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# Rare Diseases in Uruguay: Focus on Infants with Abnormal Newborn Screening

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## Abstract

**Introduction:** Newborn Screening Program (NBS) in Uruguay includes congenital hypothyroidism (CHT), phenylketonuria (PKU), congenital adrenal hyperplasia (CAH), cystic fibrosis (CF), medium chain acyl-CoA dehydrogenase deficiency (MCADD), and Congenital Hearing Loss (CHL). **Objectives:** This study describe the epidemiological characteristics of newborns with abnormal neonatal screening tests diagnosed by blood drop and otoacoustic emissions in Uruguay. **Results:** Cases with abnormal NBS tests (399 newborns; 0.17%) were compared to the newborns with normal tests in the same period (239,240). Prevalence rates (per 10,000 livebirths) were 10.00 for CHL; 3.70 for CH; 1.20 for CF; 0.59 for CAH; 0.54 for PKU; 0.13 for MCADD. The Department of Artigas had the highest rate of abnormal tests. Lower maternal education, less prenatal care, increased prematurity rate and neonatal depression were more frequent in in mothers whose children had CHL. **Conclusions:** This is the first study evaluating the characteristics of newborns with abnormal screening in Uruguay. Because these results may impact the planning of health services, data transmission between clinical care and public health systems is needed to improve both follow-up and management.

## Keywords

Rare diseases, newborn screening, health policies, mandatory diseases, public health, epidemiological surveillance, congenital anomalies.

## Background

Rare diseases (RDs) are those that affect 1/2,000 people or less [1]; many of them are disabling in the long run and can be life threatening. As noted by Evangelista et al. [2], the small number of affected patients and their geographic dispersion is an obstacle for diagnosis, access to care, research and improving the medical expertise with RDs. Many RDs manifest as congenital anomalies (CAs) and affect millions of births worldwide. CAs are an urgent priority for global health [3]; seriously affecting children's health and causing disabilities [4–5]. The infant mortality rate is a very relevant indicator for analysing the health status of a population and it is globally declining. But infant mortality due to CAs remained practically constant [6], resulting in a proportional increase of its contribution for infant mortality in both developing and developed countries. Uruguay is among the five countries with the lowest infant mortality rates in the Americas (after Cuba, Canada, the USA and Chile) and has had almost static CA mortality over the last three decades [7]. Newborn screening programmes are present in most countries in the world with different characteristics. However, they share their main objective,

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which is to prevent death or disability [8–9]. At the beginning of the 1990s, Neonatal Screening Programme in Uruguay was established in some maternity hospitals in the country to detect congenital hypothyroidism (CH), and later the program has been extended to all birth in the country and was expanded to include other diseases. Since 2013, the National Neonatal and Infant Screening Programme (*Programa Nacional de Pesquisa Neonatal y del Lactante - PNPNL*) includes a set of medical procedures that are used for the obligatory neonatal detection of endocrine-genetic pathologies and others through a) blood drop tests, b) otoacoustic emissions and c) strengthening the systematic physical examination of newborn to detect minor or major congenital malformations, either internal or external, and to detect hip dysplasia by ultrasound. In Uruguay, six pathologies have mandatory testing: 1) congenital hearing loss (CHL), 2) congenital hypothyroidism CH, 3) cystic fibrosis (CF), 4) congenital adrenal hyperplasia (CAH), 5) phenylketonuria (PKU) and 6) medium-chain acyl-CoA dehydrogenase deficiency (MCADD). In Uruguay all newborns, either in public or private hospitals, are entered in the programme. If the diagnosis is confirmed, they are entitled to receive adequate, lifelong treatment and follow-up (medical, pharmacological, nutritional, surgical and speech therapy), as well as genetic counselling. The coverage is virtually 100% of births in the country. Obtaining a blood spot from the heel is routinely performed 40 hours after birth (which makes it likely that the infant has begun to consume but has not yet left hospital). If a new sample is required, the parents are contacted immediately. The Customs Plan is a programme in operation for over 30 years in the public health system, which aims to ensure that newborns and breastfeeding women can be traced following discharge from the Maternity in Montevideo: public health sector users residing in the capital are thus contacted and taken to a health facility for a repeat sample collection. Patients from the countryside are contacted through the Honorary Commission to Fight Tuberculosis and Prevalent Diseases. Both patients and their accompanying family members are entitled to transportation from their place of origin and housing during their stay at the capital. In cases where CF, PKU or MCADD are detected, patients both in the public and private sectors are referred to the Department of Medical and Surgical Specialties (DEMEQUI), since 2014 the name is National Reference Center Congenital Defects and Rare Diseases (CRENADECER) of BPS, located in Montevideo where treatment, genetic counselling and disease follow-up are centralised.[10]

The present study responds to an international need for more information regarding the burden of RDs and intends to demonstrate that secondary prevention actions are possible for some of these diseases.

