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Original article

Prevalence and mortality in children with congenital diaphragmatic hernia: a multicountry study

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ABSTRACT

Purpose: This study determined the prevalence, mortality, and time trends of children with congenital diaphragmatic hernia (CDH).
Methods: Twenty-five hospital- and population-based surveillance programs in 19 International Clearinghouse for Birth Defects Surveillance and Research member countries provided birth defects mortality data between 1974 and 2015. CDH cases included live births, stillbirths, or elective termination of pregnancy for fetal anomalies. Prevalence, cumulative mortality rates, and 95% confidence intervals (CIs) were calculated using Poisson regression and a Kaplan–Meier product-limit method. Joinpoint regression analyses were conducted to assess time trends.
Results: The prevalence of CDH was 2.6 per 10,000 total births (95% CI: 2.5–2.7), slightly increasing between 2001 and 2012 (average annual percent change = 0.5%; 95% CI:−0.6 to 1.6). The total percent mortality of CDH was 37.7%, with hospital-based registries having more deaths among live births than population-based registries (45.1% vs. 33.8%). Mortality rates decreased over time (average annual percent change = −2.4%; 95% CI: −3.8 to 1.1). Most deaths due to CDH occurred among 2- to 6-day-old infants for both registry types (36.3%, hospital-based; 12.1%, population-based).
Conclusions: The mortality of CDH has decreased over time. Mortality remains high during the first week and varied by registry type.

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Introduction

Congenital diaphragmatic hernia (CDH) is a severe birth defect characterized by a diaphragmatic malformation allowing abdominal organs to protrude into the thoracic cavity [1]. Worldwide, CDH occurs approximately 2.3 in every 10,000 live births [2]. Respiratory failure, due to pulmonary hypertension and pulmonary hypoplasia, is the leading cause of CDH-related mortality [3,4]. Approximately 64% of CDH cases are isolated, and 36% have additional anomalies [1]. Infants with CDH have significant morbidity and mortality, with a mortality rate between 30% and 60% or as high as 89% when additional chromosomal or structural anomalies are present [5–10].

The prenatal and postnatal diagnosis, clinical management, and treatment of infants with CDH have significantly improved in recent years [11–13]. Despite these advances, the total mortality rate has remained high over the last 3 decades [14–17]. Many studies have examined specific treatments and their associated mortality rates in single tertiary centers but have shown no significant improvements in survival rates [18,19]. In addition, mortality estimates may vary among registries and single institutions because of differences in case ascertainment and reporting [20].

Worldwide, CDH mortality and time trends are understudied; this study provides the opportunity to use aggregated data from multiple countries to further explore these topics. Our study's purpose was to examine (1) the prevalence, (2) mortality, and (3) time trends of infants with CDH among birth outcomes and clinical presentation using data collected by population- and hospital-based birth defects surveillance programs from countries affiliated with the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR).

Methods

Study design and setting

The ICBDSR, affiliated with the World Health Organization, is a voluntary, nonprofit organization established in 1974 (http://www.icbdsr.org/) whose aim is to prevent birth defects and reduce the related burden of their consequences by assembling birth defect surveillance and research programs worldwide. Currently, 42 surveillance programs with birth defects registries (either hospital- or population-based) from 36 countries are members, with 27 contributing data annually. Each registry contributes aggregated data on children and fetuses affected with any of 39 different birth defects. Yearly data are collected on the total number of live births and stillbirths to assist in prevalence estimation and surveillance. These data are summarized at http://www.icbdsr.org/wp-content/annual_report/Report2014.pdf.

We analyzed data from birth years 1974–2015 and further examined the prevalence estimates and mortality rates from 2001 to 2012, a period when program data were most complete. We used data from 25 ICBDSR member programs, representing 19 countries in the Middle East, Europe, and North, Central, and South America (Appendix Table A) that collected data on both CDH and associated mortality. Each program submitted information on the annual number of CDH cases and pregnancy outcomes (live birth, stillbirth, and elective termination of pregnancy for fetal anomalies (ETOPFA)). We examined the surveillance method type (hospital-based vs. population-based registries), year that surveillance began, CDH surveillance period, criteria used to define a stillbirth, national legislation regarding ETOPFA, and prenatal screening service availability (Appendix Table B.1).

Congenital diaphragmatic hernia case definition

ICBDSR defines CDH as "a congenital malformation characterized by herniation into the thorax of abdominal contents through a defect of the diaphragm. Includes: total absence of the diaphragm. Excludes: hiatus hernia, eventration of the diaphragm, and phrenic palsy." CDH corresponds to ICD-10 code Q79 and ICD-9 code 756.6. Each program provided information on the number of CDH cases and the pregnancy outcomes (live birth, stillbirth, or ETOPFA) per year. Each case was also classified by clinical presentation for 18 programs (72%). Isolated cases were defined as infants or fetuses with CDH, but no other unrelated major birth defects. Cases with multiple congenital anomalies (MCAs) were defined as CDH with any unrelated major anomalies [21]. Syndromic cases were defined as having CDH as part of a recognized syndrome or a genetic disorder [21].

Mortality

Appendix Table B.2 presents the methods of each program for follow-up of live-born cases. Each program provided information on mortality based on their follow-up methods. These methods included follow-up until discharge from the maternity hospital (20 of 25 programs), follow-up by a clinician or registry staff (9 of 25 programs), or follow-up by linkage with death certificates (12 of 25 programs). Mortality was examined using six age-at-death categories: less than 1 day, 2–6 days, 7–27 days, 28–364 days, 1–4 years, and greater than or equal to 5 years.

Statistical analysis

CDH prevalence was calculated for each program and registry type (hospital-vs. population-based) as the total number of CDH cases (live births + stillbirths + ETOPFA) divided by the total number of births (live births + stillbirths). ETOPFA was not included in the denominator of the prevalence formula because of incomplete information on terminations for each program. A Poisson approximation of the binomial distribution was used for prevalence estimation and associated 95% confidence intervals (CIs). The proportion of CDH cases resulting in a stillbirth or ETOPFA were also calculated.

