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The Latin American network for congenital malformation surveillance: ReLAMC

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Abstract

The early detection of congenital anomaly epidemics occurs when comparing current with previous frequencies in the same population. The success of epidemiologic

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surveillance depends on numerous factors, including the accuracy of the rates available in the base period, wide population coverage, and short periodicity of analysis. This study aims to describe the Latin American network of congenital malformation surveillance: ReLAMC, created to increase epidemiologic surveillance in Latin America. We describe the main steps, tasks, strategies used, and preliminary results. From 2017 to 2019, five national registries (Argentina [RENAC], Brazil [SINASC/SIM-BRS], Chile [RENACH], Costa Rica [CREC], Paraguay [RENADECOPY-PNPDC]), six regional registries (Bogotá [PVSDC-Bogota], Cali [PVSDC-Cali], Maule [RRMC SSM], Nicaragua [SVDC], Nuevo-León [ReDeCon HU], São Paulo [SINASC/SIM-MSP]) and the ECLAMC hospital network sent data to ReLAMC on a total population of 9,152,674 births, with a total of 101,749 malformed newborns (1.1%; 95% CI 1.10–1.12). Of the 9,000,651 births in countries covering both live and stillbirths, 88,881 were stillborn (0.99%; 95% CI 0.98–0.99), and among stillborns, 6,755 were malformed (7.61%; 95% CI 7.44–7.79). The microcephaly rate was 2.45 per 10,000 births (95% CI 2.35–2.55), hydrocephaly 3.03 (2.92–3.14), spina bifida 2.89 (2.78–3.00), congenital heart defects 15.53 (15.27–15.79), cleft lip 2.02 (1.93–2.11), cleft palate and lip 2.77 (2.66–2.88), talipes 2.56 (2.46–2.67), conjoined twins 0.16 (0.14–0.19), and Down syndrome 5.33 (5.18–5.48). Each congenital anomaly showed heterogeneity in prevalence rates among registries. The harmonization of data in relation to operational differences between registries is the next step in developing the common ReLAMC database.

KEYWORDS
congenital anomaly, Down syndrome, Latin America, microcephaly, stillbirths, surveillance

1 | INTRODUCTION

The last century saw an increased understanding of the causes of congenital anomalies. The genetic origin of several congenital malformation syndromes was described since 1900, but only between 1940 and 1960 did identification of the chromosomal and environmental causes occur (Lancaster, 2011). As opposed to congenital anomalies with genetic causes, the environmental causes appeared in endemic or epidemic status as observed by Gregg (1991) in the rubella embryopathy and by Lenz (1961), Lenz and Knapp (1962), and McBride (1961) in the thalidomide embryopathy. These two are paradigmatic preventable environmental syndromes. After the thalidomide embryopathy epidemic, several surveillance systems were created (Holtzman & Khoury, 1986), aiming at the early detection of congenital anomaly epidemics and at identifying and modifying the causal agent.

Nowadays, congenital anomalies are still a leading cause of infant deaths in the world. The well-known morbidity and mortality burden associated with congenital anomalies led to the Resolution 63.17 of the 63rd Assembly of the World Health Organization (WHO) in 2010. This Resolution recommended the development and strengthening of registry and surveillance systems to prevent congenital defects. Since its creation in 1967, ECLAMC (Latin American Collaborative Study of Congenital Malformations) made many efforts to meet these goals in Latin American and Caribbean countries (Poletta, Gili, & Castilla, 2014). The Pan American Health Organization and the World Bank (2019) have provided an updated description of the more recent efforts in the Region, including the Training Programs initiative to create new surveillance systems.

WHO declared the Zika virus (ZIKV) epidemic a public health emergency in 2016 (https://www.who.int/news/item/01-02-2016-who-statement-on-the-first-meeting-of-the-international-health-regulations-(2005)-(ihr-2005)-emergency-committee-on-zika-virus-and-observed-increase-in-neurological-disorders-and-neonatal-malformations), after increased rates of a newly described congenital ZIKV syndrome (Oliveira Melo et al., 2016; Schuler-Faccini et al., 2016). Brazilian information available at DATASUS (Marinho et al., 2016) and at ECLAMC databases (Orioli et al., 2017) provided insights into the microcephaly crisis by providing baseline prevalence for the Brazilian Northeast region before the virus entered the continent. Limitations included underreporting of microcephaly cases in DATASUS and the corrections that were required to the hospital-based prevalence estimates of ECLAMC as well as the small coverage of ECLAMC in epidemic areas. By 2015, Latin America had also established many registries of congenital anomalies and information systems working at regional or national levels. However, those data systems were not networked, preventing further, standardized, and

more accurate analyses of the microcephaly rates. In 2016, answering calls from the Brazilian National Council for Scientific and Technological Development (CNPq) and European Union Zika-PLAN project (Wilder-Smith et al., 2019), we proposed creating a Latin American network of congenital malformation registries. We describe here the strategy and methods used and the first results obtained.

2 | METHODS

2.1 | Latin American network for congenital malformation surveillance (ReLAMC): Creation

ReLAMC's primary goal is strengthening congenital anomaly surveillance to provide public, online, updated, and reliable reference frequencies for congenital anomalies in Latin America. A new program on congenital anomaly surveillance with a common protocol and mechanisms for information sharing was agreed on for periodic assessment of frequencies of congenital anomalies to detect increases at an earlier stage and confirm rumors coming from any region. ReLAMC also aims to contribute to establishing new registries in the Region and promoting collaborative research on the causes of congenital anomalies.

One strategy used in the construction of ReLAMC was to profit from 50 years of ECLAMC experience in networking. We chose the ECLAMC annual meetings as a host from 2016 to 2019 to discuss with the invited Surveillance Program directors the proposed ReLAMC creation project and its further development. When defining the ReLAMC database, another strategy used was following as closely as possible the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) since several Latin American programs already send data to the ICBDSR network (Table 1). We also followed the European Surveillance of Congenital Anomalies (EUROCAT) model for the initial design of the Terms of Agreement, data sharing options, the use of data quality and public health indicators, and web page contents, particularly prevalence tables. The Skeleton Plan with the main steps, definition, and strategies for ReLAMC creation, as well as the initial history, are in Table S1.

2.2 | ReLAMC procedures and databases content

ReLAMC members send individual or aggregate data every 6 months to the shared network database via a secure server. The common public dataset contains:

1. The number of defects registered for 97 selected types of congenital anomalies, ICD-10 coded, stratified by sex in each group of live birth or stillbirth, isolated or associated with other defects, and three maternal age categories
2. The number of newborns classified in 20 broad groups of congenital anomalies stratified by sex for each group of live births and stillbirths
3. The number of all live births and stillbirths stratified by sex and by six maternal age quinquennium categories during the 6 months (denominators)

Optionally, the program can transmit data to the central database on individual cases that cover these variables plus a further 10: birth date, place or code of the hospital, mother's place of residence, maternal number of pregnancies, gestational age at birth, birth weight, birth length, cephalic circumference, death date, and prenatal detection of a congenital anomaly. The individual database is automatically converted to the public dataset (aggregate numbers), and the required denominators are similar in the two operational modes. Data not publicly published on the website will remain protected for the exclusive use of ReLAMC and the registry that produced them.