## Objectives

This study aims to describe the epidemiological characteristics of newborns with abnormal neonatal screening tests diagnosed by blood drop and otoacoustic emissions in Uruguay.

## Methods

A descriptive cross-sectional study of births that occurred in Uruguay between January 1<sup>st</sup>, 2010 and December 31<sup>th</sup>, 2014 was performed with data available from two main sources: a) Vital Statistics of the Ministry of Health of Uruguay [11], with the death records searched until 12/31/2015; and b) the National Registry of Congenital Anomalies and Rare Diseases (RND CER). Since the RND CER [12] has begun operating in 2011, the cases with abnormal neonatal screening born in 2010 were searched in the Social Insurance Bank (BPS) Screening Laboratory and Honorary Commission to Fight Tuberculosis and Prevalent Diseases [10]. The outcomes for endocrine/metabolic diseases, the notifications to RND CER, encoded by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) – WHO Version 2016 [13] were selected; the chapters included were: IV (E00-E07; E25, E70-E71, E84), VIII - Diseases of the ear and mastoid (H60-H95), XVII (Q0-99) and XXI (Z96.2). The epidemiological variables analysed were gestational age at first prenatal visit and total consultations, controlled pregnancy, births attended by a doctor or midwife, delivery mode, gestational age at birth, gender, neonatal depression, mother's and father's ages and mother's education.

In Uruguay, Social Insurance Bank (BPS) Screening Laboratory centralises the country's newborn screening in a single laboratory, in order to ensure uniformity and rapid diagnostic confirmation.[10]

## Methods used for detection

- a. Congenital Hearing Loss (CHL): Before a newborn is discharged from the hospital, the first otoacoustic emissions (OAE) test is performed; if it is abnormal, a second one is performed; and a third is performed if there is no response. If this test is abnormal, auditory brainstem evoked potentials (BAEP) (and steady state) are performed. If newborns have risk factors [14], the same protocol is used in relation to the OAE. In this case, the BAEP are performed in all cases, regardless of the OAE result. The OAE test included four frequencies: 500, 1000, 2000 and 4000 Hertz and two tones: 65 and 75 decibels simultaneously, if you listen to three frequencies, pass the test.
- b. Congenital Hypothyroidism (CH): The thyroid-stimulating hormone (TSH) concentration is measured. The cut-off points vary according to: umbilical cord blood serum levels: > 25  $\mu$ IU/ml (MEIA, AXSYM, ADVIA Centaur); cord blood on filter paper: > 15  $\mu$ IU/ml (ELISA method, Biorad); and blood obtained by heel puncture on filter paper: > 10  $\mu$ IU/ml (ELISA method, BioRad) [15–16].
- c. Cystic Fibrosis (CF): Immunoreactive trypsin (IRT) is employed via a whole blood immunoassay technique on filter paper from a heel puncture starting at 40 hours of life [15]. The cut-off point for TIR was 43 ug/L for the first sample and 22 ug/L at 15 days. Since 2011, pancreatitis

associated protein (PAP) [17] is quantified only in cases with high IRT, the cut-off point for PAP was 1.6 ng/mL, which improves the screening specificity. The diagnosis is confirmed by a sweat test. The reagents used were TIR of BIORAD (ELISA) and Muco PAP of DINABIO (ELISA). A molecular study of the most frequent mutations is also conducted in confirmed cases.

- d. Congenital Adrenal Hyperplasia (CAH): 17-hydroxyprogesterone hormone (17-OHP) was studied by ELISA method of Biorad, was quantified by a competitive whole blood immunoassay enzyme on filter paper from a heel puncture starting at 40 hours of life. The diagnosis is confirmed by the concentration of the enzyme in the newborn serum, cut-off point 12ng/ml. The values that are considered pathological vary according to the weight and gestational age [15].
- e. Phenylketonuria (PKU) and Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCADD): These tests are performed by tandem mass spectrometry (MS/MS) on filter paper from heel blood samples starting at 40 hours of life. For PKU screening, the phenylalanine and tyrosine peaks are identified and quantified, as is their relationship. Cut-off Phe 49  $\mu\text{mol/L}$ , Tyr 150  $\mu\text{mol/L}$  and Phe/Tyr 3. When altered, PKU is diagnosed after obtaining a second altered sample. The profile of acylcarnitines is identified and quantified for MCADD. Confirmation for this pathology is made by examining the organic acids in the urine via gas chromatography with a mass detector [15]. Cut-off for C0, C6, C8 and C10 was 11.7, 0.39, 0.5 and 0.72  $\mu\text{mol/l}$  respectively and 3.02, 0.02, 0.3 to the relation C8/C10, C8/C2, C10:1 respectively

There are also two Pilot Programmes related to the neonatal screening programme in Uruguay for conditions that are detected by blood drop but whose pathologies are not part of the mandatory detection [10]; these were not considered in this study.

