute of Rare Diseases Research (IIER), Instituto de Salud Carlos III, Madrid, Spain

[7]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas

[8]Metropolitan Atlanta Congenital Defects Program, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

[9]Health Services Management Research Centre, Tabriz University of Medical Sciences, Tabriz, Iran

[10]Division of Medical Genetics, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah

[11]Utah Birth Defect Network, Bureau of Children with Special Health Care Needs, Division of Family Health and Preparedness, Utah Department of Health, Salt Lake City, Utah

[12]Malta Congenital Anomalies Registry, Directorate for Health Information and Research, Valletta, Malta

[13]National Network of Congenital Anomalies of Argentina (RENAC), National Center of Medical Genetics, National Administration of Laboratories and Health Institutes, National Ministry of Health and Social Development, Buenos Aires, Argentina

[14]Department of Basic Sciences of Health, School of Health, Pontificia Universidad Javeriana Cali, Cali, Colombia

[15]National Board of Health and Welfare, Stockholm, Sweden

[16]Department of Neonatology, Soroka Medical Center, Beer-Sheva, Israel

[17]REMAPAR, Paris Registry of Congenital Malformations, Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in Pregnancy, Paris Descartes University, Paris, France

[18]ECLAMC, Center for Medical Education and Clinical Research (CEMIC-CONICET), Buenos Aires, Argentina

Wendy N. Nembhard and Jorieke E. H. Bergman contributed equally to this study.

[19]Genetics Department, Hospital Universitario Dr Jose E. Gonzalez, Universidad Autonóma de Nuevo León, Nuevo León, Mexico
[20]The Congenital Anomaly Register and Information Service for Wales, Singleton Hospital, Swansea, Wales, UK
[21]Institute of Clinical Physiology, National Research Council/Fondazione Toscana Gabriele Monasterio, Tuscany Registry of Congenital Defects, Pisa, Italy
[22]Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty, Otto-von-Guericke University, Magdeburg, Germany
[23]Department of Medical Genetics, Thomayer Hospital, Prague, Czech Republic
[24]Slovak Teratologic Information Centre (FPH), Slovak Medical University, Bratislava, Slovakia
[25]Lombardy Congenital Anomalies Registry, Cancer Registry Unit, Fondazione IRCCS, Istituto Nazionale dei tumori, Milan, Italy
[26]Omni-Net for Children International Charitable Fund, Rivne, Ukraine
[27]Human Genetics Institute, Pontificia Universidad Javeriana, Bogotá, Colombia
[28]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia
[29]International Center on Birth Defects, International Clearinghouse for Birth Defects Surveillance and Research, Rome, Italy

Correspondence
Wendy N. Nembhard, Department of Epidemiology, Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot #820, Little Rock, AR 72205-7199.
Email: wnnembhard@uams.edu

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Abstract

Background: Omphalocele is the second most common abdominal birth defect and often occurs with other structural and genetic defects. The objective of this study was to determine omphalocele prevalence, time trends, and mortality during early childhood, by geographical region, and the 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 that submitted data on cases ascertained from 2000 through 2012, approximately 16 million pregnancies were surveyed that resulted in live births, stillbirths, or elective terminations of pregnancy for fetal anomalies (ETOPFA) and cases with omphalocele were included. Overall prevalence and mortality rates for specific ages were calculated (day of birth, 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: The prevalence of omphalocele was 2.6 per 10,000 births (95% CI: 2.5, 2.7) and showed no temporal change from 2000–2012 (average annual percent change = −0.19%, $p = .52$). The overall mortality rate was 32.1% (95% CI: 30.2, 34.0). Most deaths occurred during the neonatal period and among children with multiple anomalies 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 showed no temporal change from 2000–2012. Approximately one-third of children with omphalocele did not survive early childhood with most deaths occurring in the neonatal period.

KEYWORDS
mortality, omphalocele, prevalence, registry, surveillance

1 | 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 (Byron-Scott et al., 1998; European Network of Population-Based Registries for the Epidemiological Surveillance of Congenital Anomalies, 2019; Forrester &

Merz, 1999; Goldkrand, Causey, & Hull, 2004; Hemminki, Saloniemi, Kyyronen, & Kekomaki, 1982; Marshall et al., 2015; Parker et al., 2010; Rankin, Dillon, & Wright, 1999; Salihu, Pierre-Louis, Druschel, & Kirby, 2003; Springett et al., 2014; St Louis et al., 2017; Tan et al., 1996). Characterized by a defect of the midline abdominal wall, a common feature is a thin membranous sac in which organs protrude into the base of the umbilical cord (Prefumo & Izzi, 2014). Cases range in severity and can be small, giant or ruptured (Biard et al., 2004; Kamata et al., 1996; Tsakayannis, Zurakowski, & Lillehei, 1996).

