

## 1 RESEARCH ARTICLE

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## 3 The Latin American Network for Congenital Malformation Surveillance: ReLAMC

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23

## 1 Abstract

2  
3 The early detection of congenital anomaly epidemics occurs when comparing current with  
4 previous frequencies in the same population. The success of epidemiologic surveillance depends  
5 on numerous factors, including the accuracy of the rates available in the base period, wide  
6 population coverage, and short periodicity of analysis. This study aims to describe the Latin  
7 American Network of Congenital Malformation Surveillance: ReLAMC, created to increase  
8 epidemiologic surveillance in Latin America. We describe the main steps, tasks, strategies used,  
9 and preliminary results. From 2017 to 2019, five national registries (Argentina (RENAC), Brazil  
10 (SINASC/SIM-BRS), Chile (RENACH), Costa Rica (CREC), Paraguay (RENADECOPY-PNPDC)), six  
11 regional registries (Bogotá (PVSDC-Bogota), Cali (PVSDC-Cali), Maule (RRMC SSM), Nicaragua  
12 (SVDC), Nuevo-León (ReDeCon HU), São Paulo (SINASC/SIM-MSP)) and the ECLAMC hospital  
13 network sent data to ReLAMC on a total population of 9,152,674 births, with a total of 101,749  
14 malformed newborns (1.1%; 95% CI 1.10-1.12). Of the 9,000,651 births in countries covering both  
15 live and stillbirths, 88,881 were stillborn (0.99%; 95% CI 0.98-0.99), and among stillborns, 6,755  
16 were malformed (7.61%; 95% CI 7.44-7.79). The microcephaly rate was 2.45 per 10,000 births  
17 (95% CI 2.35-2.55), hydrocephaly 3.03 (2.92-3.14), spina bifida 2.89 (2.78-3.00), congenital heart  
18 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  
19 2.56 (2.46-2.67), conjoined twins 0.16 (0.14-0.19), and Down syndrome 5.33 (5.18-5.48). Each  
20 congenital anomaly showed heterogeneity in prevalence rates among registries. The  
21 harmonization of data in relation to operational differences between registries is the next step  
22 in developing the common ReLAMC database.

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## 1 **1 INTRODUCTION**

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

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

21           WHO declared the Zika virus (ZIKV) epidemic a public health emergency in 2016  
22 ([https://www.who.int/news/item/01-02-2016-who-statement-on-the-first-meeting-of-the-](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)  
23 [international-health-regulations-\(2005\)-\(ihr-2005\)-emergency-committee-on-zika-virus-and-](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)  
24 [observed-increase-in-neurological-disorders-and-neonatal-malformations](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  
25 of a newly described congenital ZIKV syndrome (Oliveira Melo et al., 2016; Schuler-Faccini et al.,  
26 2016). Brazilian information available at DATASUS (Marinho et al., 2016) and at ECLAMC  
27 databases (Orioli et al., 2017) provided insights into the microcephaly crisis by providing baseline  
28 prevalence for the Brazilian Northeast region before the virus entered the continent. Limitations  
29 included underreporting of microcephaly cases in DATASUS and the corrections that were

1 required to the hospital-based prevalence estimates of ECLAMC as well as the small coverage of  
2 ECLAMC in epidemic areas. By 2015, Latin America had also established many registries of  
3 congenital anomalies and information systems working at regional or national levels. However,  
4 those data systems were not networked, preventing further, standardized, and more accurate  
5 analyses of the microcephaly rates. In 2016, answering calls from the Brazilian National Council  
6 for Scientific and Technological Development (CNPq) and European Union Zika-PLAN project  
7 (Wilder-Smith et al., 2019), we proposed creating a Latin American network of congenital  
8 malformation registries. We describe here the strategy and methods used and the first results  
9 obtained.

10

## 11 **2 METHODS**

### 12 **2.1 Latin American Network for Congenital Malformation Surveillance**

#### 13 **(ReLAMC): creation**

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

21 One strategy used in the construction of ReLAMC was to profit from 50 years of ECLAMC  
22 experience in networking. We chose the ECLAMC annual meetings as a host from 2016 to 2019  
23 to discuss with the invited Surveillance Program directors the proposed ReLAMC creation project  
24 and its further development. When defining the ReLAMC database, another strategy used was  
25 following as closely as possible the ICBDSR (International Clearinghouse for Birth Defects  
26 Surveillance and Research) since several Latin American programs already send data to the  
27 ICBDSR network (Table 1). We also followed the EUROCAT (European Surveillance of Congenital  
28 Anomalies) model for the initial design of the Terms of Agreement, data sharing options, the use

1 of data quality and public health indicators, and web page contents, particularly prevalence  
2 tables. The Skeleton Plan with the main steps, definition, and strategies for ReLAMC creation, as  
3 well as the initial history, are in Table S1 (Supplementary Material).