## Results

### *Epidemiological characteristics of the affected population*

The total number of live births in Uruguay between January 1<sup>st</sup>, 2010, and December 31<sup>th</sup>, 2014, was 239,240. A total of 399 (0.17%) children had a congenital anomaly diagnosed through compulsory investigation by National Neonatal and Infant Screening Programme and were reported to National Registry of Congenital Anomalies and Rare Diseases (12), within an overall prevalence of 15.6/10,000 births (Table 1). Congenital hearing loss was the most frequent abnormality, followed by CH and CF. Table 2 shows the distribution of total number of births in Uruguay in the period analysed according to the service where the delivery occurred; more than half of the births (59%) had occurred in private hospital and 40% of children were born in public hospitals. A higher rate of CHL was observed in children born in public comparing to private hospitals ( $P < 0.001$ ). Non-institutional births (births occurred outside the hospital) were rare in both groups, representing 1% of all births; only one case of CH was born at home.

Figure 1 shows the distribution of cases according to the place of birth (A) and maternal residence (B) departments. More than half of the cases (53%) occurred in the capital of the country (in the Department of Montevideo), where nearly half of the population lives. The Department of Artigas had nearly triple the national rate (15.5/10,000), with 40.7 and 44.2 (for A and B, respectively). Considering only the place of birth, the Department of Flores showed the lowest rate (5.9/10,000). Salto showed the lowest rate (7.1/10,000) when we consider the department of maternal residence. Only four departments showed identical distributions of cases in both A and B (Paysandú, Rivera, Rocha and Soriano). In all departments except Montevideo, there were more children living in these departments than there were institutional births (Table S1 and Table), which indicated

**Table 1.** Prevalence of diseases detected by the Newborn and Infant Screening Programme and reported to National Registry for Birth Defect and Rare Diseases in Uruguay, from 2010 to 2014.

Congenital Anomalies	Cases (n)	Prevalence in PNPNL (1/10,000) (/10,000)	95% CI	Global Prevalence (*) (1/10,000)
Congenital hearing loss – CHL	251	10	9.00-12.00	10-20
Congenital hypothyroidism – CH	89	3.7	3.00-4.60	2.5 -5
Cystic fibrosis – CF	29	1.2	0.08-1.70	1.0-1.25
Congenital adrenal hyperplasia – CAH	14	0.59	0.32-0.98	0.75
Phenylketonuria – PKU	13	0.54	0.29-0.93	0.6-1.0
Medium-chain acyl CoA dehydrogenase deficiency – MCADD	3	0.13	0.04-0.30	0.69

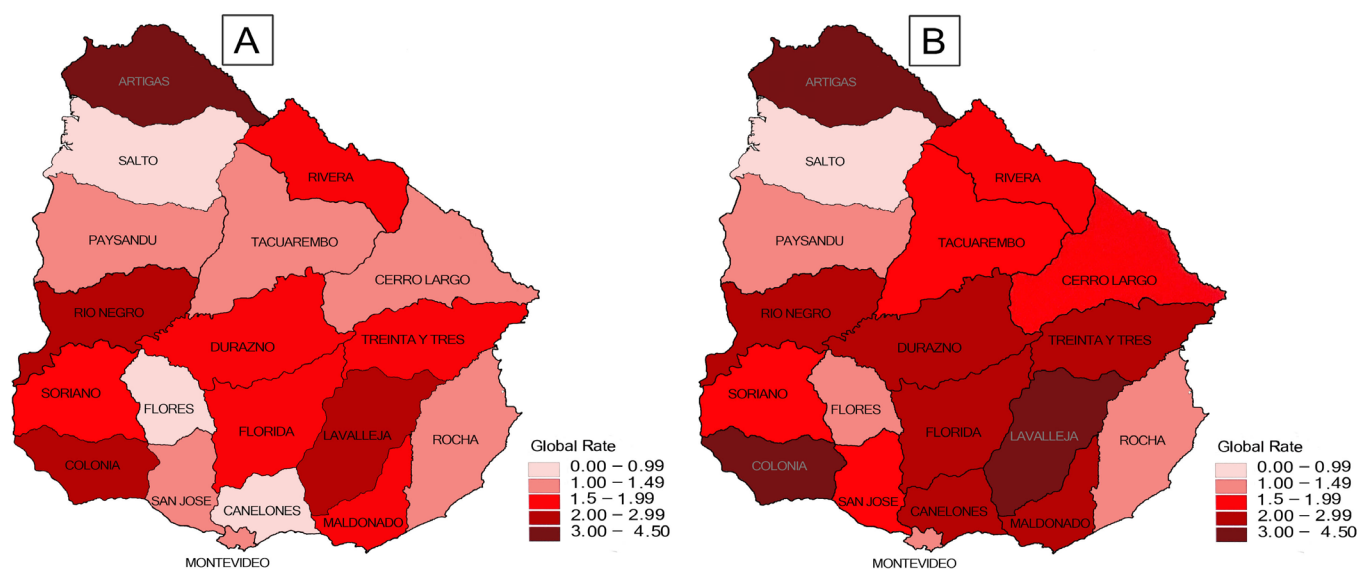
CI: Confidence Interval (\*): Ref [18].