The specific etiology of omphalocele remains largely unknown, but could be due to failure of the abdomen to completely close at the umbilical ring (Vermeij-Keers, Hartwig, & van der Werff, 1996). Risk factors for omphalocele include: very young and advanced maternal age (Frolov, Alali, & Klein, 2010; Reefhuis & Honein, 2004; Salihu et al., 2003); maternal prepregnancy overweight or obesity (Frolov et al., 2010; Waller et al., 2007); nulliparity (Agopian, Marengo, & Mitchell, 2009); multiparity (Duong et al., 2012); maternal prenatal alcohol (Mac Bird et al., 2009), cigarette smoking (Feldkamp et al., 2014; Mac Bird et al., 2009), asthma medication (Lin et al., 2012), or selective serotonin reuptake inhibitor use (Alwan, Reefhuis, Rasmussen, Olney, & Friedman, 2007); and the 677C–T mutation in the methylenetetrahydrofolate reductase gene (Frolov et al., 2010). Additionally, alterations in glycemic control (Frolov et al., 2010), history of febrile illness (Frolov et al., 2010), multiple gestation pregnancies (Agopian et al., 2009; Doyle, Beral, Botting, & Wale, 1991; Frolov et al., 2010; Hwang & Kousseff, 2004; Mac Bird et al., 2009; Mastroiacovo et al., 1999; Riley, Halliday, & Lumley, 1998), and in vitro fertilization treatments also increase the risk (Agopian et al., 2009; Frolov et al., 2010; Kirby, 2017; Kirby et al., 2013; Marshall et al., 2015). Folic acid fortification may decrease omphalocele risk (Frolov et al., 2010). The occurrence of omphalocele cases in developed countries has been consistent over time (Allman et al., 2016; Bugge et al., 2017; Bugge & Holm, 2002; Marshall et al., 2015; Prefumo & Izzi, 2014). It occurs more frequently in males than females (Agopian et al., 2009; Bugge et al., 2017; Bugge & Holm, 2002; Calzolari, Bianchi, Dolk, & Milan, 1995; Frolov et al., 2010; Hemminki et al., 1982; Kirby, 2017; Marshall et al., 2015; Tan et al., 1996), in Hispanic populations (Agopian et al., 2009; Kirby, 2017) more than non-Hispanic (NH) whites, and least frequently among United States of America (USA) NH blacks (Kirby, 2017).

Omphalocele can occur in isolation, but more often is associated with other major defects (Benjamin & Wilson, 2014; Conner, Vejde, & Burgos, 2018; Marshall et al., 2015; Springett et al., 2014; Stoll, Alembik, Dott, & Roth, 2008). Associated defects mainly occur in the heart, urogenital, musculoskeletal, or central nervous systems (Benjamin & Wilson, 2014; Frolov et al., 2010; Marshall et al., 2015; Springett et al., 2014; Stoll et al., 2008). In about half of the nonisolated cases, chromosomal anomalies (e.g., trisomy 13 and/or 18) or genetic defects (e.g., Beckwith-Wiedemann syndrome) are found (Benjamin & Wilson, 2014; Corey et al., 2014; Prefumo & Izzi, 2014; Springett et al., 2014).

Prior studies show that omphalocele survival rates depend upon the severity of the associated anomalies (Brantberg, Blaas, Haugen, & Eik-Nes, 2005; Marshall et al., 2015). Children born with isolated omphalocele usually have better survival than those with nonisolated omphalocele (Cohen-Overbeek et al., 2010; Heider, Strauss, & Kuller, 2004; Porter, Benson, Hawley, & Wilkins-Haug, 2009). A USA-based study reported an overall survival rate of 92% in live births (Conner et al., 2018), but estimates were based on a very small number of prenatally diagnosed cases. Only a few population-based studies have investigated early childhood mortality in omphalocele (Deng et al., 2014; Hijkoop et al., 2019; Marshall et al., 2015; Springett et al., 2014). Most studies conducted to date focused on clinical populations and inpatient mortality with a small numbers of cases (Akinkuotu et al., 2015; Conner et al., 2018; Corey et al., 2014; Fratelli et al., 2007; Raymond et al., 2018; Sakonidou, Ali, Farmer, Hickey, & Greenough, 2018). One USA study pooled data from several birth-defect registries and reported infant mortality rates (Marshall et al., 2015), early and late neonatal mortality was studied in Europe (Groen et al., 2017), and a study from China reported perinatal mortality rates using data from a single registry (Deng et al., 2014). Therefore, the purpose of this study was to investigate total and live birth prevalence, time trends, and mortality related to omphalocele during early childhood overall, by country/geographical region, and by presence of associated anomalies.