## 4 **2.2 ReLAMC procedures and databases content**

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

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

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

22 Among the 97 selected types of congenital anomalies transmitted to ReLAMC as  
23 aggregate data, 21 conditions are listed outside ICD-10 chapter XVII (Congenital malformations,  
24 deformations, and chromosomal abnormalities). Seven are embryopathies with or without  
25 neonatal infection caused by maternal infection by syphilis (A50), human immunodeficiency virus  
26 (HIV) (B24), rubella (P35.0), cytomegalovirus (P35.1), herpes simplex (P35.2), chickenpox virus  
27 (P35.8), and *Toxoplasma gondii* (P37.1), known collectively as STORCH infections which are in

1 ICD-10 chapter I (Certain infectious and parasitic diseases) and XVI (Certain conditions originating  
2 in the perinatal period). Also, the newly created code for Zika virus syndrome (P35.4) is in chapter  
3 XVI, even if in ReLAMC until 2019, it was P35.8 (Other congenital viral diseases). Table S2  
4 (Supplementary Material) shows the ReLAMC list of the 76 congenital anomalies with their ICD-  
5 10 chapter XVII codes and observations and the 21 coded outside ICD-10 chapter XVII.

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

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

### 18 **2.3 Data analysis**

19 The twelve registries described in this work joined ReLAMC at different times, which  
20 extended the pilot data sharing from 2017 to 2018. The pilot study tested the data collection  
21 forms, last revised in 2019. With the material sent during the pilot study and subsequently, we  
22 analyzed the prevalence rates of stillbirths, congenital anomalies, congenital anomalies in  
23 stillbirths, and nine selected congenital anomalies for each registry and the combined total. The  
24 definition of stillbirth is not uniform among registries, including the delivery of the dead fetus at  
25 or after 20 weeks gestation or weighing 350 grams or more when gestation time is unknown. The  
26 prevalence rate of stillbirths was calculated per 1,000 births (live births and stillbirths). The  
27 prevalence rate of congenital anomalies was calculated per 100 births, and selected congenital  
28 anomalies per 10,000 births. The prevalence rate of congenital anomalies in stillbirths was



1 calculated per 100 stillbirths. The nine selected anomalies were those with the following  
2 International Classification of Diseases 10 (ICD-10) codes:

- 3 • Microcephaly (Q02)
- 4 • Hydrocephaly (Q03)
- 5 • Spina bifida (Q05)
- 6 • Congenital heart defects (Q20 to Q26)
- 7 • Cleft lip (Q36)
- 8 • Cleft lip and palate (Q37)
- 9 • Talipes (Q66)
- 10 • Conjoined twins (Q89.4)
- 11 • Down syndrome (Q90)

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

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

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

21

## 22 **3 RESULTS**

### 23 **3.1 Creation history**

24 The ReLAMC initiative of networking registries in Latin America came as a response to the  
25 increase of microcephaly rates during the ZIKV pandemic. In 2016 we invited 11 Latin American

1 congenital anomaly registries to participate in ReLAMC. The meeting was held together with the  
2 48th ECLAMC annual meeting, and the concept was met with enthusiasm. We invited six new  
3 registries in the following year totaling 17 registries involved with the ReLAMC creation. Fourteen  
4 registries continued to be involved, and 12 could share data from 2017/1 (Table 1, Figure 1). We  
5 have summarized the history of ReLAMC creation and development in Table S1 (Supplementary  
6 Material).

### 7 **3.2 Shared data**

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

14 ReLAMC covered 3,502,706 Latin American live births in 2017, excluding overlapping  
15 live births, 3,484,085 live births from national and regional registries, and 18,621 live births  
16 from ECLAMC hospitals not covered by those registries. National registries covered 82.2% of  
17 live births in Argentina, Brazil, Chile, Costa Rica, and Paraguay (3,436,478/4,179,773 live births).  
18 In comparison, the regional registries covered 59.3% of live births in Bogotá D.C. (Colombia),  
19 Cali city (Colombia), Maule region (Chile), North-Western Nicaragua (Chinandega and León  
20 departments), Nuevo-León state (Mexico), and São Paulo municipality (Brazil)  
21 (256,321/432,153) (Table 1). The coverage of live births is heterogeneous among national  
22 registries varying from 29.7 to 96%, the same occurring among regional registries with a  
23 broader range from 12 to 100% (Table1). The duration of data collection for each registry varies  
24 from 53 years for ECLAMC to four years for national registries in Chile and Paraguay (Table 1).