Among the 97 selected types of congenital anomalies transmitted to ReLAMC as aggregate data, 21 conditions are listed outside ICD-10 chapter XVII (Congenital malformations, deformations, and chromosomal abnormalities). Seven are embryopathies with or without neonatal infection caused by maternal infection by syphilis (A50), human immunodeficiency virus (HIV) (B24), rubella (P35.0), cytomegalovirus (P35.1), herpes simplex (P35.2), chickenpox virus (P35.8), and Toxoplasma gondii (P37.1), known collectively as STORCH infections which are in ICD-10 chapter I (certain infectious and parasitic diseases) and XVI (certain conditions originating in the perinatal period). Also, the newly created code for Zika virus syndrome (P35.4) is in chapter XVI, even if in ReLAMC until 2019, it was P35.8 (other congenital viral diseases). Table S2 shows the ReLAMC list of the 76 congenital anomalies with their ICD-10 chapter XVII codes and observations and the 21 coded outside ICD-10 chapter XVII.

Mexico City, along with Cuba and Uruguay, are the only places in Latin America where women can undergo abortions during the first 12 weeks of pregnancy regardless of the circumstances (https://www.bbc.com/mundo/noticias-america-latina-45132307). Voluntary termination of pregnancy for fetal anomalies (TOPFA) or other causes occurs in some Latin American countries, although there is a vast difference in accepted legal reasons. This heterogeneity concerning termination of pregnancy for fetal anomaly (TOPFA) and the few cases registered during 2017 and 2018 led us to decide to drop this variable from the data form, but it can be reinstated when appropriate.

ReLAMC data quality control calculates the proportion of missing data on obligatory fields and checks that totals are compatible among related fields. Further data quality control is currently done at registry level. More detailed information on ReLAMC structure, governance, operations, data security, and ethics can be found in the ReLAMC Terms of Agreement and Commitments upon request.

2.3 | Data analysis

The 12 registries described in this work joined ReLAMC at different times, which extended the pilot data sharing from 2017 to 2018. The pilot study tested the data collection forms, last revised in 2019. With the material sent during the pilot study and subsequently, we

TABLE 1 Coverage of Latin American live births in 2017 by ReLAMC registries

Registry initials	Start year	Name	Coverage	Country or region	Length of observation	Mandatory	Registry annual live births 2017	Country/region annual live births 2017	% Country/region covered
SINASC-SIM BRAZIL	1975–2000	Sistema de Informação sobre Nascidos Vivos - Sistema de Informação sobre Mortalidade do Brasil	National	Brasil	At birth (SINASC) 1 year (SIM)	Yes	2,923,535	3,045,349	96.0
CREC[c]	1987	Centro de Registro de Enfermedades Congénitas	National	Costa Rica	1 year	Yes	68,479	71,332	96.0
RENAC[c]	2009	Registro de Anomalías Congénitas de Argentina	National	Argentina	Maternity discharge	No	274,079	728,011	37.7
RENACH	2016	Registro Nacional de Anomalías Congénitas de Chile	National	Chile	Maternity discharge	Yes	136,453	219,186	62.2
RENADECOPY-PNPDC	2016	Programa Nacional de Prevención de Defectos Congénitos	National	Paraguay	1 year	No	33,932	115,895	29.7
SINASC-SIM MSP[a]	1975–2000	Sistema de Informação sobre Nascidos Vivos - Sistema de Informação sobre Mortalidade do Município de São Paulo	Regional	São Paulo municipality	At birth (SINASC) 1 year (SIM)	Yes	196,082	196,082	100.0
PVSDC Bogotá[c]	2001	Programa de Vigilancia y Seguimiento de Defectos Congénitos Bogotá	Regional	Bogota	Maternity discharge	No	15,255	94,896	16.1
RRMC SSM Maule[a,c]	2003	Registro regional de Malformaciones Congénitas del Maule	Regional	Maule	Maternity discharge	No	12,632	14,114	89.5
SVDC	2006	Sistema de Vigilancia de Defectos Congénitos	Regional	Nicaragua	Maternity discharge	No	10,684	15,263	70.0
PVSDC Cali[c]	2010	Programa de Vigilancia y Seguimiento de Defectos Congénitos Cali	Regional	Cali	Maternity discharge	No	12,399	34,556	35.9
ReDeCon HU[c]	2011	Registro de Defectos Congénitos hospital Universitario UANL	Regional	Nuevo-León	Maternity discharge	No	9,269	77,242	12.0
ECLAMC[c]	1967	Estudo Colaborativo Latino Americano de Malformaciones Congénitas	Hospitals[b] without overlapping with populational registries	Multinational	Maternity discharge	No	18,621	–	–
National total							3,436,478	4,179,773	82.2
Regional total							256,321	432,153	59.3
Nacional + Regional total							3,692,799	4,611,926	–
Non-overlapping Nacional + Regional total							3,484,085	4,401,730	79.2
Hospital based total							58,744	–	–

[a]Regional registries that overlapped with the national registries in ReLAMC data.

[b]Hospitals from La Plata and Lomas de Zamorra (Buenos Aires province, Argentina); La Paz (La Paz province) and Tarija (Tarija province), Bolivia; Lima Autonomous Province (Peru); Pereira (Risaralda province, Colombia); Coro (Falcon state, Venezuela).

[c]Latin American registries also sending data to the ICBDSR.

analyzed the prevalence rates of stillbirths, congenital anomalies, congenital anomalies in stillbirths, and nine selected congenital anomalies for each registry and the combined total. The definition of stillbirth is not uniform among registries, including the delivery of the dead fetus at or after 20 weeks gestation or weighing 350 g or more when gestation time is unknown. The prevalence rate of stillbirths was calculated per 1,000 births (live births and stillbirths). The prevalence rate of congenital anomalies was calculated per 100 births, and selected congenital anomalies per 10,000 births. The prevalence rate of congenital anomalies in stillbirths was calculated per 100 stillbirths. The nine selected anomalies were those with the following International Classification of Diseases 10 (ICD-10) codes:

- Microcephaly (Q02)
- Hydrocephaly (Q03)
- Spina bifida (Q05)
- Congenital heart defects (Q20 to Q26)
- Cleft lip (Q36)
- Cleft lip and palate (Q37)
- Talipes (Q66)
- Conjoined twins (Q89.4)
- Down syndrome (Q90)

Each anomaly was counted regardless of the presence or absence of another type of congenital anomaly in the same newborn.