2 | METHODS

2.1 | Study design

We conducted a retrospective study using data from 23 birth defect surveillance systems that are members of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR [The Centre of the International Clearinghouse for Birth Defects Surveillance and Research, 2014]). 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 the prevention and reduction of their consequences. As of 2018, 42 birth defects surveillance systems from 36 countries were members and 27 programs submit yearly aggregated data on 39 birth defects for the ICBDSR annual report.

Twenty-three programs of the ICBDSR from 18 countries in North and South America, Europe, and the Middle East submitted data for this project. Surveillance systems 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), the year the program began surveillance, the years of ascertainment of omphalocele cases, the follow-up period for ascertainment of death, the method of confirming death, the program's definitions of stillbirth and elective terminations, the national policy on elective terminations of pregnancy for fetal anomalies (ETOPFA), and availability of prenatal screening and diagnostic services.

2.2 | 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; *International Classification of Disease* (ICD)-10-British Pediatric Association extension code (BPA) code Q79.2 or ICD-9-BPA code 756.70) 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" (International Clearinghouse for Birth Defects Surveillance and Research, 2014). Omphalocele cases were classified based on clinical presentation (i.e., isolated, multiple congenital anomalies [MCA], and syndromic) by 18 programs with available data. We defined isolated cases as omphalocele with no other major malformation based on the ICBDSR definition. We defined MCA cases as those occurring with two or more major unrelated anomalies in different organ systems (e.g., an infant having omphalocele and craniosynostosis was defined as MCA) (WHO/CDC/ICBDSR, 2014). We defined syndromic cases as those having related chromosomal or genetic abnormalities. The Latin American Collaborative Study of Congenital Malformations in South America and the Soroka Medical Center in Israel had data on isolated and MCA cases, and Czech Republic had data only on syndromic cases.

2.3 | Ascertainment of mortality

Surveillance systems 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 (Tables S1 and S2); some programs used more than one mortality ascertainment method. Length of follow-up for vital status varied by program, for example, from birth until hospital discharge, first week, first year or longer (Table S2). Some surveillance systems identified death through examination of the medical files by a clinician or registry staff and others ascertained death by linking to death certificates.

2.4 | 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 16 programs that include ETOPFA. We examined the prevalence estimates and mortality rates from 2000 through 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. We calculated the average annual percent change (AAPC) in prevalence and mortality using the Joinpoint Regression Program Version 4.7.0.0 (NCI, Bethesda, MD) (Kim, Fay, Feuer, & Midthune, 2000). Each regression model began with 0 joinpoints; up to 4 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 was selected (Kim et al., 2000). Among live births with omphalocele, we calculated age-specific mortality as the number of deaths at different ages: day of birth, 2–6 days (early neonatal), 7–27 days (late neonatal), 28–364 days (infant), 1–4 years, and $\geq$ 5 years of age divided by the total number of live births with omphalocele. We also examined cumulative percent mortality (with corresponding CIs) at the specific age groups using a modified Kaplan–Meier Product-Limit method for each program, registry type, and total to account for censoring. We generated cumulative Kaplan–Meier survival graphs (which adjust for differential follow-up time)

for North American and European programs because 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, MCA, and syndromic cases for the programs where data was available (18 programs; 78.0%). SAS version 9.4 (SAS Inc., Cary, NC) and the Joinpoint Regression Program were used for the analyses.

2.5 | Human subjects

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

3 | RESULTS

Approximately 16 million births occurred during the study period in the areas monitored by the 23 surveillance systems in 18 countries. Most programs that participated in the study were population-based (n = 15, 65%). There were 3 programs that monitored entire states, and 5 that 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 (Table S1). Seventy percent (16/23) of registries included ETOPFA in their case ascertainment methods during the entire study period (Table S1) and 22 registries were in areas that had access to prenatal screening services.

3.1 | Prevalence of omphalocele

From 2000 through 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 these, 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 (83%), France (71%), and Italy (Tuscany; 66%). ETOPFA was more often performed in syndromic cases (67%) compared to MCA (23%) and isolated omphalocele (20%) (Table S3). Prevalence varied by case ascertainment method: hospital-based systems had a higher prevalence than population-based systems for total omphalocele cases (3.1 vs. 2.4 per 10,000 births) and for live birth cases (2.4 vs. 1.4) (Table 1). The highest prevalences were seen in France (5.8) and the UK (4.1), whereas the lowest prevalences were seen in cigarette smoking Slovak Republic (0.8) and Israel (0.9). The 3-year rolling average prevalence from 2000 to 2012 for omphalocele cases by pregnancy outcomes is displayed in Figure S1a, and the 3-year rolling average prevalence from 2000 to 2012 for omphalocele cases by pregnancy outcomes for surveillance systems that included ETOPFA is displayed in Figure S1b. Joinpoint analyses revealed no temporal trend in the overall prevalence from 2000 to 2012 (AAPC = −0.19%; $p = .52$) (data not shown).