Age-specific mortality was calculated for each of the six age-at-death categories as the number of deaths among the live-born cases divided by the total number of live-born CDH cases. The cumulative percent mortality and corresponding CIs were calculated using a Kaplan–Meier product-limit method for each program, registry type, and the total to account for censoring. Mortality was examined by clinical presentation (isolated, MCA, syndromic) when available.

Total prevalence was calculated as a 3-year rolling average and graphed for each registry type and geographic region of the participating programs from 2001 to 2012. Joinpoint regression analysis was used to identify statistically significant temporal trends in CDH prevalence and mortality by registry type. Iran-TROCA was excluded from the Joinpoint regression analysis because of outliers in its prevalence rates compared with the other registries. Survival probability of live births was calculated and graphed for North American and European programs, which had the highest number of participating programs and a follow-up period of 5 years or more. Survival probability was calculated as the cumulative proportion of cases that died at different time periods after birth subtracted from the total number of live births with CDH.

Each program had locally approved ethics procedures, and because this study was conducted using aggregated data, no additional ethics committee approval was required.

Results

Of the 25 ICBDSR member programs we studied (Appendix Table A), eight were hospital-based and 17 were population-based. Most population-based programs had regional coverage ($n = 9$) (the remaining had national coverage [$n = 5$] or state coverage [$n = 3$]). The ascertainment period and stillbirth definition varied among programs. Six of the 25 programs did not allow ETOPFA. Most of the 25 programs did offer prenatal screening services in recent years (Appendix Table B.1).

Prevalence

All programs combined, from 1974 to 2015, reported 28,701,270 births and 7581 CDH cases, resulting in a total CDH prevalence of 2.6 per 10,000 births (95% CI: 2.5–2.7). Table 1 presents the program-specific CDH prevalence (per 10,000 births) and pregnancy outcome types (live births, stillbirths, and ETOPFA) by registry type from 2001 to 2012, a period when program data were most complete. For this time period, the average CDH prevalence was 2.8 per 10,000 births (95% CI: 2.7–2.9). Hospital-based registries had an average CDH prevalence of 2.8 per 10,000 births (95% CI: 2.6–2.9), similar to population-based registries (2.8 per 10,000 births; 95% CI: 2.7–2.9). Programs with the lowest CDH prevalence were hospital-based registries (Spain-ECEMC, Mexico-RYVEMCE [1.1 per 10,000 for both]). The average proportion of stillbirths for all registries was 3.7% (95% CI: 3.2–4.3), similar to the proportion of stillbirths among population-based registries (3.0% [95% CI: 2.5–3.6]), whereas hospital-based registries had a higher proportion of stillbirths (5.6% [95% CI: 4.4–7.0]). Population-based registries were more often from countries that allowed ETOPFA and, therefore, had a higher proportion of ETOPFA (10.2%) than the two hospital-based registries in regions where ETOPFA was allowed (2.8%).

Data on birth defects co-occurring with CDH were provided by 18 programs (72%) (Table 1). The percentages of isolated CDH cases were similar between hospital-based and population-based programs. In total, 63.8% of CDH cases were isolated. For CDH cases that were MCA or syndromic, the differences between hospital-based and population-based programs were larger. Hospital-based registries had higher percentages of CDH cases with MCA than population-based registries (32.2% and 27.9%, respectively), whereas proportions of syndromic cases were higher among population-based registries (10.0%) than those among hospital-based registries (2.1%). The highest percentages of stillbirth cases among all total stillbirths were MCA and syndromic cases identified from hospital-based registries (13.5% and 13.0%, respectively).

Figure 1 displays the 3-year rolling averages of total CDH prevalence by registry type and region from 2001 to 2012. Population-based registries had the highest averages; hospital-based programs had the lowest, with the total average in the middle. Regionally, Central and South America showed an increased 3-year rolling average prevalence. Figure 2A–C display the Joinpoint regression graphs for total prevalence, as well as for each registry. Joinpoint regression showed an increasing linear trend in prevalence between 2001 and 2012, with an average annual percent change (AAPC) of 0.5% (95% CI: −0.6 to 1.6). Time trends also differed by registry type. Population-based registries had a greater AAPC during this period than hospital-based registries (0.9% (95% CI: −0.6 to 2.4) vs. −0.2% (95% CI: −2.3 to 2.0)).

Table 1
Total number of births, total number of CDH cases, prevalence per 10,000 births, stillbirth proportion, ETOPFA proportion, and pregnancy outcome of infants affected by CDH in accordance with clinical presentation by registry type for the surveillance period of 2001–2012