### 25 **3.3 Health Indicators**

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

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

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

### 8           **3.4 Congenital anomaly prevalence**

9           National registries in Argentina, Brazil, Chile, and Costa Rica, and the regional registry  
10 of Nuevo-León (8,336,969 births) registered cases for syphilis, cytomegalovirus, and  
11 toxoplasmosis, summing up 19 syphilis, five cytomegalovirus, and nine toxoplasmosis cases for  
12 2017, a rate of 3.96 per 10,000 births (95% CI 2.72 - 5.56). ReLAMC did not receive data from  
13 all registries for the selected congenital anomalies coded outside the ICD-10 chapter XVII,  
14 including the embryopathies caused by maternal infections during pregnancy.

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

## 21           **DISCUSSION**

22           Two transnational networks provide a forum for congenital anomaly registries to share  
23 data in surveillance and research. The ICBDSR congregate registries from across the world since  
24 1974 (Bermejo-Sanchez et al., 2018), and EUROCAT is a network of population-based registries  
25 in the European Union created in 1979 (Boyd et al., 2011). Latin America has a hospital-based  
26 network, ECLAMC, with a central database, created in 1967 by Eduardo Castilla (Castilla and  
27 Orioli, 2004), that has conducted congenital anomaly surveillance to detect and investigate  
28 unusual occurrences in time or space. For time clusters, or epidemics, routine monitoring is  
29

1 performed, and quarterly data are compared against other equivalent surveillance systems  
2 through the ICBDSR, of which ECLAMC was one of the founders. From 1985 with the Registro  
3 Cubano de Malformaciones Congénitas (RECUMAC), and 1987, with the Centro de Registro de  
4 Enfermedades Congénitas en Costa Rica (CREC), until recent years, population-based national or  
5 regional congenital anomaly registries have been set up in many countries in Latin America.  
6 Although many are members of ICBDSR, these systems are not networked on a Latin American  
7 basis. ReLAMC was created to fill this gap as a transnational network of the Latin American  
8 national or regional registries, also integrated with ECLAMC.

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

21 To estimate some public health indicators, we analyzed all data sent to ReLAMC from  
22 2017 to 2019, a total of 9,152,674 births. Stillbirth rates ranged from 4 to 11 per 1,000 births.  
23 They were above 8 per 1,000 in the national registries of Argentina, Brazil, and in ECLAMC. The  
24 ECLAMC hospital-based population suffers from the hospital referral effect (Orioli et al., 2017),  
25 where prenatally diagnosed fetuses cause referral of delivery to high complexity hospitals,  
26 probably explaining the higher ECLAMC mortality rate. The regional stillbirth rate of 7.84 in São  
27 Paulo municipality is lower than the national rate of 10.26 per 1.000 births. It is at the upper end  
28 of the confidence limits for the aggregate mean rate from 2010 to 2014 (7.65, 95% CI 7.47 - 7.84)  
29 in São Paulo municipality (Andrews et al., 2017). These authors found high heterogeneity among

1 municipalities of the São Paulo state in this period (0 to 29.7 per 1,000 births), mirroring what  
2 happens throughout Brazil (Andrews et al., 2017). Also, they observed that the stillbirth rate  
3 exceeded the neonatal mortality rate (newborn death until 27 completed days) in the perinatal  
4 mortality rate (Lawn et al., 2016), increasing the importance of the stillbirth rate as a health  
5 indicator.

6 In 2013, the fetal death rate of 5.96 per 1,000 live births and fetal deaths, described in  
7 the USA (McDorman and Gregory, 2015), was lower than the Latin American stillbirth rate (9.6  
8 per 1,000). Also lower than ReLAMC, the rate of fetal deaths at  $\geq 23$  weeks was 2.8 per 1,000 live  
9 births, in Friuli Venezia Giulia, 2005 to 2013, excluding termination of pregnancy for fetal anomaly  
10 (TOPFA) (Monasta et al., 2020). Lower stillbirth rates were also published for Australia, 7.1 per  
11 1,000, from 2013 to 2014 (Australian Institute of Health and Welfare, 2018), and the U.K. stillbirth  
12 rate is 3.74 per 1,000 (Draper et al., 2019).