Of the registries that reported clinical presentation (n = 2,499), 37% were isolated, 42% were MCA, and 21% were syndromic (Table S3). The prevalence of omphalocele cases from 2000 to 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 MCA cases, and 0.7 per 10,000 births (95% CI: 0.6, 0.8) for syndromic cases (data not shown).

3.2 | Overall mortality

From 2000 to 2012, the overall mortality rate was 32.1% (95% CI: 30.2, 34.0) (Table 2); however, the rate varied when calculated by the method of case ascertainment and the age at death. Fifteen registries were followed up to 1 year (65.2%) and 10 registries were followed up for longer than 1 year (43.5%). For hospital-based systems, the overall mortality rate was 40.8% (95% CI: 37.4, 44.3), whereas for population-based systems the overall mortality rate was 27.8% (95% CI: 25.7, 30.0). On the day of birth, 12.2% of live born omphalocele cases died (18.9% for hospital-based and 8.7% for population-based), compared to 8.7% in the 2–7 day period (11.5% for hospital-based and 7.5% for population-based). The mortality was highest in the neonatal period, in which 25.9% of live born omphalocele cases died (39.7% for hospital-based and 19.9% for population-based). Between 28 and 364 days of life, 4.8% of live born cases died and the overall mortality rate at 1 year was 30.7%. Overall 5-year mortality rates were higher for surveillance systems in countries that did not include or register ETOPFA (42.4%) than those did (27.3%) (Table 2).

Figure 1 shows Kaplan–Meier survival curves up to age 5 years for all live birth cases with omphalocele in 10 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%; 10 cases) and

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 defect surveillance systems in 18 countries for surveillance period 2000–2012

Country—registry	Surveillance period	Total births	Number of cases	Total prevalence[c] per 10,000 births (95% CI)	Live birth prevalence (95% CI)	Live birth % (95% CI)	Stillbirth % (95% CI)	ETOPFA% (95% CI)
Hospital-based systems								
Argentina—RENAC[a]	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[a]	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[a]	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[a]	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[a]	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[b]	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 systems								
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[a]	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[d]	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[d]	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)
USA—Atlanta[d]	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)

TABLE 1 (Continued)

Country—registry	Surveillance period	Total births	Number of cases	Total prevalence[c] per 10,000 births (95% CI)	Live birth prevalence (95% CI)	Live birth % (95% CI)	Stillbirth % (95% CI)	ETOPFA% (95% CI)
Total[d]	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[d]	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)

Abbreviations: ECEMC, Spanish Collaborative Study of Congenital Malformations; ECLAMC, Latin American Collaborative Study of Congenital Malformations; ETOPFA, elective termination of pregnancy for fetal anomalies; 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; SMC, Soroka Medical Center; TROCA, Tabriz Registry of Congenital Anomalies.

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

[b]Data on live birth children with omphalocele from one hospital.

[c]Denominator includes live births and stillbirths.

[d]Percentages of live birth, stillbirth, and ETOPFA do not add up to 100% due to unknown pregnancy outcome of some cases.

the Czech Republic (83.3%; 168 cases) and lowest in Malta (49.9%; 12 cases) and USA (Arkansas) (59.0%; 100 cases).

Time trend analyses for mortality rates from 2000 to 2012 showed an overall pattern of decline during the time period but was not constant. From 2000 through 2004, mortality rates declined (AAPC = −5.51%; p = .14), but increased from 2004 and 2007 (AAPC = 8.59%; p = .47), and decreased again from 2007 to 2012 (AAPC = −10.47%; p = .02). For population-based systems, no time trends in mortality rates were observed (AAPC = −.01%; p = .96) and hospital-based systems showed a very minor decline in mortality rates from 2000 to 2012 (AAPC = −2.15%; p = .20) (data not shown).