The Poisson or Binomial exact confidence intervals at 95% level were calculated for each prevalence rate using the Stata 12 software. All prevalence rates and their lower and upper 95% confidence intervals for stillbirths, congenital anomalies, congenital anomalies in stillbirths, and nine selected anomalies were displayed graphically in forest plots to allow inter-registry comparison.

Each registry provided both the total live birth numbers in their region/nation, and the number covered by the registry. The registry's population coverage in 2017 was calculated.

3 | RESULTS

3.1 | Creation history

The ReLAMC initiative of networking registries in Latin America came as a response to the increase of microcephaly rates during the ZIKV

FIGURE 1 National and Regional Registries, and ECLAMC hospital network sending data to ReLAMC, 2017–2019

pandemic. In 2016 we invited 11 Latin American congenital anomaly registries to participate in ReLAMC. The meeting was held together with the 48th ECLAMC annual meeting, and the concept was met with enthusiasm. We invited six new registries in the following year totaling 17 registries involved with the ReLAMC creation. Fourteen registries continued to be involved, and 12 could share data from 2017/1 (Table 1, Figure 1). We have summarized the history of ReLAMC creation and development in Table S1.

3.2 | Shared data

Table 1 shows the coverage of Latin American live births in 2017 by the 12 registries sharing data and each registry's start year. There were overlapping data in Brazil and Chile national and regional registries, corrected in Table 1 for the national plus regional total. The ECLAMC hospital-based registry has overlapping data with registries from Argentina, Chile, Bogotá, and Cali. Only 18,621 from 58,744 ECLAMC live births are non-overlapping data from Argentina, Bolivia, Peru, and Venezuela hospitals.

ReLAMC covered 3,502,706 Latin American live births in 2017, excluding overlapping live births, 3,484,085 live births from national and regional registries, and 18,621 live births from ECLAMC hospitals not covered by those registries. National registries covered 82.2% of live births in Argentina, Brazil, Chile, Costa Rica, and Paraguay (3,436,478/4,179,773 live births). In comparison, the regional registries covered 59.3% of live births in Bogotá D.C. (Colombia), Cali city (Colombia), Maule region (Chile), North-Western Nicaragua (Chinandega and León departments), Nuevo-León state (Mexico), and São Paulo municipality (Brazil) (256,321/432,153) (Table 1). The coverage of live births is heterogeneous among national registries varying from 29.7 to 96%, the same occurring among regional registries with a broader range from 12 to 100% (Table 1). The duration of data collection for each registry varies from 53 years for ECLAMC to 4 years for national registries in Chile and Paraguay (Table 1).

3.3 | Health indicators

From 2017 to 2019, ReLAMC received data on 9,152,674 births. Excluding Paraguay, with data only on live births, there were 88,881 stillbirths in 9,000,651 total births, a general stillbirth prevalence of 9.87 per 1,000 (95% CIs 9.81–9.94). The rates range from 4 to 11 stillbirths per 1,000 births (Figure 2).

Among the 9,152,674 births, there were 101,749 newborns registered with congenital anomalies, a rate of 1.11% (95% CIs 1.10–1.12). These rates range from 1 to 4% (Figure 3).

There were 6,755 stillbirths with congenital anomaly among the 88,723 stillbirths, excluding N. León stillbirth data, indicating that 7.61% (95% CI 7.44–7.80) of the mortality is associated with congenital anomalies in the ReLAMC data for this period. The proportion of congenital anomalies in stillbirths ranges from 3% in Costa Rica to 19% in Chile and 23% in the ECLAMC hospital network (Figure 4).

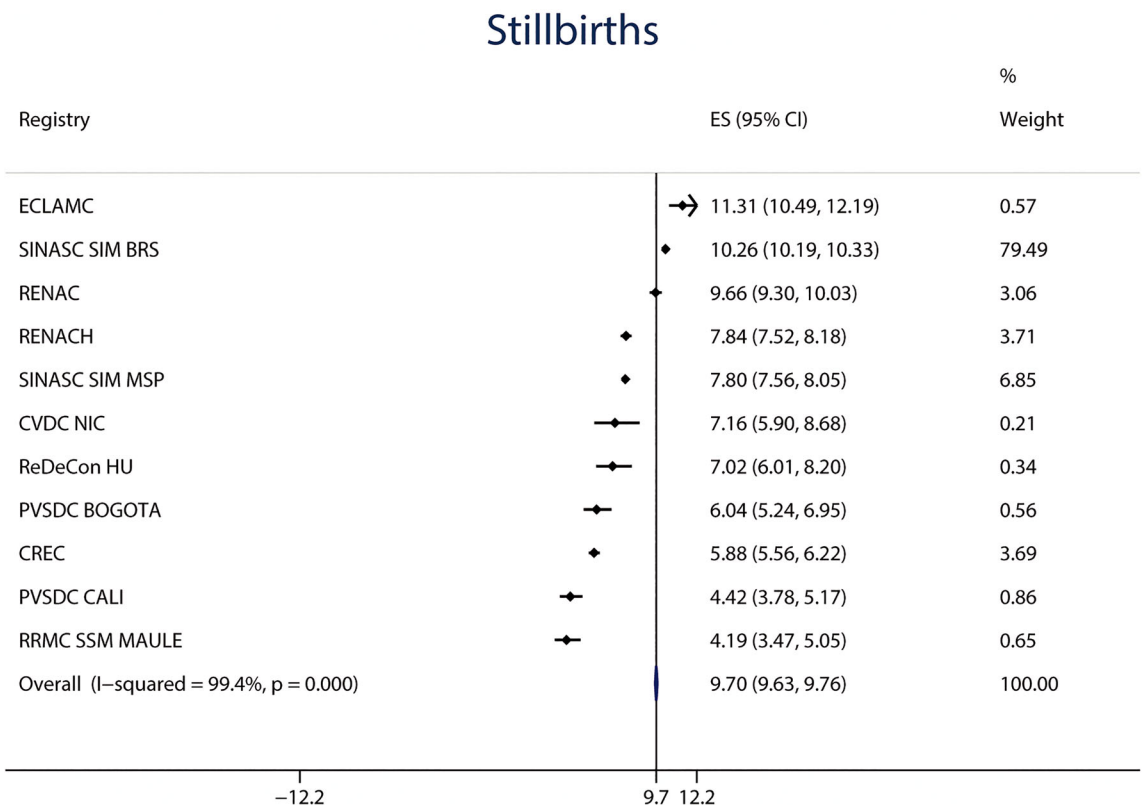

FIGURE 2 ReLAMC prevalence of stillbirths per 1,000 births, 2017–2019 [Color figure can be viewed at wileyonlinelibrary.com]