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

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

1           The congenital anomaly rate has several components  
2 (<https://www.who.int/publications/i/item/9789241548724>). These prevalence rates among  
3 ReLAMC registries ranged from 1% to 4%. Choosing a cut-off congenital anomaly rate to indicate  
4 under registration is not useful due to the different registries' characteristics. EUROCAT had  
5 proposed that rates below 2% suggest under registration in their system (Loane et al., 2011).  
6 National registries had a larger number of births, usually under mandatory rules. Their lower  
7 congenital anomaly rates than regional registries possibly occurred because their hospitals  
8 preferentially register visible and major defects. The Costa Rica register is an exception having a  
9 congenital anomaly rate of over 2.5%, like Cali, Bogotá, and ECLAMC. Another factor that may  
10 influence these rates is the length of observation. The length of observation in Costa Rica is until  
11 one-year-old, and there is an active search of patients with congenital anomalies, differently from  
12 other national registries (Benavides-Lara et al., 2011). The ReLAMC congenital anomaly rate was  
13 lower compared to Europe (2017 - 2018), (EUROCAT) (2.54%; 95% CI 2.51 - 2.57), the same  
14 occurring with the rate of 2.03% (95% CI 1.98 - 2.09) described for Utah (USA), 2005 - 2009,  
15 (Feldkamp et al., 2017). With ReLAMC consolidation and standardized reporting and quality  
16 criteria applied, we expect the prevalence of congenital anomaly to be closer to those reported  
17 in Europe and the United States.

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

25           Head circumference is a significant factor in the suspicion and diagnosis of microcephaly  
26 and hydrocephaly, alongside image studies and clinical neurology evaluation. Several authors  
27 have also associated hydrocephaly and other associated brain damage with the Zika congenital  
28 syndrome since the earlier complete descriptions (Mlakar et al., 2016; Soares de Oliveira-  
29 Szejnfeld et al., 2016; Alvarado & Schwartz, 2017; Del Campo et al., 2017). The primary focus on

1 head circumference measures and the different definitions of microcephaly and hydrocephaly  
2 among registries could be the main factors in explaining heterogeneity in rates during the ZIKV  
3 epidemic and afterward. In ECLAMC, another factor in explaining increased rates of microcephaly  
4 and hydrocephaly derived from its participation in ReLAMC data being restricted to the 2017  
5 year. During this year, the ZIKV epidemics were active in several ECLAMC hospital cities.

6 Brazil's microcephaly rate in 2017 - 2019 (1.65 per 10,000) was lower than rates in other  
7 registries. Nevertheless, it was almost three times greater than the Brazilian microcephaly  
8 prevalence rate in the 2000 - 2014 period (0.56 per 10,000) (Marinho et al., 2016). The inclusion  
9 of the 2017 epidemic year in the more recent rate must explain part of the increase, but an  
10 increase in the completeness of microcephaly reporting due to the ZIKV epidemic may also  
11 contribute to this increase. In the case of Costa Rica, where the prevalence was several times  
12 higher than most of the registries, the congenital Zika epidemic, whose peak of cases occurred  
13 between 2017 and 2018, caused its baseline to increase almost four times  
14 ([https://www.inciensa.sa.cr/vigilancia\\_epidemiologica/informes\\_vigilancia/2018/Malformacion  
15 es%20Congenitas/Informe%20epidemiologico%20anual%20defectos%20congenitos.%20Costa  
16 %20Rica%202018.pdf](https://www.inciensa.sa.cr/vigilancia_epidemiologica/informes_vigilancia/2018/Malformaciones%20Congenitas/Informe%20epidemiologico%20anual%20defectos%20congenitos.%20Costa%20Rica%202018.pdf)).

17 The prevalence rates of spina bifida were heterogeneous among ReLAMC registries. Since  
18 they are a useful measure of the folic acid fortification health policy (Crider et al., 2018), the  
19 registries initiated a spina bifida epidemiological research study to better explain this  
20 heterogeneity. The same occurred for congenital heart defects, where the collaborative  
21 epidemiological study that has been initiated is to clarify which differences resulted from coding  
22 or resulted from differences in perinatal care resources. Operational changes in 2018 occurred  
23 in the forms to send aggregate data to ReLAMC. We added ten new congenital heart defect ICD-  
24 10 codes to the earlier seven and eliminated the "other cardiopathies" code. The contribution of  
25 these changes to the heterogeneity of congenital heart defect rates must be small since the  
26 registries had sent a higher volume of data with the new forms.