3.3 | Mortality by geographic location

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

3.4 | Mortality by clinical presentation

Mortality rates varied by clinical presentation (Table S4). During the time period, the overall mortality of isolated omphalocele cases was 17.2%. Hospital-based systems had a higher rate (23.7%) than the population-based systems (8.9%). Similar to the pattern observed for all cases, the majority of isolated omphalocele deaths occurred at the day of birth (6.1%), days 2–6 (46%), and days 7–27 (4.6%) (data not shown). During the time period, the overall mortality of MCA cases was 48%. Hospital-based systems had a higher rate (56.7%) than population-based systems (28.5%). Similar to the pattern observed for all cases, the majority of MCA deaths occurred within the first week of life and the neonatal period. During the time period, the overall mortality of syndromic cases was the highest (55.8%). However, hospital-based systems had a lower mortality rate (46.4%) than population-based systems (54.7%). Unlike the pattern observed for all cases, a higher proportion of deaths in syndromic omphalocele occurred during days 2–6 (17.5%) rather than at the day of birth (15.6%). Additionally, rather than a steady decline in mortality rates as age increases, mortality rates in syndromic cases almost doubled between the 7–27 days period (6.7%) and 28–364 days period (13.2%) (data not shown).

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 live births	Number of deaths	Kaplan–Meier mortality estimates for age at Death[3]								
				Day 1	2–6 days	7–27 days	1–27 days	28–364 days	1-year	1–4 years	≥5 years	5-year (95% CI)[c]
Hospital-based systems												
Argentina—RENAC[a]	2009–2012	97	42	43.3%		—	43.3%	-	43.3%	—	—	43.3% (33.4, 53.2)
Colombia—Bogotá[a]	2000–2012	50	10	20.0%	0.0%	—	20.0%	—	20.0%	—	—	20.0% (8.9, 31.1)
Colombia—Cali[a]	2011–2012	3	0	0.0%	0.0%	—	0.0%	—	0.0%	—	—	0.0% (0.0, 0.0)
South America – ECLAMC[a]	2000–2012	639	265	23.2%	8.0%	9.2%[e]	40.4%	1.1%[e]	41.5%	—	—	41.5% (37.7, 45.3)
Spain - ECEMC	2000–2012	14	1	0.0%	7.1%	—	7.1%	—	7.1%	—	—	7.1% (0.0, 20.6)[d]
Mexico—RYVEMCE[a]	2000–2012	49	11	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, 0.0)
Israel—SMC[b]	2000–2012	15	0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0% (0.0, 0.0)
Total	2000–2012	900	329	18.9%	11.5%	9.3%	39.7%	1.1%	40.8%	0.0%	0.0%	40.8% (37.4, 44.3)
Population-based systems												
Czech Republic	2000–2012	168	27	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	4	5.9%	2.0%	0.0%	7.8%	—	7.8%	—	—	7.8% (0.5, 15.2)
Germany—Saxony Anhalt	2000–2012	22	1	0.0%	0.0%	4.5%	4.5%	0.0%	4.5%	—	—	4.5% (0.0, 13.2)[d]
Italy—Lombardy	2003–2012	10	1	0.0%	0.0%	0.0%	0.0%	10.0%	10.0%	0.0%	0.0%	10.0% (0.0, 28.6)[d]
Italy—Tuscany	2000–2012	24	6	8.3%	8.3%	8.3%	25.0%	0.0%	25.0%	0.0%	0.0%	25.0% (7.7, 42.3)
Malta—MCAR[a]	2000–2012	12	6	16.7%	0.0%	16.6%	33.3%	16.7%	50.0%	—	—	50.0% (37.3, 62.7)
Netherlands—North	2000–2012	29	8	3.4%	13.8%	6.9%	24.2%	3.4%	27.6%	—	—	27.6% (11.3, 43.9)
Slovak Republic	2001–2012	51	8	0.0%	13.7%	2.0%	15.7%	—	15.7%	—	—	15.7% (5.7, 25.7)
Sweden	2000–2012	149	26	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	21	5.6%	12.5%	0.0%	18.1%	9.7%	27.8%	1.4%	0.0%	29.2% (18.7, 39.7)

TABLE 2 (Continued)

Country—registry	Surveillance period	Number live births	Number of deaths	Kaplan–Meier mortality estimates for age at Death[3]								
				Day 1	2–6 days	7–27 days	1–27 days	28–364 days	1-year	1–4 years	≥5 years	5-year (95% CI)[c]
Ukraine—OMNI-Net	2000–2012	48	10	6.3%	6.2%	6.2%	18.7%	2.1%	20.8%	—	—	20.8% (9.3, 32.3)
USA—Arkansas	2000–2012	100	41	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	22	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	243	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	42	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	466	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	795	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	334	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	461	8.5%	7.4%	3.6%	19.5%	6.3%	25.8%	1.3%	0.2%	27.3% (25.2, 29.5)

Abbreviations: ECEMC, Spanish Collaborative Study of Congenital Malformations; ECLAMC, Latin American Collaborative Study of Congenital Malformations; 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; SMC, Soroka Medical Center; TROCA, Tabriz Registry of Congenital Anomalies.

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

[b]Data on live birth children with congenital omphalocele from one hospital.

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

[d]Lower limit confidence intervals fitted to 0.