Country- registry	Total births	Total cases of CDH	Total prevalence per 10,000 births (95% CI)	SB %	ETOPFA %	Isolated CDH				MCA CDH				Syndromic CDH			
						Total cases N (%)	Pregnancy outcome			Total cases N (%)	Pregnancy outcome			Total cases N (%)	Pregnancy outcome		
							LB %	SB %	ETOPFA %		LB %	SB %	ETOPFA %		LB %	SB %	ETOPFA %
Hospital-based registries																	
Argentina-RENAC[*]	422,173	139	3.3 (2.7, 3.9)	4.3	—	100 (71.9)	99.0	1.0	0.0	35 (25.2)	91.4	8.6	0.0	4 (2.9)	50.0	50.0	0.0
Colombia-Bogotá[†]	356,454	72	2.0 (1.6, 2.5)	2.8	—	58 (80.6)	98.3	1.7	0.0	12 (16.7)	91.7	8.3	0.0	2 (2.7)	100	0.0	0.0
SA-ECLAMC[*,‡]	1,847,181	716	3.8 (3.4, 4.2)	7.4	—	443 (61.9)	91.5	2.5	0.0	273 (38.1)	84.6	15.4	0.0	—	—	—	—
Spain-ECEMC	1,195,025	130	1.1 (0.9, 1.3)	1.3	25.4	84 (64.6)	75.0	0.0	25.0	32 (24.6)	68.8	6.2	25.0	14 (10.8)	64.3	7.1	28.6
Mexico-RYVEMCE[*]	264,306	30	1.1 (0.8, 1.6)	10.0	—	19 (63.3)	89.5	10.5	0.0	8 (26.7)	87.5	12.5	0.0	3 (10.0)	100	0.0	0.0
Iran-TROCA[§]	160,755	92	5.7 (4.6, 7.0)	1.1	1.1	—	—	—	—	—	—	—	—	—	—	—	—
Israel-SMC[‖]	157,544	39	2.5 (1.8, 3.4)	0.0	—	36 (92.7)	100	0.0	0.0	3 (7.3)	100	0.0	0.0	0 (0.0)	0.0	0.0	0.0
TOTAL	4,403,438	1218	2.8 (2.6, 2.9)	5.6	2.8	740 (65.7)	95.1	2.0	2.9	363 (32.2)	84.3	13.5	2.2	23 (2.1)	69.6	13.0	17.4
Population-based registries																	
Costa Rica-CREC[*,¶]	876,607	137	1.6 (1.3, 1.8)	1.5	—	95 (69.3)	100	0.0	0.0	—	—	—	—	—	—	—	—
Czech Republic[#]	1,273,386	326	2.6 (2.3, 2.9)	0.0	18.7	—	—	—	—	—	—	—	—	7 (2.1)	57.1	0.0	42.9
France–Paris	319,636	85	2.7 (2.1, 3.3)	2.4	30.5	53 (62.4)	86.8	1.9	11.3	18 (21.2)	50.0	0.0	50.0	14 (16.4)	14.3	7.1	78.6
Germany-Saxony Anhalt	208,108	58	2.8 (2.1, 3.6)	3.4	20.7	37 (63.8)	89.2	2.7	8.1	14 (24.1)	50.0	0.0	50.0	7 (12.1)	57.1	14.3	28.6
Italy-Lombardy	133,182	37	2.8 (2.0, 3.8)	16.2	16.2	16 (43.2)	81.3	12.5	6.2	21 (52.5)	57.1	19.0	23.8	3 (7.5)	33.3	0.0	66.7
Italy-Tuscany	352,844	76	2.2 (1.7, 2.7)	1.3	19.8	—	—	—	—	—	—	—	—	—	—	—	—
Malta-MCAR[*]	48,202	26	5.4 (3.5, 7.9)	7.7	—	17 (65.4)	94.1	5.9	0.0	6 (23.1)	100	0.0	0.0	3 (11.5)	66.7	33.3	0.0
Netherlands-Northern	221,846	60	2.7 (2.1, 3.5)	10.0	15.0	41 (68.3)	82.9	7.3	9.8	8 (13.3)	62.5	12.5	25.0	11 (18.4)	54.5	18.2	27.3
Slovak Republic[†]	667,992	119	1.8 (1.5, 2.1)	1.7	0.8	81 (68.1)	97.6	1.2	1.2	38 (31.9)	97.4	2.6	0.0	—	—	—	—
Sweden	1,230,002	397	3.2 (2.9, 3.6)	1.3	28.7	224 (56.4)	83.5	0.9	15.6	137 (34.5)	62.0	1.5	36.5	36 (9.1)	16.6	2.8	80.6
Ukraine-OMNI-Net	347,418	105	3.0 (2.5, 3.7)	16.2	21.9	68 (64.8)	64.7	13.2	20.6	33 (31.4)	45.4	24.2	24.2	4 (3.8)	75.0	0.0	25.0
United Kingdom–Wales	404,385	160	4.0 (3.4, 4.6)	0.6	26.9	86 (54.0)	82.5	1.2	16.3	47 (29.6)	72.3	0.0	27.7	26 (16.4)	50.0	0.0	50.0
USA–Arkansas[§,**]	470,593	144	3.1 (2.6, 3.6)	2.8	0.0	—	—	—	—	—	—	—	—	—	—	—	—
USA–Atlanta[§,**]	609,837	208	3.4 (3.0, 3.9)	3.8	9.1	—	—	—	—	—	—	—	—	—	—	—	—
USA–Texas	4,668,071	1289	2.8 (2.6, 2.9)	2.6	1.2	—	—	—	—	—	—	—	—	—	—	—	—
USA–Utah	624,990	217	3.5 (3.0, 4.0)	6.0	2.8	132 (60.8)	96.2	2.3	1.5	59 (27.2)	88.1	10.2	1.7	26 (12.0)	73.1	15.4	11.5
Total	12,457,099	3444	2.8 (2.7, 2.9)	3.0	10.2	850 (62.1)	87.6	2.8	9.4	381 (27.9)	68.8	5.8	24.9	137 (10.0)	43.8	7.3	48.9
All registries	16,860,537	4662	2.8 (2.7, 2.9)	3.7	8.3	1590 (63.8)	91.1	2.5	6.4	744 (29.8)	76.3	9.5	13.8	160 (6.4)	47.5	8.1	44.4

CREC = Costa Rican Birth Defect Registry; ECEMC = Spanish Collaborative Study of Congenital Malformations; ECLAMC = Latin American Collaborative Study of Congenital Malformations; LB = live birth; 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 External Congenital Malformations; SA = South America; SB = stillbirth; SMC = Soroka Medical Center; TROCA = Tabriz Registry of Congenital Anomalies; USA = United States of America.

[*] ETOPFA not allowed.
[†] ETOPFA not registered.
[‡] Data only provided for isolated and MCA cases.
[§] No data provided for clinical presentation.
[‖] Data on live-born children with congenital diaphragmatic hernia from one hospital.
[¶] Data only provided for isolated cases.
[#] Data only provided for syndromic cases.
[**] Percentages of live birth, stillbirth, and ETOFA do not add up to 100% because of unknown pregnancy outcome of some cases.

Mortality

Table 2 displays mortality among live births with CDH by age of death. About 37.7% of live births with CDH resulted in death among all registries from 2001 to 2012. Hospital-based registries had a higher cumulative percent mortality (45.1%) than population-based registries (33.8%).

Time trend analyses for mortality rates using Joinpoint regression graphs are displayed in Figure 2D–F. The time trend analyses showed a significant linear decrease in mortality rates from 2001 to 2012 (AAPC = −2.4%; 95% CI: −3.8 to 1.1). However, time trends in mortality rates varied by registry type. For population-based registries, mortality rates decreased almost imperceptibly with an AAPC of −0.2% (95% CI:−2.2 to 1.8), whereas hospital-based registries had a more profound decrease in mortality with an AAPC of −0.7% (95% CI: −2.7 to 1.3).