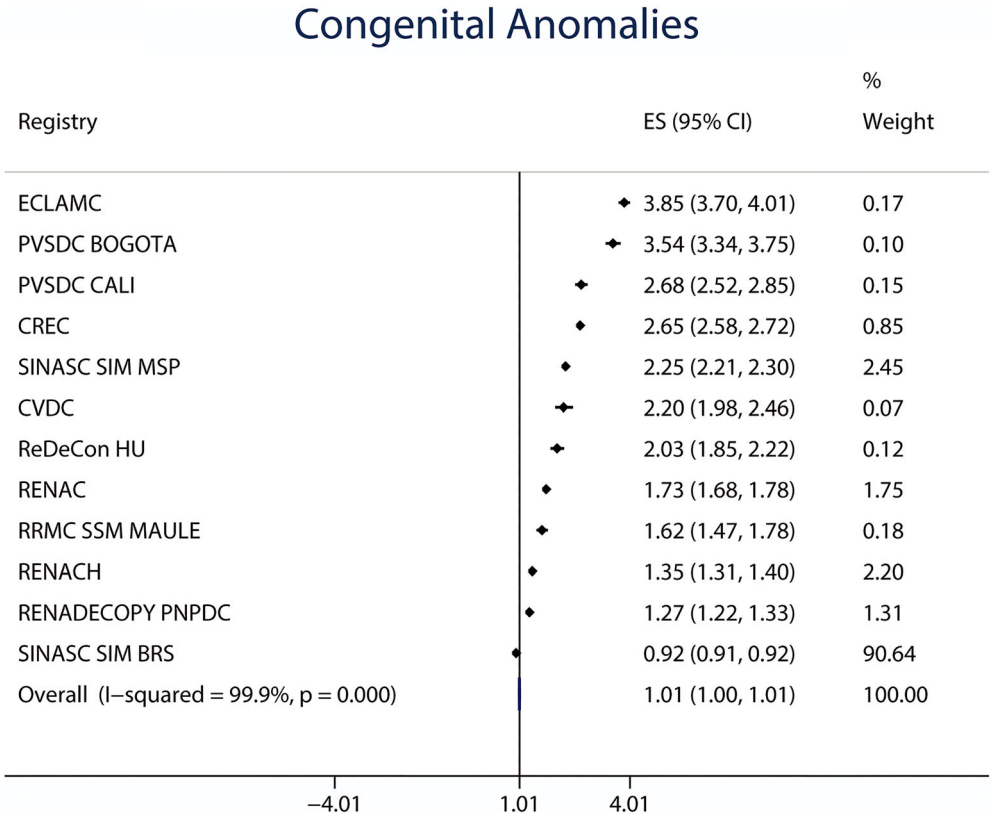

FIGURE 3 ReLAMC prevalence of congenital anomalies per 100 births, 2017–2019 [Color figure can be viewed at wileyonlinelibrary.com]

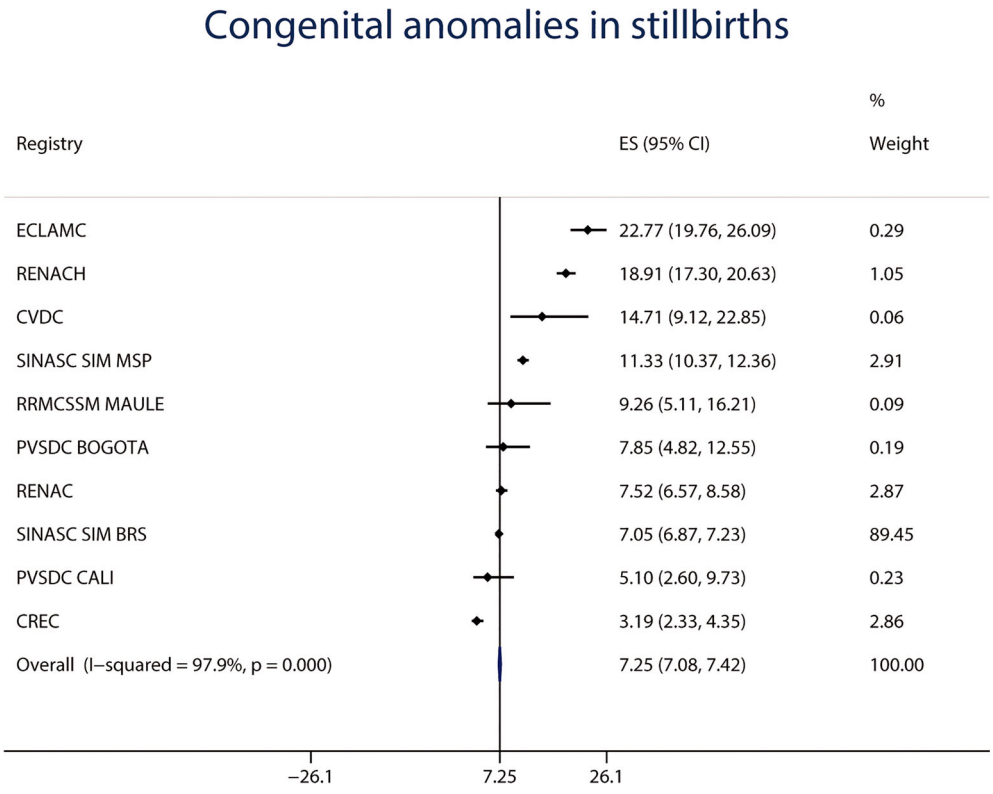

FIGURE 4 ReLAMC prevalence of congenital anomalies in stillbirths per 100 stillbirths, 2017–2019 [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Congenital anomaly prevalence

National registries in Argentina, Brazil, Chile, and Costa Rica, and the regional registry of Nuevo-León (8,336,969 births) registered cases for syphilis, cytomegalovirus, and toxoplasmosis, summing up 19 syphilis, five cytomegalovirus, and nine toxoplasmosis cases for 2017, a rate of 3.96/10,000 births (95% CI 2.72–5.56). ReLAMC did not receive data from all registries for the selected

congenital anomalies coded outside the ICD-10 chapter XVII, including the embryopathies caused by maternal infections during pregnancy.

Table 2 shows each registry's prevalence rate per 10,000 for microcephaly (Figure 5), hydrocephaly, spina bifida, congenital heart defects, cleft lip, cleft lip and palate, talipes, conjoined twins, and Down syndrome (Figure 6). The total number of births used for prevalence rate calculations was 9,133,299 due to missing congenital anomaly information on 19,374 births. The data covers 83% of the expected semesters in the period. All the selected anomalies show heterogeneity in prevalence rate between registries.