[e]Incomplete follow-up, but deaths reported.

3.5 | Mortality by clinical presentation and geographic location

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

Figure 2 displays Kaplan–Meier curves up to age 5 years for isolated, MCA, and syndromic omphalocele cases. Survival for isolate cases ranged from 66.7% (Italy-Lombardy) to 94.5% (Sweden). For MCA cases, survival ranged from 33.3% (Italy-Tuscany) to 86% (Sweden) and 100% (Italy-Lombardy) based on 66 cases. Survival for syndromic cases ranged from 25.0% (Italy-Tuscany) to 70.8% (UK) and 100% (Italy-Lombardy; 1 case).

4 | DISCUSSION

4.1 | Main findings

The prevalence of omphalocele in our multi-country retrospective study from 2000 to 2012 was 2.6 per 10,000 births. Approximately one-third of children born with omphalocele died before age 5 years. Most deaths occurred on the day of birth, followed by the first week of life. Once children survived to 1 year of age, few deaths occurred at older ages. Children born with syndromic omphalocele had a higher mortality rate than children born with isolated omphalocele or MCA.

4.2 | Interpretation

Our prevalence estimate of 2.6 per 10,000 births is consistent with the published literature which reports prevalence estimates that range from 2.1 to 3.8 per 10,000 for studies conducted in the US, UK, and Australia (Byron-Scott et al., 1998; Goldkrand et al., 2004; Salihu et al., 2003; Springett et al., 2014; Stallings et al., 2019). Our live birth prevalence of 1.6 per 10,000 births is also consistent with previous reports (1.3 to 1.92 per 10,000 live births) (Byron-Scott et al., 1998; Kirby, 2017; Marshall et al., 2015; Salihu et al., 2003; Springett et al., 2014). In agreement with prior studies (Allman et al., 2016; Bugge & Holm, 2002; Marshall et al., 2015), we observed no temporal change in the overall prevalence from 2000 to 2012 (AAPC = −0.19%; $p = 0.52$). Forty-two percent of our omphalocele cases were MCA and 21% were syndromic. Comparing our results to the published literature is somewhat challenging because the prevalence of MCA and syndromic cases varied greatly. Springett et al. observed that 31% of their cases were MCA and 32% were syndromic (Springett et al., 2014). A New York-based study reported that 8% of their cases were syndromic (Salihu et al., 2003). In a USA multi-state study, more than 50% of cases were MCA and 16.7% were syndromic (Marshall et al., 2015). Conner et al. found that 48% of cases were MCA and 19% of cases were syndromic (Conner et al., 2018). Agopian et al. reported that 17.4% of their cases were syndromic (Agopian et al., 2009).

Our study demonstrated an overall 5-year mortality rate of 32.1% and a 1-year overall mortality rate of 30.7%. For isolated cases, the overall 5-year mortality rate was 17.2%. We observed that children with syndromic omphalocele had the highest mortality rates (55.8%). The 5-year mortality rate should be interpreted with caution, as the 5-year follow up was not applied to all registries. Most studies in the literature focused on infant mortality and thus only reported the 1-year mortality rates. Our infant mortality rate is generally consistent with the published literature. A study based on 1992–1999 data from New York reported a 23% infant mortality rate (Salihu et al., 2003). A 2005–2011 study from six British Isles Network of Congenital Anomaly Regional (BINOCAR) registries in England and Wales reported an overall infant mortality rate of 16% (Springett et al., 2014). Marshall et al. used 1995–2005 data from 12 state birth defect registries in the USA National Birth Defects Prevention Network and reported a 28.7% 1-year mortality rate (Marshall et al., 2015). An Australian study using 1980–1990 data reported a 15.6% 1-year mortality rate (Byron-Scott et al., 1998).

We also demonstrated that in most cases, hospital-based surveillance systems had higher prevalence and mortality compared to population-based surveillance systems. Furthermore, surveillance systems in countries that do not include ETOPFA also had higher prevalence and mortality. A possible explanation could be that the most severe (MCA or syndromic) cases in these countries are not terminated during pregnancy, leading to a higher mortality in live birth, compared to countries where ETOPFA is included.