27 Several ReLAMC registries presented prevalence rates for cleft lip (Q36) and cleft lip and  
28 palate (Q37) that suggested under registration or coding problems. Oral cleft information such  
29 as the proportion of each type of cleft could be used when establishing data quality indicators

1 for congenital anomaly registries (Groisman et al., 2019), and indicated several coding problems  
2 in the live birth part of the Brazilian registry (Nascimento et al., 2017). The ICD-10 classification  
3 of oral clefts could induce oral cleft coding errors in those registries that use the ICD-10  
4 classification without any extension such as the BPA (Nascimento et al., 2017). The ICD-10 BPA  
5 codes Q36.90 and Q36.99 allow the separation of unilateral cleft lip from a unspecified cleft lip,  
6 and the Q37.99 code allows the registration of an unspecified cleft lip with cleft palate case. The  
7 cleft lip prevalence rate is not expected to be close to or greater than the cleft lip and palate rate,  
8 and this error can also result when registries primarily register cases with cleft lip with and  
9 without cleft palate (Q36 plus Q37) combined. For a long time, this entity has been considered  
10 the same anomaly based on the usual occurrence of cleft lip only and cleft lip and palate in the  
11 same families (Fogh-Andersen, 1942).

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

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

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

27 This study presented what we believe should be practical steps, tasks, and processes to  
28 help others set up a collaborative network to diminish the burden of congenital anomalies. There  
29 were at least two planning weaknesses to mention. First, we did not achieve a more direct



1 approach of WHO and PAHO to the country health authorities supporting collaboration with  
2 ReLAMC, for all Latin American registries that depend on this. PAHO and the WHO sent  
3 representatives to the annual meetings. Their support is essential since ReLAMC is not an  
4 initiative of a single country, but an agreement between registries with the periodically elected  
5 steering committee and director, according to the Terms of Agreement.

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

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

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

1 including voluntary networks as the ICBDsr (Bermejo-Sanchez et al., 2018), with positive  
2 repercussions for Latin America and other parts of the world.

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

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

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## 12 **CONFLICT OF INTEREST**

13 The authors have no conflict of interest to declare.

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## 15 **AUTHOR CONTRIBUTIONS**

16

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## 25 **DATA AVAILABILITY STATEMENT**

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

28

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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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## FIGURE LEGENDS

Fig. 1. National and Regional Registries, and ECLAMC hospital network sending data to ReLAMC, 2017 to 2019.

Fig. 2. ReLAMC prevalence of stillbirths per 1,000 births, 2017 to 2019.

Fig. 3. ReLAMC prevalence of congenital anomalies per 100 births, 2017 to 2019.

Fig. 4. ReLAMC prevalence of congenital anomalies in stillbirths per 100 stillbirths, 2017 to 2019.

Fig. 5. ReLAMC prevalence of microcephaly per 10,000 births, 2017 to 2019.

Fig. 6. ReLAMC prevalence of Down syndrome per 10,000 births, 2017 to 2019.

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 §	1987	Centro de Registro de Enfermedades Congénitas	National	Costa Rica	1 year	Yes	68,479	71,332	96.0
RENAC §	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†	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	196082	100.0
PVSDC Bogotá §	2001	Programa de Vigilancia y Seguimiento de Defectos Congénitos Bogotá	Regional	Bogota	Maternity discharge	No	15,255	94,896	16.1
RRMC SSM Maule† §	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 §	2010	Programa de Vigilancia y Seguimiento de Defectos Congénitos Cali	Regional	Cali	Maternity discharge	No	12,399	34,556	35.9
ReDeCon HU §	2011	Registro de Defectos Congénitos Hospital Universitario UANL	Regional	Nuevo-León	Maternity discharge	No	9,269	77,242	12.0

ECLAMC §	1967	Estudo Colaborativo Latino Americano de Malformaciones Congénitas	Hospitals ‡ 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	—	—

†Regional registries that overlapped with the national registries in ReLAMC data.

‡ 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) .

§ Latin American registries also sending data to the ICBDSR.

Table S1. Skeleton Plan for ReLAMC creation: steps, definition, and history.

ReLAMC SKELETON PLAN	DESCRIPTION
STEPS	1. To design a complete network project including a Terms of Agreement and Commitments to be signed by participating Surveillance Programs and ReLAMC regarding statutory aspects and the basic operational mode manual.
	2. To define the ReLAMC databases, classifying the variables as obligatory or optional to allow wider participation of the programs.
	3. To put together the principal actors to discuss the project and to decide the final operational mode.
	4. To construct a web platform to allow the secure sending and reception of data, semiannual updating of the ReLAMC databases, and public consultation on congenital anomalies frequencies.
STRATEGIES	<p>1. To profit from ECLAMC experience on networking:</p> <ul style="list-style-type: none"> <li>○ Conjoined ECLAMC/ReLAMC meetings 2016-2019</li> </ul> <p>2. To use the ICBDSDR databases specifications as a model.</p> <p>3. To use the EUROCAT model for the initial design of:</p> <ul style="list-style-type: none"> <li>○ the Term of Agreement: registries retaining ownership of their data</li> <li>○ data sharing options: <ul style="list-style-type: none"> <li>i. e.g. choice for registries between sharing individual or aggregate data</li> <li>ii. e.g. use of core versus non-core variables</li> </ul> </li> <li>○ use of data quality indicators: <ul style="list-style-type: none"> <li>i. (Loane et al. 2011) (Eu-Rd: <a href="https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/data-quality_en">https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/data-quality_en</a>)</li> </ul> </li> <li>○ use of public health indicators: <ul style="list-style-type: none"> <li>i. (Khoshnood et al., 2011) (Eu-Rd: <a href="https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/key-public-health-indicators_en">https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/key-public-health-indicators_en</a>)</li> </ul> </li> <li>○ web page contents, particularly prevalence tables <ul style="list-style-type: none"> <li>i. (Eu-Rd: <a href="https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en">https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en</a>)</li> </ul> </li> </ul>