4 | DISCUSSION

Two transnational networks provide a forum for congenital anomaly registries to share data in surveillance and research. The ICBDSR congregate registries from across the world since 1974 (Bermejo-Sánchez, Botto, Feldkamp, Groisman, & Mastroiacovo, 2018), and EUROCAT is a network of population-based registries in the European Union created in 1979 (Boyd et al., 2011). Latin America has a hospital-based network, ECLAMC, with a central database, created in 1967 by Eduardo Castilla (Castilla & Orioli, 2004), that has conducted congenital anomaly surveillance to detect and investigate unusual occurrences in time or space. For time clusters, or epidemics, routine monitoring is performed, and quarterly data are compared against other equivalent surveillance systems through the ICBDSR, of which ECLAMC was one of the founders. From 1985 with the Registro Cubano de Malformaciones Congénitas (RECUMAC), and 1987, with the Centro de Registro de Enfermedades Congénitas en Costa Rica, until recent years, population-based national or regional congenital anomaly registries have been set up in many countries in Latin America. Although many are members of ICBDSR, these systems are not networked on a Latin American basis. ReLAMC was created to fill this gap as a transnational network of the Latin American national or regional registries, also integrated with ECLAMC.

National registries cover 82% of births in the five countries where they operate, with coverage almost complete in Brazil and Costa Rica and lower in Argentina, Chile, and Paraguay. Births not covered are mainly from private hospitals or hospitals not yet participating in the recently created registries as in Chile and Paraguay. Regional registries in three countries that do not have national registries sending data to ReLAMC cover 7.9% in Nicaragua, 3.7% in Colombia, and 0.4% in Mexico. All seven regional registries cover 59.3% of the cities, municipalities, or states they aim to cover. The higher national than regional registry coverage is expected because most national registries have a mandatory reporting requirement in their country. The initial ReLAMC decision to collect data on overlapping registries, correcting when necessary, was useful to identify differences between national or regional registries in the same country. Also, ReLAMC aims to promote new Latin American registries, and collaborative research on congenital anomalies will be better fulfilled working together with all interested people.

To estimate some public health indicators, we analyzed all data sent to ReLAMC from 2017 to 2019, a total of 9,152,674 births. Stillbirth rates ranged from 4 to 11 per 1,000 births. They were above 8 per 1,000 in the national registries of Argentina, Brazil, and in ECLAMC. The ECLAMC hospital-based population suffers from the hospital referral effect (Orioli et al., 2017), where prenatally diagnosed fetuses cause referral of delivery to high complexity hospitals, probably explaining the higher ECLAMC mortality rate. The regional stillbirth rate of 7.84 in São Paulo municipality is lower than the national rate of 10.26 per 1.000 births. It is at the upper end of the confidence limits for the aggregate mean rate from 2010 to 2014 (7.65, 95% CI 7.47–7.84) in São Paulo municipality (Andrews et al., 2017). These authors found high heterogeneity among municipalities of the São Paulo state in this period (0 to 29.7 per 1.000 births), mirroring what happens throughout Brazil (Andrews et al., 2017). Also, they observed that the stillbirth rate exceeded the neonatal mortality rate (newborn death until 27 completed days) in the perinatal mortality rate (Lawn et al., 2016), increasing the importance of the stillbirth rate as a health indicator.

In 2013, the fetal death rate of 5.96 per 1,000 live births and fetal deaths, described in the USA (McDorman & Gregory, 2015), was lower than the Latin American stillbirth rate (9.6 per 1,000). Also lower than ReLAMC, the rate of fetal deaths at ≥23 weeks was 2.8 per 1,000 live births, in Friuli Venezia Giulia, 2005 to 2013, excluding TOPFA (Monasta et al., 2020). Lower stillbirth rates were also published for Australia, 7.1 per 1,000, from 2013 to 2014 (Australian Institute of Health and Welfare, 2018), and the U.K. stillbirth rate is 3.74 per 1,000 (Draper et al., 2019).

There were 7.6% of stillbirths with registered congenital anomalies. ECLAMC had higher rates of stillbirth, congenital anomaly, and congenital anomaly in stillbirth (22.8%). Costa Rica presented the lowest rate of malformed stillbirths among the registries with 3.2%. EUROCAT Public Health Indicators calculate congenital anomalies in stillbirths as a proportion of total births, with a rate of 0.5 per 1,000 births (Khoshnood, Greenlees, Loane, & Dolk, 2011) which with an average stillbirth rate below 3 per 1,000 births means that approximately 16% (0.5/3) are associated with a congenital anomaly. The lower proportions in ReLAMC are likely to be associated with the greater importance of other stillbirth causes and the under-reporting of congenital anomalies among stillbirths.

Fetal deaths occurring antepartum are more prevalent and are associated with many maternal and fetal causes in the developed world (Smith, 2010), while intrapartum stillbirths are generally imputed to lack of high-quality delivery care and represent only 10 % of stillbirths (Lawn et al., 2016). The time of fetal death is not available in our data to separate these two groups. However, the socioeconomic differences in the Latin American populations are likely to play a key role in explaining the observed differences in stillbirth rate and congenital anomaly rate in stillbirth among the registries.

The congenital anomaly rate has several components (https://www.who.int/publications/i/item/9789241548724). These

TABLE 2 Prevalence rates per 10,000 births of nine congenital anomalies, by ReLAMC registries localities, 2017–2019