4.3 | Strengths and limitations

One of the main strengths of our study is its large study population. It is the largest study to date of omphalocele

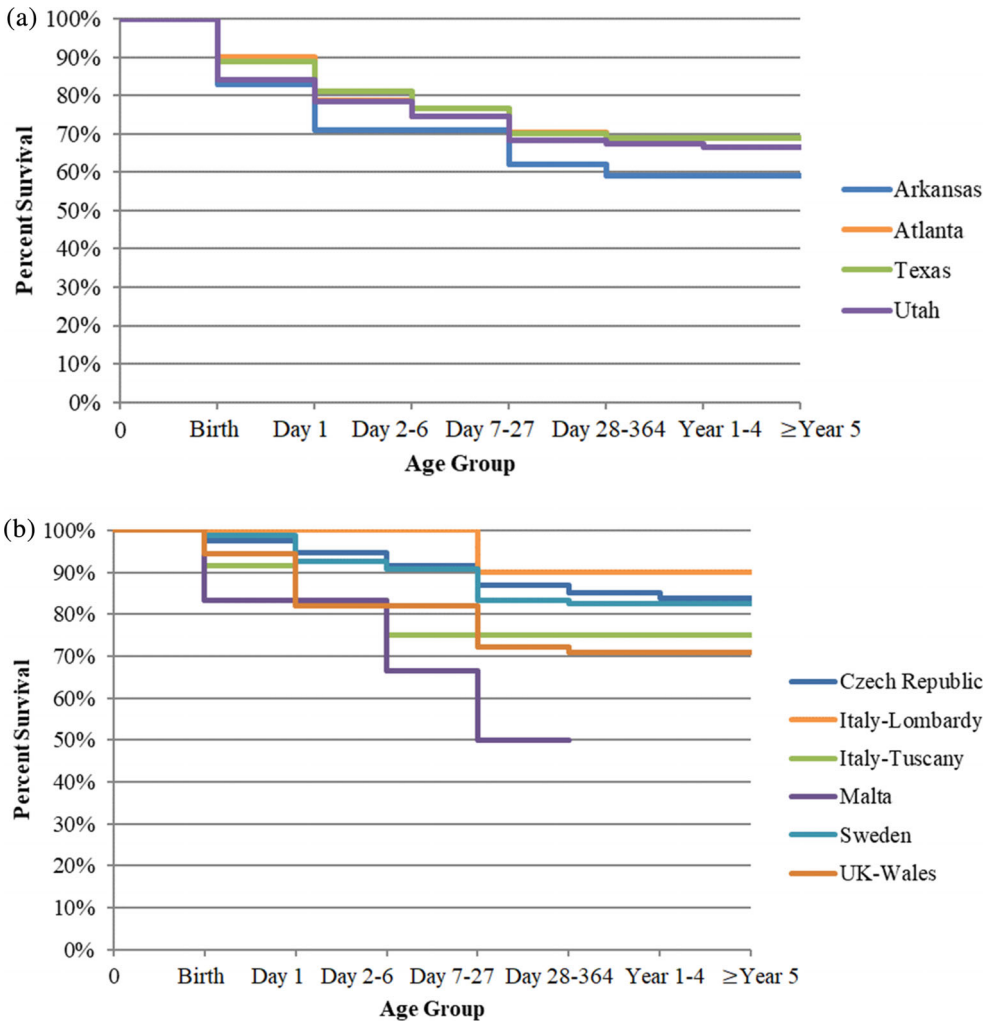

FIGURE 1 Kaplan–Meier survival curves up to age 5 years for all live birth cases with omphalocele in 10 birth defects surveillance systems with linkage to death certificates by continent, 2000–2012 (a) North America. (b) Europe: Czech, Italy Lombardy, Italy Tuscany, Malta, Sweden, UK Wales

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. Live births, stillbirths, and ETOPFA were included, which allowed us to assess the impact of ETOPFA on prevalence and mortality estimates. In addition, data for most registries were available on the clinical presentation, allowing us to compare mortality between isolated, MCA, and syndromic omphalocele cases.

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, severity), sociodemographic factors, and comorbidities. 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 6 registries only having information on first week mortality and 9 registries having follow-up available through age 5 years. Moreover, our 5-year mortality rates were based on 9 registries; 1 in Israel, 5 in Europe, and 3 in the US, and is, therefore, not representative for the worldwide omphalocele mortality. 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, risk factors for a poor prognosis, time of diagnosis (prenatal or postnatal), or the type of treatment. Variability in the data is 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.

5 | CONCLUSION

Based on a very large multi-country sample of pregnancies and children affected by omphalocele, one-third of live births will not survive the first 5 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 aspects 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