The total mortality for the first 24 hours of life was 7.4% and for the first week of life was 26.4% (data not shown). MCA cases had higher first week mortality than isolated cases in both hospital-based registries (58.8% vs. 36.2%) and population-based registries (29.4% vs. 21.3%); however, syndromic cases had a higher first week mortality in population-based registries than in hospital-based registries (46.7% vs. 18.8%) (data not shown). The highest proportion of death occurred among infants aged 2–6 days (19.0%) among all the programs, with the hospital-based registries having a higher proportion of death than population-based registries (36.3% vs. 12.1%). Syndromic and MCA cases had higher 1-week mortality rates (45.2% and 40.8%) than isolated cases (28.6%) (data not shown). The total mortality rate during the 27-day neonatal period (31.8%) was only slightly higher than that in the first week of life (26.4%). Registries in countries or regions where ETOPFA was prohibited had higher first-week mortality than those where ETOPFA was allowed. The total cumulative 5-year mortality rate was 37.7%, 45.1% among hospital-based registries, and 33.8% among population-based registries.

Figure 3 presents the Kaplan–Meier survival curves from 2001 to 2012 for total cases and by registry type. Population-based registries had the highest survival probability and hospital-based registries had the lowest.

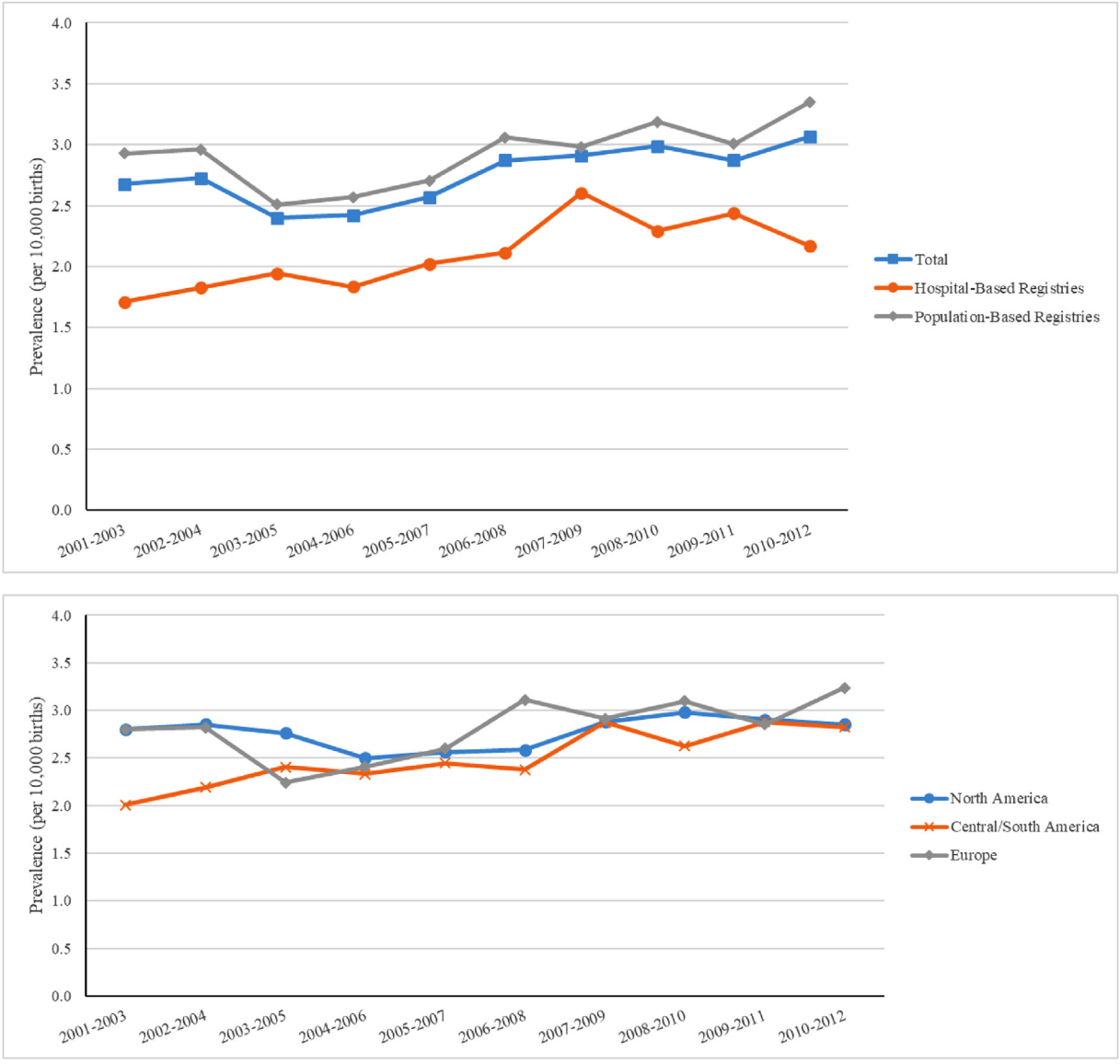

Fig. 1. Three-year rolling averages of congenital diaphragmatic hernia prevalence by registry type and continent for 25 surveillance systems in 19 countries from 2001 to 2012. [a] Iran-TROCA and Israel-SMC are not included in these graphs.