	Brazil	São Paulo	Argentina	Chile	Costa rica	Paraguay	Eclamc	Cali	Bogotá	Nuevo león	Nicaragua	Maule	Total
Q002 cases	1,245	108	89	135	461	84	49	21	19	10	12	1	2,234
Microcephaly prev.,	1.65	2.17	3.25	4.98	22.77	5.53	8.25	5.91	6.01	4.44	8.42	1.56	2.45
95% CI[a]	1.55–1.74	1.76–2.58	2.57–3.92	4.14–5.82	20.69–24.85	4.34–6.71	5.94–10.56	3.38–8.44	3.31–8.71	1.69–7.20	3.66–13.19	−1.50-4.62	2.35–2.55
Q03 cases	1961	207	215	74	78	60	111	10	30	10	10	0	2,766
Hydrocephaly prev.,	2.59	4.16	7.84	2.73	3.85	3.95	18.68	2.82	9.48	4.44	7.02	0.00	3.03
95% CI	2.48–2.71	3.60–4.73	6.80–8.89	2.11–3.35	3.00–4.71	2.95–4.95	15.21–22.16	1.07–4.56	6.09–12.88	1.69–7.20	2.67–11.37	0.00–0.00	2.92–3.14
Q05 cases	2022	167	155	79	57	60	56	4	5	20	12	0	2,637
Spina bifida prev.	2.67	3.36	5.66	2.91	2.82	3.95	9.43	1.13	1.58	8.88	8.42	0.00	2.89
95% CI	2.56–2.79	2.85–3.87	4.76–6.55	2.27–3.56	2.08–3.55	2.95–4.95	6.96–11.89	0.02–2.23	0.20–2.97	4.99–12.78	3.66–13.19	0.00–0.00	2.78–3.00
Q20-Q26 cases	7,033	2,926	1768	400	1,209	253	227	41	189	74	59	4	14,183
[b]CHD prev.,	9.29	58.86	64.51	14.76	59.71	16.64	38.21	11.55	59.76	32.87	41.42	6.24	15.53
95% CI	9.08–9.51	56.73–60.99	61.50–67.51	13.31–16.21	56.34–63.08	14.59–18.69	33.24–43.18	8.01–15.08	51.24–68.27	25.38–40.36	30.85–51.98	0.12–12.36	15.27–15.79
Q36 cases	1,466	100	56	78	38	33	26	19	6	9	11	2	1,844
Cleft lip prev.,	1.94	2.01	2.04	2.88	1.88	2.17	4.38	5.35	1.90	4.00	7.72	3.12	2.02
95% CI	1.84–2.04	1.62–2.41	1.51–2.58	2.24–3.52	1.28–2.47	1.43–2.91	2.69–6.06	2.94–7.76	0.77–4.13	1.39–6.61	3.16–12.28	−1.20-7.45	1.93–2.11
Q37 cases	1,595	160	266	150	122	92	84	12	16	19	8	5	2,529
Cleft lip/palate prev.,	2.11	3.22	9.71	5.53	6.03	6.05	14.14	3.38	5.06	8.44	5.62	7.80	2.77
95% CI	2.00–2.21	2.72–3.72	8.54–10.87	4.65–6.42	4.96–7.09	4.82–7.29	11.11–17.16	1.47–5.29	2.89–8.21	4.65–12.24	1.72–9.51	0.96–14.64	2.66–2.88
Q66 cases	1,171	192	190	197	158	164	115	44	99	5	4	2	2,341
Talipes prev.,	1.55	3.86	6.93	7.27	7.80	10.79	19.36	12.39	31.30	2.22	2.81	3.12	2.56
95% CI	1.46–1.64	3.32–4.41	5.95–7.92	6.25–8.28	6.59–9.02	9.14–12.44	15.82–22.89	8.73–16.05	25.13–37.47	0.27–4.17	0.06–5.56	−1.20-7.45	2.46–2.67
Q89.4 cases	128	12	0	7	1	0	0	0	0	0	1	0	149
Conjoined-twins prev.,	0.17	0.24	0.00	0.26	0.05	0.00	0.00	0.00	0.00	0.00	0.70	0.00	0.16
95% CI	0.14–0.20	0.10–0.38	0.00–0.00	0.07–0.45	−0.05-0.15	0.00–0.00	0.00–0.00	0.00–0.00	0.00–0.00	0.00–0.00	−0.67-2.08	0.00–0.00	0.14–0.19
Q90 cases	2,929	491	444	355	224	176	97	34	55	27	21	15	4,868
Down syndrome prev.,	3.87	9.88	16.20	13.10	11.06	11.58	16.33	9.58	17.39	11.99	14.74	23.40	5.33
95% CI	3.73–4.01	9.00–10.75	14.69–17.71	11.74–14.46	9.61–12.51	9.87–13.29	13.08–19.57	6.36–12.79	12.79–21.98	7.47–16.52	8.44–21.05	11.56–35.25	5.18–5.48
Number of semesters/ total	6/6	6/6	2/6	4/6	6/6	6/6	2/6	6/6	6/6	5/6	4/6	1/6	60/72
Number of births	7,566,872	497,100	274,080	271,025	202,481	152,023	59,416	35,507	31,629	22,511	14,246	6,409	9,133,299

[a]Prev., 95% CI = prevalence, 95% Confidence Intervals.

[b]CHD, congenital heart diseases.

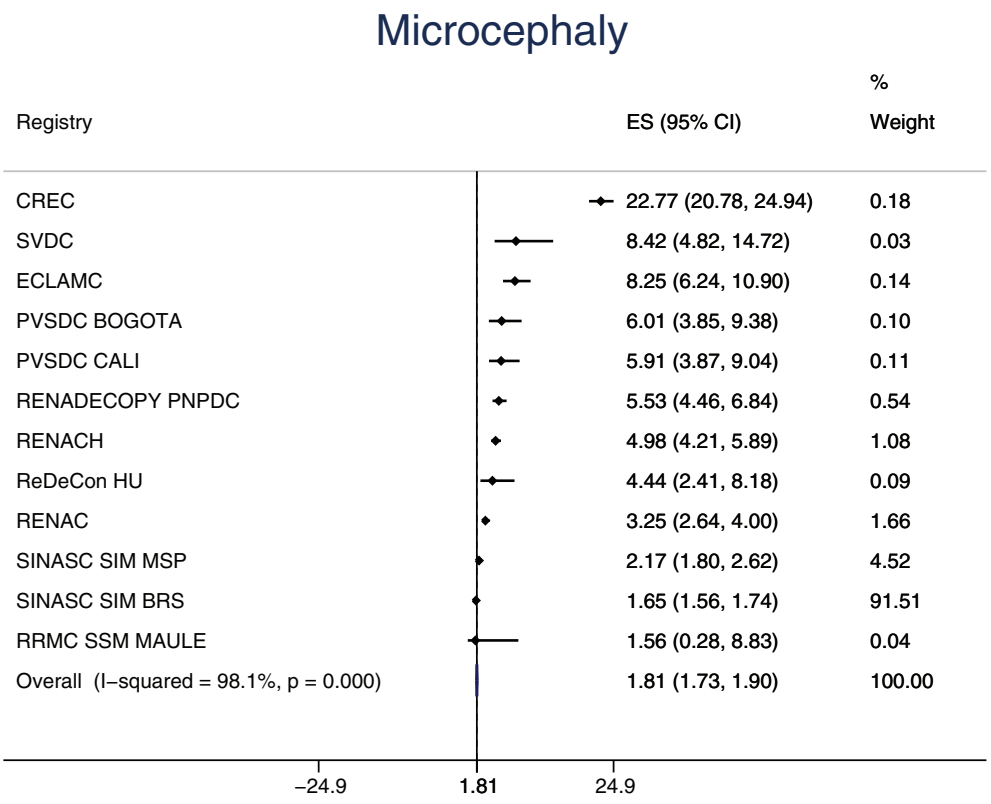

FIGURE 5 ReLAMC prevalence of microcephaly per 10,000 births, 2017–2019 [Color figure can be viewed at wileyonlinelibrary.com]