<p>ReLAMC DEFINITION</p>	<p>ReLAMC is formed by the registries that decide to take part, and that can follow the conditions set out in its Terms of Agreement and Commitments. Each registry has one vote in the annual general assembly. The right to vote is independent of the type of population covered, and whether it is multinational, national, regional, or hospital, or aggregated or individual data can be provided.</p>
<p>PRE-HISTORY 2016</p>	<p>ReLAMC project submitted for funding to CNPq - Combate ao Vírus Zika - Brasil, and CE - Horizon 2020 - Zika Plan.</p> <p>Invitation to Latin American congenital anomalies registries we knew for the First ReLAMC Meeting to be held together with the ECLAMC Annual Meeting.</p> <p>Sending previously written material with detailed ReLAMC proposition to each registry invited to participate in the ReLAMC meeting workshops.</p>
<p>HISTORY</p>	<p>Annual Meetings</p>
<p>November 2016 1<sup>st</sup> ReLAMC &amp; 48<sup>th</sup> ECLAMC Annual Meeting, Buenos Aires, Argentina.</p>	<p>Participants registries: Argentina (RENAC), Bogotá (PVSDC-Bogota), Brazil (SINASC/SIM-BRS), Cali (PVSDC-Cali), Chile (RENACH), Cuba (RECUMAC), Maule (RRMC SSM), and the ECLAMC network currently with hospitals from Argentina, Bolivia, Brazil, Chile, Colombia, Peru, and Venezuela.</p> <p>Dr. Helen Dolk, former EUROCAT director (1999 - 2014), and Dr. Joan Morris member of the EUROCAT Steering Committee.</p> <p>CDC sent representative to help on creating the network. nt representative to help on creating the network.</p> <p>The ReLAMC concept was met with enthusiasm, and negotiations around a common protocol started.</p>
<p>November 2017 2<sup>st</sup> ReLAMC &amp; 49<sup>th</sup> ECLAMC Annual Meeting, Pilar, Buenos Aires province, Argentina.</p>	<p>Participants registries: Argentina (RENAC), Bogotá (PVSDC-Bogota), Brazil (SINASC/SIM-BRS), Cali (PVSDC-Cali), Chile (RENACH), Cuba (RECUMAC), Maule (RRMC SSM), ECLAMC network, Colombia (SIVIGILA), Panamá (PNMC), Paraguay (RENADECOPY-PNPDC), Nicaragua (SVDC), Nuevo-León (ReDeCon HU), São Paulo (SINASC/SIM-MSP), Uruguay (RND CER), and Mexico (RYVENCE).</p> <p>Dr. Helen Dolk, former EUROCAT director (1999 - 2014), and Dr. Joan Morris member of the EUROCAT Steering Committee.</p> <p>WHO, PAHO, and CDC sent representatives to share their international experience and support on creating the network.</p> <p>A protocol was exhaustively debated to ensure the feasibility of all members' participation and led to a Terms of Agreement between</p>