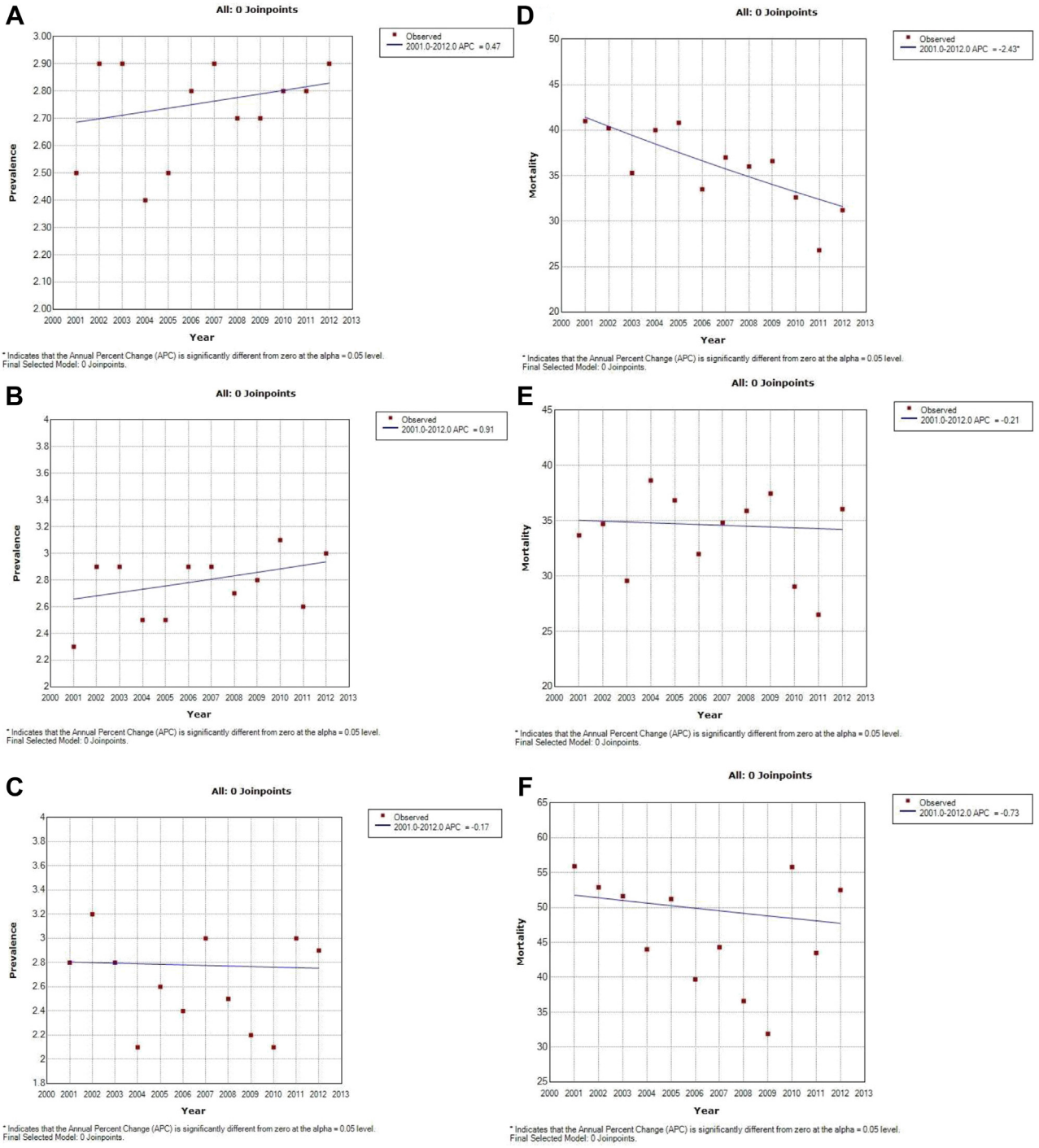

Fig. 2. Joinpoint regression models for prevalence and mortality of congenital diaphragmatic hernia by registry type from 2001 to 2012. (A) total prevalence; (B) prevalence for population-based registries; (C) prevalence for hospital-based registries; (D) total mortality; (E) mortality for population-based registries; (F) mortality for hospital-based registries.

Discussion

This study is one of the first studies to examine CDH mortality across multiple countries. The CDH prevalence from 2001 to 2012 was 2.8 per 10,000 births. The majority of CDH cases were isolated (63.8%). We found that the highest mortality among infants with CDH occurred in the first week (26.1%) in many countries. The average survival probability for children 5 years or older with CDH varied between 64% and 77%.

The CDH prevalence (2.6 per 10,000 births from 1974 to 2015) is similar to previously published estimates. In a large European population-based study, the prevalence was 2.3 per 10,000 births from 1980 to 2009 [22]. Among other population-based registries in the United States of America, the prevalence ranged from 2.5 to

Table 2
Mortality in CDH-affected live births for the surveillance period of 2001–2012

Country registry	Surveillance period	Live births with CDH	Age at death						
			Day 1	Day 2–day 6	Day 7–day 27	Day 28–day 364	Years 1–4	Year 5 and above	Kaplan–Meier mortality estimate (95% CI)
Hospital-based registries									
Argentina-RENAC*	2009–2012	133	48.9%§		—	—	—	—	48.9% (40.4, 57.4)
Colombia-Bogotá†	2001–2012	70	20.0%	—	—	—	—	—	20.0% (10.6, 29.4)
South America-ECLAMC*	2001–2012	663	0.2%	50.1%	5.6%	0.9%	—	—	56.7% (52.9, 60.5)
Spain-ECEMC	2001–2012	94	7.4%	4.3%	—	—	—	—	11.7% (5.2, 18.2)
Mexico-RYVEMCE*	2001–2012	27	3.7%	3.7%	—	—	—	—	7.4% (0.0, 17.3)‖
Iran-TROCA	2004–2012	90	2.2%	0.0%	—	—	—	—	2.2% (0.0, 5.3)‖
Israel-SMC‡	2001–2012	39	23.1%	7.7%	17.9%	5.1%	—	—	53.8% (38.2, 69.5)
Total		1116	3.0%	36.3%	3.9%	0.7%	-	-	45.1% (42.0, 48.1)
Population-based registries									
Costa Rica-CREC*	2001–2012	135	6.7%	37.0%	6.7%	2.2%	2.2%	0.0%	54.8% (46.4, 63.2)
Czech Republic	2001–2013	265	8.7%	12.8%	2.3%	3.4%	1.1%	0.0%	28.3% (22.9, 33.7)
France–Paris†	2001–2012	57	5.3%	22.8%	5.3%	—	—	—	33.4% (21.1, 45.6)
Germany-Saxony Anhalt	2001–2012	44	15.9%	4.5%	2.3%	4.5%	0.0%	0.0%	27.2% (14.1, 40.4)
Italy-Lombardy	2003–2012	25	0.0%	16.0%	8.0%	—	—	—	24.0% (7.2, 40.7)
Italy-Tuscany	2001–2012	60	6.7%	8.3%	8.3%	0.0%	—	—	23.3% (12.6, 34.0)
Malta-MCAR*	2001–2012	24	33.3%	4.2%	0.0%	0.0%	0.0%	0.0%	37.5% (18.1, 56.9)
Netherlands-Northern	2001–2012	45	11.1%	4.4%	2.2%	15.6%	0.0%	0.0%	33.3% (19.5, 47.1)
Slovak Republic	2001–2012	116	0.0%	41.4%	3.4%	—	—	—	44.8% (35.8, 53.9)
Sweden	2001–2012	278	10.4%	3.6%	2.9%	5.4%	1.1%	0.4%	23.8% (18.7, 28.7)
Ukraine-OMNI-Net	2001–2012	62	16.1%	21.0%	0.0%	6.5%	—	—	43.6% (31.2, 55.9)
United Kingdom–Wales	2001–2012	116	8.6%	17.2%	3.4%	5.2%	1.7%	0.0%	36.1% (27.5, 44.9)
USA–Arkansas	2001–2012	139	14.4%	10.8%	4.3%	2.9%	2.2%	0.0%	34.6% (26.6, 42.4)
USA–Atlanta	2001–2012	161	8.7%	6.8%	6.8%	1.9%	0.0%	0.0%	24.2% (17.6, 30.8)
USA–Texas	2001–2012	1240	8.3%	9.4%	8.5%	7.7%	1.4%	0.1%	35.4% (32.7, 38.0)
USA–Utah	2001–2012	198	12.6%	7.1%	4.5%	7.6%	0.5%	0.0%	32.3% (25.8, 38.8)
Total		2965	9.1%	12.1%	5.9%	5.5%	1.1%	0.1%	33.8% (32.1, 35.5)
All registries	2001–2012	4081	7.4%	19.0%	5.4%	4.9%	0.9%	0.1%	37.7% (36.2, 39.2)