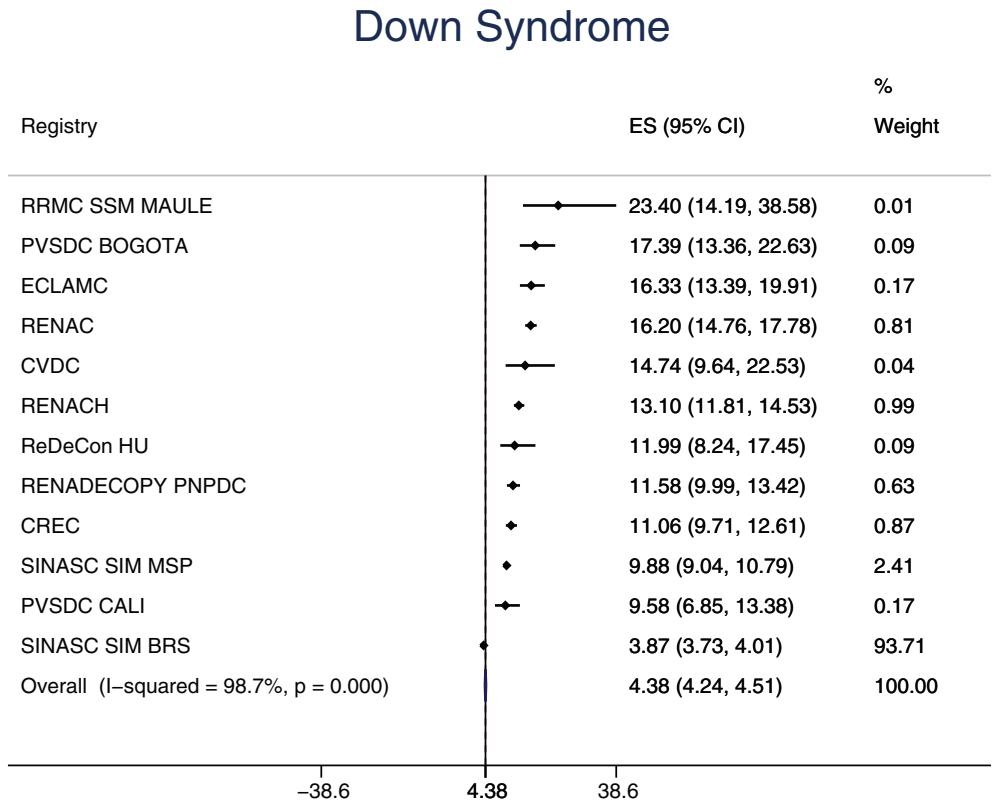

FIGURE 6 ReLAMC prevalence of Down syndrome per 10,000 births, 2017–2019 [Color figure can be viewed at wileyonlinelibrary.com]

prevalence rates among ReLAMC registries ranged from 1 to 4%. Choosing a cut-off congenital anomaly rate to indicate under registration is not useful due to the different registries' characteristics. EUROCAT had proposed that rates below 2% suggest under registration in their system (Loane, Dolk, Garne, & Greenlees, 2011). National registries had a larger number of births, usually under mandatory

rules. Their lower congenital anomaly rates than regional registries possibly occurred because their hospitals preferentially register visible and major defects. The Costa Rica register is an exception having a congenital anomaly rate of over 2.5%, like Cali, Bogotá, and ECLAMC. Another factor that may influence these rates is the length of observation. The length of observation in Costa Rica is until one-year-old, and there is an active search of patients with congenital anomalies, differently from other national registries (Benavides-Lara, Faerron Ángel, Solís, José, & Zúñiga, 2011). The ReLAMC congenital anomaly rate was lower compared to Europe (2017–2018), (EUROCAT) (2.54%; 95% CI 2.51–2.57), the same occurring with the rate of 2.03% (95% CI 1.98–2.09) described for Utah (United States), 2005–2009, (Feldkamp, Carey, Byrne, Krikov, & Botto, 2017). With ReLAMC consolidation and standardized reporting and quality criteria applied, we expect the prevalence of congenital anomaly to be closer to those reported in Europe and the United States.

We compared the prevalence of nine congenital anomalies among registries as preliminary examples of ReLAMC data sharing. We chose microcephaly and hydrocephaly because of their link to the ZIKV epidemic, spina bifida to allow the evaluation of folic acid health policies, congenital heart defects, and Down syndrome because of their high frequency, conjoined twins because there was a suspicion this year (September 2020) of an increase in frequency, and cleft lip, cleft lip and palate, and talipes, together with the defects mentioned before, because they need early detection and treatment.

Head circumference is a significant factor in the suspicion and diagnosis of microcephaly and hydrocephaly, alongside image studies and clinical neurology evaluation. Several authors have also associated hydrocephaly and other associated brain damage with the Zika congenital syndrome since the earlier complete descriptions (Alvarado & Schwartz, 2017; Del Campo et al., 2017; Mlakar et al., 2016; Soares de Oliveira-Szejnfeld et al., 2016). The primary focus on head circumference measures and the different definitions of microcephaly and hydrocephaly among registries could be the main factors in explaining heterogeneity in rates during the ZIKV epidemic and afterward. In ECLAMC, another factor in explaining increased rates of microcephaly and hydrocephaly derived from its participation in ReLAMC data being restricted to the 2017 year. During this year, the ZIKV epidemics were active in several ECLAMC hospital cities.

Brazil's microcephaly rate in 2017–2019 (1.65 per 10,000) was lower than rates in other registries. Nevertheless, it was almost three times greater than the Brazilian microcephaly prevalence rate in the 2000–2014 period (0.56 per 10,000; Marinho et al., 2016). The inclusion of the 2017 epidemic year in the more recent rate must explain part of the increase, but an increase in the completeness of microcephaly reporting due to the ZIKV epidemic may also contribute to this increase. In the case of Costa Rica, where the prevalence was several times higher than most of the registries, the congenital Zika epidemic, whose peak of cases occurred between 2017 and 2018, caused its baseline to increase almost four times (https://www.inciensa.sa.cr/vigilancia_epidemiologica/informes_vigilancia/2018/Malformaciones%20Congenitas/Informe%20epidemiologico%20anual%20defectos%20congenitos.%20Costa%20Rica%202018.pdf).

The prevalence rates of spina bifida were heterogeneous among ReLAMC registries. Since they are a useful measure of the folic acid fortification health policy (Crider, Qi, Devine, Tinker, & Berry, 2018), the registries initiated a spina bifida epidemiological research study to better explain this heterogeneity. The same occurred for congenital heart defects, where the collaborative epidemiological study that has been initiated is to clarify which differences resulted from coding or resulted from differences in perinatal care resources. Operational changes in 2018 occurred in the forms to send aggregate data to ReLAMC. We added 10 new congenital heart defect ICD-10 codes to the earlier seven and eliminated the "other cardiopathies" code. The contribution of these changes to the heterogeneity of congenital heart defect rates must be small since the registries had sent a higher volume of data with the new forms.