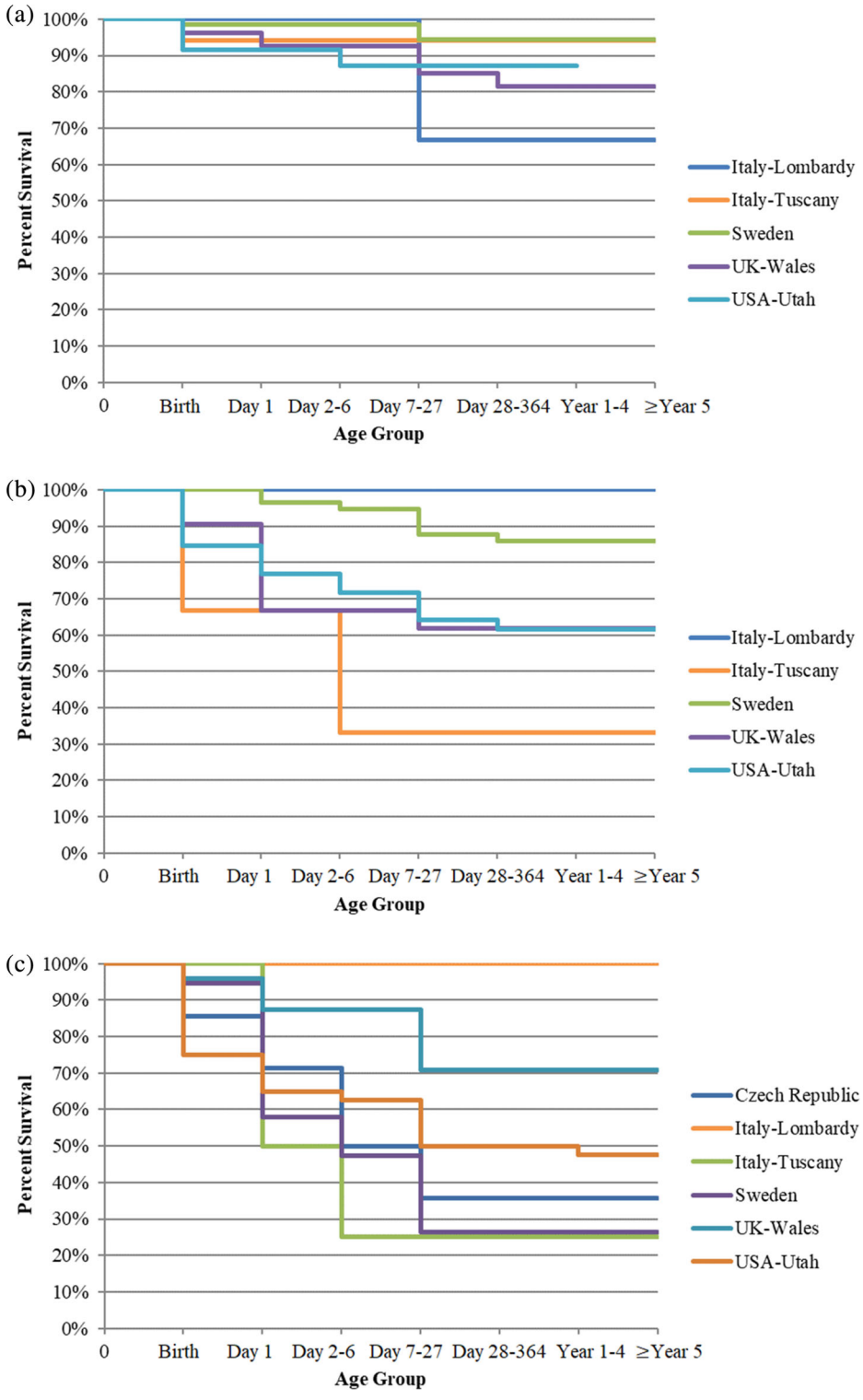

FIGURE 2 Kaplan–Meier survival curves up to age 5 for isolated, multiple congenital anomalies, and syndromic omphalocele in six surveillance systems with available data, 2000–2012. (a) Isolated Cases: Italy Lombardy, Italy Tuscany, Sweden, UK Wales, USA Utah. (b) Omphalocele with multiple congenital anomalies: Italy Lombardy, Italy Tuscany, Sweden, UK Wales, USA Utah. (c) Syndromic Omphalocele: Czech Republic (Czech Republic only provided data on syndromic cases), Italy Lombardy, Italy Tuscany, Sweden, UK Wales, USA Utah

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.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, funding, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the International Clearinghouse for Birth Defects Surveillance and Research. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Wendy N. Nembhard https://orcid.org/0000-0002-8318-4049
Jorieke E. H. Bergman https://orcid.org/0000-0002-3929-3619
Maria D. Politis https://orcid.org/0000-0002-7511-8383
Marcia L. Feldkamp https://orcid.org/0000-0001-9171-7848
Amy Nance https://orcid.org/0000-0002-4326-890X
Boris Groisman https://orcid.org/0000-0001-6263-2562
Anke Rissmann https://orcid.org/0000-0002-9437-2790
Wladimir Wertelecki https://orcid.org/0000-0001-5864-5985
Vijaya Kancherla https://orcid.org/0000-0002-2803-8030

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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