CREC = Costa Rican Birth Defect Registry; 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 External Congenital Malformations; SMC = Soroka Medical Center; TROCA = Tabriz Registry of Congenital Anomalies; USA = United States of America.

* ETOPFA not allowed.

† ETOPFA not registered.

‡ Data on live-born children with congenital diaphragmatic hernia from one hospital.

§ Percentage refers to first-week mortality.

‖ Lower limit confidence intervals fitted to zero.

3.8 per 10,000 births [23,24]. Our study found a nonsignificant upward trend in prevalence of CDH, with an AAPC of 0.5%. This is similar to a study, which found an annual percent change of 0.3% of prevalence of CDH [10]. In addition, we found that mortality decreased over time. This may suggest that in general, treatment and management has improved. Trends in both prevalence and mortality from Joinpoint did not have any inflection points, which implies that the change has stayed constant over time.

Our mortality results are similar to previously published studies that showed CDH-related infant mortality rates ranging from 20% to 50% [25–28]. A U.S. population-based study reported a mortality rate of 28% for infants with CDH up to the first week of life, similar to the total mortality rate for the first week of life in our study (26.1%) for 2001 to 2012 [29]. 'Hidden mortality' (unreported CDH cases involving death during gestation, shortly after birth, or before surgery) may exist among hospital-based registries and referral institutions [30]. Many of the outcomes derived from population-based studies have shown lower survival than studies from single institutions [23,31,32]. Our study contrasts with this concept, with population-based registries showing a lower mortality rate than hospital-based registries. This may be due to the fact that only two of the seven hospital-based registries included ETOPFA, and none of the registries reported treatment type. In addition, Israel-SMC was the only single-hospital registry; other hospital-based registries contained from 3 to 70 hospitals in their programs. Many other factors such as geographic regions, socioeconomic status, case ascertainment, and case selection biases need to be studied to examine the differences in mortality among hospital- and population-based registries. Prevalence rates were similar among the hospital- and population-based registries; however, hospital-based registries had higher cumulative percent mortality than population-based registries. Both registry types had the highest mortality among infants with CDH aged 2–6 days, with hospital-based registries having double the mortality rate of population-based registries.

Currently, there is no common protocol in the treatment and management of infants with CDH. The use of early versus delayed surgical correction is not clearly defined for infants with CDH;

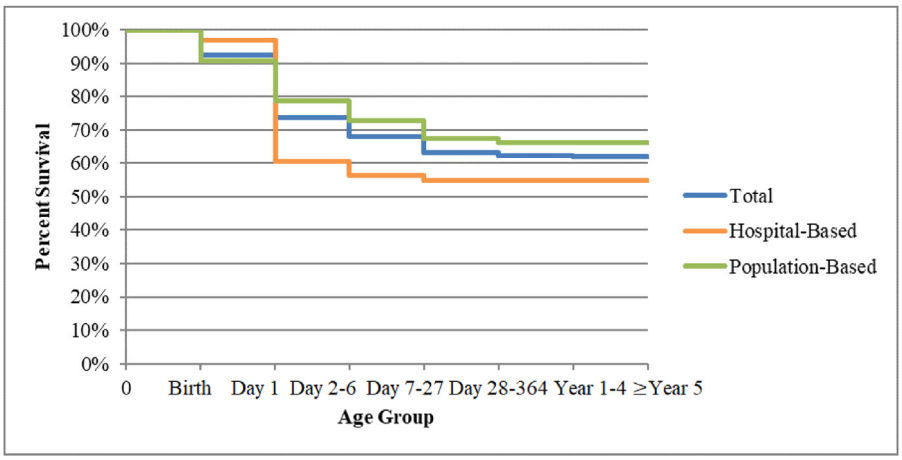

Fig. 3. Kaplan–Meier survival curves up to age 5 for total mortality and by registry type from 2000 to 2012.

however, there is a general trend toward delaying repair until after a stabilization period [33–36]. Often, the stabilization period is supported by an effort to reduce the risk of pulmonary hypertension [18]. Gentili et al. found a stabilization interval of 43.9 ± 38.7 hours (range 22–168 hours) before patients underwent surgical correction [37]. It is possible that the lack of a standardized treatment protocol before surgical repair might contribute to infant mortality within the first week of life [35,38]. In addition, many of the hospital-based registries are in developing countries. The higher mortality rate during the first week could be explained by fewer resources, underreporting, and less health care access in these more resource-constrained countries compared with the higher-income countries that have population-based registries.