	<p>parties. The participants discussed details about the network's structure and governance and appointed a pro-tempore director and steering committee.</p>
<p>November 2018 3<sup>st</sup> ReLAMC &amp; 50<sup>th</sup> ECLAMC Annual Meeting Pilar, PABA, Argentina.</p>	<p>Participants registries: Argentina (RENAC), Bogotá (PVSDC-Bogota), Brazil (SINASC/SIM-BRS), Cali (PVSDC-Cali), Chile (RENACH), Costa Rica (CREC), Cuba (RECUMAC), Maule (RRMC SSM), ECLAMC network, Panamá (PNMC), Paraguay (RENADECOPY-PNPDC), Nicaragua (SVDC), Nuevo-León (ReDeCon HU), São Paulo (SINASC/SIM-MSP).</p> <p>Dr. Helen Dolk, former EUROCAT director (1999 - 2014), and Dr. Joan Morris member of the EUROCAT Steering Committee.</p> <p>WHO and the PAHO sent representatives that actively participate in lectures and workshops.</p> <p>The data-sharing pilot project results were discussed. the first General Assembly was realized, and elected the definitive board members.</p>
<p>November 2019 4<sup>st</sup> ReLAMC &amp; 51<sup>th</sup> ECLAMC Annual Meeting Caxias do Sul, RS, Brasil</p>	<p>Participants registries: Bogotá (PVSDC-Bogota), Brazil (SINASC/SIM-BRS), Cali (PVSDC-Cali), Chile (RENACH), Costa Rica (CREC), Cuba (RECUMAC), Maule (RRMC SSM), ECLAMC network, Panamá (PNMC), Paraguay (RENADECOPY-PNPDC), Nicaragua (SVDC), São Paulo (SINASC/SIM-MSP).</p> <p>Dr. Joan Morris member of the EUROCAT Steering Committee.</p> <p>The WHO sent representative that actively took part in lectures and workshops</p> <p>The results from the first ReLAMC collaborative research project on microcephaly were presented.</p> <p>The ReLAMC assembly approved three news collaborative projects, on spina bifida, on congenital anomalies in adolescent mothers, and on congenital heart defects proposed respectively by RENACH, RECUMAC, and CREC.</p>
<p>November 2020 5<sup>st</sup> ReLAMC &amp; 52<sup>th</sup> ECLAMC Annual Meeting</p>	<p>Cancelled the annual meeting programed to August 30 - September 3rd New virtual meeting programmed to December 11 - 12.</p>
<p>MEMBERSHIP HISTORY 2017-2020</p>	<p>Registries from Argentina (RENAC), Bogotá (PVSDC-Bogota), Cali (PVSDC-Cali), Costa Rica (CREC), Maule (RRMC SSM), ECLAMC network, Panamá (PNMC), Paraguay (RENADECOPY-PNPDC), Nicaragua (SVDC), and Nuevo-León (ReDeCon HU) have signed the Terms of Agreement with ReLAMC.</p>



Table 2. Prevalence rates per 10,000 births of nine congenital anomalies, by ReLAMC registries localities, 2017 to 2019

	BRAZIL	SÃO PAULO	ARGENTINA	CHILE	COSTA RICA	PARAGUAY	ECLAMC	CALI	BOGOTÁ	NUEVO LEÓN	NICARAGUA	MAULE	TOTAL
Q002 cases	1245	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†	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	7033	2926	1768	400	1209	253	227	41	189	74	59	4	14,183
‡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	1466	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	1595	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	1171	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	2929	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

† prev., 95% CI = prevalence, 95% Confidence Intervals

‡CHD = Congenital heart diseases

Supplementary material

Table S2. International Classification of Diseases - 10 codes used in the ReLAMC form Selected Anomalies

<b>Códigos CIE-10</b>	Description	Example or Observation
<b>A50 + Q86.8</b>	Congenital syphilis	Embryopathy with or without natal infection
<b>B24 + Q86.8</b>	Unspecified human immunodeficiency virus disease [HIV]	Embryopathy with or without natal infection
<b>E00</b>	Congenital iodine deficiency syndrome	
<b>E25</b>	Congenital adrenogenital disorders with enzyme deficiency	Congenital adrenal hyperplasia
<b>E70</b>	Phenylketonuria and other disorders of aromatic aa metabolism	
<b>H90</b>	Conductive and sensorineural hearing loss	Congenital deafness
<b>K40</b>	Inguinal hernia	
<b>O30.0</b>	Double pregnancy	
<b>O30.1</b>	Triple pregnancy	

<b>O30.2</b>	Quadruple pregnancy	
<b>O36.2</b>	Maternal care for hydrops fetalis	Hydrops fetalis not associated with isoimmunization
<b>O36.5</b>	Maternal care for fetal growth deficit	PEG
<b>O40</b>	Polyhydramnios	
<b>O41.0</b>	Oligohydramnios	
<b>P35.0 + Q86.8</b>	Congenital infection due to congenital rubella	Embryopathy with or without natal infection
<b>P35.1 + Q86.8</b>	Congenital infection due to cytomegalic virus	Embryopathy with or without natal infection
<b>P35.2 + Q86.8</b>	Congenital infection due to herpes simplex	Embryopathy with or without natal infection
<b>P35.8 + Q86.8</b>	Congenital infection due to chickenpox and other congenital viral diseases	Embryopathy with or without natal infection
<b>P37.1 + Q86.8</b>	Congenital infection due to Toxoplasma gondii	Embryopathy with or without natal infection
<b>P94.1</b>	Congenital hypertonia	
<b>P94.2</b>	Congenital hypotonia	