Several ReLAMC registries presented prevalence rates for cleft lip (Q36) and cleft lip and palate (Q37) that suggested under registration or coding problems. Oral cleft information such as the proportion of each type of cleft could be used when establishing data quality indicators for congenital anomaly registries (Groisman et al., 2019), and indicated several coding problems in the live birth part of the Brazilian registry (Nascimento, Castilla, Dutra, & Orioli, 2018). The ICD-10 classification of oral clefts could induce oral cleft coding errors in those registries that use the ICD-10 classification without any extension such as the BPA (Nascimento et al., 2018). The ICD-10 BPA codes Q36.90 and Q36.99 allow the separation of unilateral cleft lip from a unspecified cleft lip, and the Q37.99 code allows the registration of an unspecified cleft lip with cleft palate case. The cleft lip prevalence rate is not expected to be close to or greater than the cleft lip and palate rate, and this error can also result when registries primarily register cases with cleft lip with and without cleft palate (Q36 plus Q37) combined. For a long time, this entity has been considered the same anomaly based on the usual occurrence of cleft lip only and cleft lip and palate in the same families (Fogh- Andersen, 1942).

The heterogeneity of talipes prevalence rates could be explained by different interpretation of registries sending aggregate as to what must be counted under talipes (Q66). Some registries recorded only equinovarus feet (Q66.0) even if the code Q66 has nine subgroups of feet deformities. Also, there were differences among the registries about the registration of defects according to severity.

The Down syndrome prevalence rate is also a useful data quality indicator when shown by maternal age category. We did not analyze the prevalence rates for Down syndrome by maternal age because this stratification of the entire population is not always available. However, all registries except for Brazil have prevalence above 1 per 1,000 births, as described in the United States and other parts of the world (reviewed by Antonarakis et al., 2020).

There was a recent inquiry in ReLAMC about the current conjoined twins' prevalence rates. The ReLAMC registries did not register conjoined twins in the same way. Some registries consider the twins only one case, and others follow other rules considering two cases when there is a theoretical possibility of separation by surgery. Even with this difference in registration, there is no sign of conjoined-twin increased frequency in ReLAMC data.

This study presented what we believe should be practical steps, tasks, and processes to help others set up a collaborative network to diminish the burden of congenital anomalies. There were at least two planning weaknesses to mention. First, we did not achieve a more direct approach of WHO and PAHO to the country health authorities supporting collaboration with ReLAMC, for all Latin American registries that depend on this. PAHO and the WHO sent representatives to the annual meetings. Their support is essential since ReLAMC is not an initiative of a single country, but an agreement between registries with the periodically elected steering committee and director, according to the Terms of Agreement.

The second planning weakness was constructing the ReLAMC database too closely like the ICBDSR to spare duplicate work since several registries already take part in that network. These differences include periodicity of data sending and using coding outside the ICD-10 Chapter XVII when registering the avoidable embryopathies due to maternal infections. We conclude that the few differences with ICBDSR forms are enough that sending data to ReLAMC is a full job, with no saving in time. ReLAMC could not eliminate those differences to carry out its objectives.

A successful strategy used in the ReLAMC creation was to profit from 50 years of ECLAMC experience networking. Since 2016, four ReLAMC meetings were held accompanying the ECLAMC Annual Meeting, sharing financial resources and building critical mass for analytical and decision-making discussions. The collaborative spirit of ECLAMC putting together many researchers, pediatricians, and students over the past 52 years plays a key role in ReLAMC development.

The construction of networks of institutions for the study of causes, epidemiological surveillance, and proposals for preventive measures for congenital anomalies has been taking place in Latin America and the rest of the world for a long time (Bermejo-Sánchez et al., 2018; Cardoso-dos-Santos et al., 2020). In low- and middle-income countries, these constructions are hampered by the lack of continuity of technical staff in charge of implementing public policies, as ReLAMC experienced through its relationship with the registries. In this unfavorable context, the voluntary network of individuals, such as ECLAMC, has preserved institutional collaboration long enough to return technical teams capable of carrying out the institutional execution of health policies. The supranational health agencies, like WHO and regional agencies like PAHO, must recognize and continue supporting these volunteer networks in the under-developed world. It is essential to acknowledge the March of Dimes (Walani, & Biermann, 2017) and CDC roles, which have long been collaborating for international epidemiological surveillance (Mumpe-Mwanja et al., 2019), including voluntary networks as the ICBDSR (Bermejo-Sánchez et al., 2018), with positive repercussions for Latin America and other parts of the world.

The creation of ReLAMC required and still requires an intense effort to gather people around a common interest. It is an ongoing project with as yet uncompleted tasks such as the complete online platform. Since ReLAMC plans to incorporate new registries and help them check their data quality, it will include in its automatic routine the 40 data quality indicators (DQI) developed by Groisman et al. (2019) as Excel DQIs tool, freely available in http://www.icbdsr.org/data-quality-indicators-tool/. The next steps also include making the information on birth prevalence rates of select congenital anomalies publicly available on the website portal relamc.org, including charts and tables for the place, birth condition, and time. Consultants will be able to select data for total defects or selected anomalies, for total ReLAMC or any country or register, for live or stillbirths or total, each semester or year. Regarding public health indicators, stillbirth rates by country or registry for the entire population covered and the proportion of stillbirths due to specific or total congenital anomalies will be available.

The ReLAMC results of the first 3 years included data from the pilot study and should be interpreted with caution because they may not represent the reality of the regions analyzed. However, the possibility of comparing data from these 12 Latin American registries allowed a better understanding of operational differences or deficiencies in the registries of congenital anomalies. We expect more rapid progress in improving the epidemiological surveillance of congenital anomalies in Latin America.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Study conception and design: Iêda Maria Orioli, Helen Dolk. Acquisition of data: Marta Ascurra, Adriana Benavides, Jorge Lopez Camelo, Aurora Canessa, Giovanny França, Boris Groisman, Paula Hurtado-Villa, Marisol Ibarra-Ramírez, Rosa Pardo, Dania Maria Pastora, Eliana de Aquino Bonilha, Ignacio Zarante. Data organization, and analyses: Lucas Gabriel Gimenez, Mariana Piola, Iêda Maria Orioli. Manuscript first draft, preparation, and revisions: Daniel Correa Mattos, Flávia Mahatma Schneider, Flávia Martinez de Carvalho, Helen Dolk, Jorge Lopez Camelo, Boris Groisman Adriana Benavides, Iêda Maria Orioli.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request, and after permission of the involved congenital anomaly registries.

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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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