We observed higher proportions of ETOPFA among population-based registries and higher proportions of stillbirths among hospital-based registries. This association may be due to the higher number of programs that include ETOPFA belonging to population-based registries, whereas the higher stillbirth rates among hospital-based registries may be due to the fact that only two programs reported ETOPFA. Among the hospital-based registries, Mexico-RYVEMCE had the highest stillbirth proportion, yet the lowest CDH prevalence among all the programs. This program was also the only program that did not offer prenatal screening services, which may affect a mother's decision on the outcome of the pregnancy if CDH is detected early. Most countries or regions that allowed ETOPFA had higher proportions of ETOPFA than stillbirths, especially in the European countries. The proportion of cases resulting in live births, stillbirths, and ETOPFA for population-based registries was similar to McGivern et al.'s study, which found 10.0% of cases resulted in an ETOPFA and 3.6% of cases resulted in a stillbirth (compared with 10.2% and 3.0%, respectively, in our data) [22]. In addition, mortality was higher among the countries or regions that allowed ETOPFA, which may be due to the most severe cases surviving until birth but dying soon after.

In our study, MCA and syndromic CDH cases had higher 1-week mortality rates than isolated cases. In general, prognosis of isolated CDH cases is better than that of MCA cases [39]. Prior studies have reported similar findings [1,19,40]. We found a higher survival rate among all registries for isolated cases at 1 week (71.4%; data not shown), similar to the recent finding by McGivern et al. that 72.7% of isolated cases survived the first week of life [22]. CDH cases with other anomalies present are more likely to be terminated than isolated CDH cases [19].

A major strength of our study is its large sample size and inclusion of registries from multiple countries. In addition, it included stillbirths and ETOPFA as well as live births and reported prevalence and mortality rates for each outcome and clinical presentation. Despite these strengths, there are some limitations. First, our study is based on combined yearly data and not individual data; therefore, it does not include information on prenatal diagnoses or postbirth treatment and management. In addition, some surveillance programs did not contribute data on clinical presentation and not all the programs were able to link to death certificates; therefore, some deaths may be missing. Furthermore, we did not have data on the specific subtypes of CDH (posterolateral Bochdalek hernia, anterior Morgagni hernia, and hiatus hernia). Data on the subtypes of CDH could provide further information on the prevalence and mortality of the specific subtypes, leading to improved treatment and management. Another minor limitation is not including stillbirths in the denominator for the prevalence calculations. We only had data on the stillbirths that had CDH, not all stillbirths for the entire program or region. In addition, these data do not reflect contemporary practice in that they do not account for treatment. The use of inhaled nitric oxide, extracorporeal membrane oxygenation, and changes in ventilation strategies all have profound effects on mortality. Furthermore, there were inconsistencies in data collection across registries and multiple countries, leading to data variability. However, we describe the characteristics of each registry, and our results are similar to other studies previously published.

Our study provides prevalence and mortality estimates for infants with CDH using registries from 19 countries. CDH is not a widely researched birth defect, and this study investigated the prevalence, mortality, and time trends of infants with CDH, adding importance by examining each by the type of registry. The CDH mortality rate remains high, especially during the first week of life, but it has decreased slightly over the period we studied. Clinical presentation of CDH and its association with other anomalies is a major concern and may indicate a specific etiologic or genetic cause. Further research is needed to examine the differences between population- and hospital-based registries and the 'hidden mortality' that might be present. Additional data on treatment procedures and prenatal diagnostic services would be useful to further examine the differences in mortality among the countries and programs. Our study provides data regarding mortality among CDH cases, which can aid the development of measures and interventions to decrease deaths among infants with CDH.

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Appendix

Appendix Table A
Congenital diaphragmatic hernia surveillance period, by country, registry, and type of registry, International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

Country	Registry	Surveillance years (1974–2015)																										N‡
		74–77	78–79	80	81–85	86–90	91	92	93	94	95	96	97	98	99	00	01	02	03	04–08	09	10	11	12	13	14	15	
Hospital-based registries																												
Argentina	RENAC	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6
Colombia	Bogotá	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	15
Colombia	Cali	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4
S. America	ECLAMC	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	20
Spain	ECEMC*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	28
Mexico	RYVEMCE	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	36
Iran	TROCA	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9
Israel	SMC	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	15
Population-based registries																												
Costa Rica	CREC	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	15
Czech Rep.	National	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	21
France	Paris	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	34
Germany	Saxony Anhalt	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	35
Italy	Lombardy	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10
Italy	Tuscany	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	22
Malta	MCAR	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	19
Netherlands	Northern	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	34
Slovak Rep.	National	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	14
Sweden	National†	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	28
Ukraine	OMNI-Net	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	14
UK	Wales	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	17
Mexico	Nuevo León	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
USA	Arkansas	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	20
USA	Atlanta	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	39
USA	Texas	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	17
USA	Utah	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	14

CREC = Costa Rican Birth Defect Registry; 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 External Congenital Malformations; SMC = Soroka Medical Center; TROCA = Tabriz Registry of Congenital Anomalies; UK = United Kingdom; USA = United States of America.

* Spain included information on elective termination of pregnancy for fetal anomalies from 1995 to 2014.

† Sweden included information on elective terminations of pregnancy for fetal anomalies from 1999 to 2014.

‡ Number of surveillance years.