Q00	Anencephaly	Includes craniorachischisis and iniencephaly
Q01	Encephalocele	
Q02	Microcephaly	
Q03	Hydrocephalus	
Q04.1; Q04.2; Q87.0	Arrhinencephaly and Holoprosencephaly	Includes Ciclopia (Q87.0)
Q05	Spina bifida	
Q11.1;Q.11.2	Anophthalmia / Microphthalmia	
Q12.0	Congenital cataract	
Q15.0	Congenital glaucoma	
Q16.0; Q17.2	Anotia / Microtia	
Q20.0	Common trunk arteriosus	
Q20.1	Transposition of the great vessels in the right ventricle	
Q20.3	Ventriculoarterial connection mismatch	
Q20.4	Double Inlet Ventricle, Common Ventricle	
Q21.0	Ventricular septum defect	

Q21.1	Atrial septum defect	
Q21.2	Atrioventricular septal defect	
Q21.3	Tetralogy of Fallot	
Q22.0	Pulmonary valve atresia	
Q22.1	Congenital pulmonary valve stenosis	
Q22.4	Congenital stenosis / atresia of the tricuspid valve	
Q22.5	Ebstein anomaly	
Q23.0	Congenital aortic valve stenosis / atresia	
Q23.4	Left heart hypoplasia syndrome	
Q25.1	Coarctation of the aorta	
Q25.2	Atresia of the aorta	
Q26.2	Total anomalous connection of the pulmonary veins	
Q30.0	Choanal atresia	
Q35	Cleft palate	Excludes cleft lip
Q36	Lip cleft	Excludes cleft palate

Q37	Cleft palate with cleft lip	
Q39.0 .... Q39.4	Esophageal atresia / stricture with or without fistula	
Q41.0	Absence, atresia, and congenital stenosis of the duodenum	
Q41.1..... Q41.9	Other small bowel atresia / stenosis	Other absences, atresias, and stenosis of the small intestine
Q42	Anorectal and large bowel atresia / stenosis	
Q43.1	Hirschsprung's disease	
Q44.2; Q44.3	Atresia and stenosis of the bile ducts	
Q53	Cryptorchidism	
Q54, excl. Q54.4	Hypospadias	
Q56	Indeterminate sex	
Q60.0; Q60.1; Q60.2	Renal agenesis	
Q61	Cystic kidney disease	

Q64.0	Epispadias	
Q64.1	Urinary bladder exstrophy	
Q66.0	Talipes equinovarus	
Q69.1- Q69.2 including only accessory hallux	Polydactyly, pre-axial	
Some Q69.0; some Q69.2 excluding accessory hallux	Polydactyly, post-axial	
Q69.9; some Q69.0	Polydactyly, other or unspecified	
Q70	Syndactyly	
Q71; Q72; Q73	Total limb reduction defects	Includes not specified
Q71.0; Q71.2; Q71.3; Q72.0; Q72.2; Q72.3; Q73.0	Transverse reduction	
Q71.1; Q72.1; Q72.4; Q73.1	Intercalary reduction	
Q71.4; Q72.5	Preaxial Reduction	
Q71.5; Q72.6	Postaxial Reduction	

Q71.6; Q71.8; Q71.9; Q72.7; Q72.8; Q72.9; Q73.8	Other reduction or not specified	
Q74.3	Arthrogryposis multiplex congenita	
Q75.0; Q75.1	Craniosynostosis	
Q76	Congenital malformations of the spine and bone thorax	
Q77; Q78.1....Q78.5	Osteochondrodysplasias	
Q78.0	Imperfect osteogenesis	
Q79.0; Q79.1	Diaphragmatic hernia and other abnormalities	
Q79.2	Omphalocele	
Q79.3	Gastroschisis	
Q79.4	Prune belly or prune abdomen	
Q80	Congenital ichthyosis	
Q81	Epidermolysis bullosa	
Q86.0	Fetal syndrome (dysmorphic) due to alcohol	



Q87	Other congenital malformation syndromes (not elsewhere classified)	
Q89.4	Conjoined twins	
Q90	Down's Syndrome	
Q91.0 ....Q91.3	Trisomy 18	
Q91.4..... Q91.7	Trisomy 13	
Q92; Q93	Other abnormalities of autosomes, not elsewhere classified	
Q96	Turner syndrome	
Q97; Q98; Q99	Other abnormalities of the sex chromosomes, not elsewhere classified	
Q89	Other congenital anomalies	Excludes Q89.4