Appendix Table B.1
Description of birth defects registries included in the congenital diaphragmatic hernia mortality study by type of registry: surveillance period, coverage, ascertainment period, stillbirth definition, ETOPFA allowed, and availability of prenatal screening services

Country registry	Surveillance period (n)	Coverage	Ascertainment period	Stillbirth definition	ETOPFA allowed	Prenatal screening services
Hospital-based registries						
Argentina-RENAC	2009–2014 (6)	N	Hospital discharge	>500 g	No	Yes, no official program
Colombia-Bogotá	2000–2014 (15)	R	1st day	>500 g	Yes, since 2006	Yes
Colombia-Cali	2011–2014 (4)	R	1st day	>500 g	Yes, since 2006	Yes
South America-ECLAMC	1995–2015 (21)	R*	Hospital discharge	>500 g	No‖	Yes
Spain-ECEMC	1986–2013 (28)	R†	3 d	24 wk or 500 g§	Yes, since 1985	Yes
Mexico-RYVEMCE	1978–2013 (36)	R	3	≥20 gestational weeks or ≥500 g	No	No
Iran-TROCA	2004–2012 (9)	R	1 y	20 wk	Yes, restrictions since 2013	Yes
Israel-SMC	2000–2014 (15)	R‡	Hospital discharge	Not included	Yes, but not registered	Yes
Population-based registries						
Costa Rica-CREC	2000–2014 (15)	N	1 y	20 wk or >500 g	No	Yes, only high-risk pregnancies
Czech Republic	1993–2014 (21)	N	15 y	22 wk or >500 g	Yes	Yes
France–Paris	1981–2014 (34)	R	28 d	22 wk	Yes	Yes
Germany-Saxony Anhalt	1980–2014 (35)	R	1 y	>500 g	Yes	Yes, since 1990
Italy-Lombardy	2003–2012 (10)	R	6 y	23 wk	Yes	Yes
Italy-Tuscany	1992–2014 (22)	R	1 y	20 wk	Yes	yes
Malta-MCAR	1995–2013 (19)	N	1 y	22 wk	No	Yes, gradually introduced
Netherlands-Northern	1981–2014 (34)	R	10 y	24 wk	Yes	Yes, since 2007
Slovak Republic	2001–2013 (14)	N	Hospital discharge	>500 g	Yes	Yes
Sweden	1987–2014 (28)	N	Before '87 1 mo, after '87 1 y	Until 2006: 28 wk, 2007 and after: 22 wk	Yes, registration since 1999	Yes, since early 1980s
Ukraine-OMNI-Net	2000–2013 (14)	R	1 y	Until 2006: 28 wk/>1000 g 2007 and after: 22 wk/>500 g	Yes	Yes
United Kingdom–Wales	1998–2014 (17)	R	18 y	24 weeks	Yes	Yes, since 2003
Mexico–Nuevo León	2011–2015 (5)	R	6 d	Not included	No	Yes, only US
USA–Arkansas	1993–2012 (20)	S	2 y	20 wk	Yes, until 20 weeks	Yes
USA–Atlanta	1974–2012 (39)	R	6 y	20 wk	Yes¶	Yes
USA–Texas	1996–2012 (17)	S	1 y	20 wk	Yes, until 20 weeks	Yes
USA–Utah	1999–2012 (14)	S	2 y	20 wk	Yes	Yes

CREC = Costa Rican Birth Defect Registry; ECEMC = Spanish Collaborative Study of Congenital Malformations; ECLAMC = Latin American Collaborative Study of Congenital Malformations; g = grams; MCAR = Malta Congenital Anomalies Registry; n = total number of years; N = national; OMNI-Net = Ukraine Birth Defects Prevention Program; R = regional; RENAC = National Network of Congenital Anomalies of Argentina; RYVEMCE = Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; S = statewide; SMC = Soroka Medical Center; TROCA = Tabriz Registry of Congenital Anomalies; USA = United States of America.

* Several regions in SA.

† Several regions in Spain currently covering around 18% of total births.

‡ Referral area of one hospital.

§ If gestational age of death is not determined (since 1980).

‖ Except for anencephaly.

¶ Elective terminations were ascertained from prenatal diagnostic sites beginning in 1994; before that they were only rarely ascertained from hospital records.

Appendix Table B.2
Description of the program follow-up method for live births by registry type

Country registry	Follow-up until discharge from the maternity hospital	Follow-up by a clinician or registry staff	Linkage with death certificates	Maximum follow-up period reported in study
Hospital-based registries				
Argentina-RENAC	Yes	Yes	No	2–6 d
Colombia-Bogotá	Yes	Yes	No	1 d
Colombia-Cali	Yes	Yes	No	No mortality reported for live births
South America-ECLAMC	Yes	Yes	No	28–364 d
Spain-ECEMC	Yes*	No	No	2–6 d
Mexico-RYVEMCE	Yes	No	No	2–6 d
Iran-TROCA	Yes	Yes‡	No	2–6 d
Israel-SMC	Yes	No	Yes, up to 2014	28–364 d
Population-based registries				
Costa Rica-CREC	No	No	Yes‖	≥5 y
Czech Republic	No	No	Yes	≥5 y
France–Paris	Yes	Yes	No	7–27 d
Germany-Saxony Anhalt	Yes	Yes§	No	≥5 y
Italy-Lombardy	No	No	Yes, up to 2015	7–27 d
Italy-Tuscany	No	No	Yes, up to 2015	28–364 d
Malta-MCAR	Yes†	No	Yes¶	≥5 y
Netherlands-Northern	Yes	Yes	No	≥5 y
Slovak Republic	Yes	No	No	7–27 d
Sweden	No	No	Yes, up to April 2016	≥5 y
Ukraine-OMNI-Net	Yes	Yes	No	28–364 d
United Kingdom–Wales	Yes	No	Yes, to GP system, until 18 years	≥5 y
Mexico–Nuevo León	Yes	No	No	≥5 y
USA–Arkansas	Yes	No	Yes, up to 2015	≥5 y
USA–Atlanta	Yes	No	Yes, up to 2008	≥5 y
USA–Texas	Yes	No	Yes, up to 2013	≥5 y
USA–Utah	Yes	No	Yes, until age 2	≥5 y

CREC = Costa Rican Birth Defect Registry; 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 External Congenital Malformations; SMC = Soroka Medical Center; TROCA = Tabriz Registry of Congenital Anomalies; USA = United States of America

* The participating physicians in the program are especially focused on the ascertainment of birth defects.

† Babies are followed up until discharge, and their hospital files are again seen at 1 year of age; linkage with mortality data continues indefinitely.

‡ Children in university hospital(s).

§ Until 18 years.

‖ Just for reported cases.

¶ Continuous linkage with mortality register; for this study, data have linkage up to 2015.