**Table 2.** Place of delivery of newborns from Newborn and Infant Screening Programme and the total births in Uruguay from 2010 to 2104.

Place of delivery	Total births		CHL		CH		CF		CAH		PKU		MCADD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Private Hospital	134,427	(59)	49	(22)	43	(48)	17	(61)	7	(54)	5	(38)	2	(67)
Public Hospital (*)	103,455	(40)	177	(78)	45	(51)	11	(39)	6	(46)	8	(62)	1	(33)
Home or other	873	(1)	-		1	(1)	-		-		-		-	
No data	485		25		-		1		1		-		-	
Total	239,240		251		89		29		14		13		3	

(\*) Included Hospitals from the Administration of State Health Services (ASSE); Police, Military and Clinical Hospital. Cases without information about the place of delivery were excluded from the calculations.

CHL: Congenital hearing loss; CH: Congenital hypothyroidism; CF: Cystic fibrosis; CAH Congenital adrenal hyperplasia PKU: Phenylketonuria; MCADD: Medium-chain acyl CoA dehydrogenase deficiency.



**Figure 1.** Department distribution of confirmed cases of disorders detected by abnormal screening tests between 2010 and 2014. (A) Department distribution of newborns in accordance with place of birth. (B) Department distribution of newborns in accordance with maternal residence.

the mobilization of pregnant women for reference center when they give birth.

The first prenatal visit occurred at an average of 11.7 weeks of gestational age for the total births. For the affected group, the median for first prenatal consultation were 13, 12, 11, 12, 14 and 9.7 weeks for CHL, CH, CF, CAH, PKU and MCADD, respectively. No prenatal care was reported by 2% for the total births and 5% in CHL (Table 3). There were no differences in either mean maternal or paternal age (26.9 and 31.4 years, respectively) or in the type of delivery. Most of the newborns with normal screening were born vaginally (141,683; 59%), as were those with positive screening tests by the PNPNL. Table 4 lists all cases according to the sex; in cases with CH 63 %

(55/89) of were female. Among those with CH, one case also had congenital heart disease and one case also had CHL. In the group of newborns with CF, only one presented meconium ileus, and confirmatory molecular studies were performed in 79% of the cases [23–29]. Regarding CAH cases, none of them had a severe saline depletion in the neonatal period, and two cases had clinical genital ambiguity (Table 4).

Table 5 shows the risk factors present in the CHL group. Mothers of children with congenital deafness were less educated, what could be related to lower prenatal care and higher rates of preterm birth and neonatal depressions. As expected, 90% of the cases of CHL were isolated and only 10% were syndromic or had other findings (Table 6). Most cases had bilateral impairment,

but the hearing loss spectrum was variable. Down syndrome and hydrocephalus were the most frequent conditions associated with CHL, followed by other central nervous system disorders, syndromes and specific chromosomal abnormalities, along with congenital infection. In the syndromic group, five babies died

before two years of age. Cochlear implants were placed in 14% (35/251) of the cases with profound deafness at an average of 2 years of age. It is important to note that both cochlear implants and audiphones are provided by the state for all children who are diagnosed by neonatal screening.

**Table 3.** Comparison of gestational age at first prenatal care visit in affected newborns detected by Newborn and Infant Screening Programme.

Gestational age (weeks)	CHL		CH		CF		CAH		PKU		MCADD		TOTAL	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
5 - 12	130	(58)	59	(66)	23	82	7	70	9	70	2	67	157,708	66
13-26	72	(32)	24	(7)	3	11	3	30	2	15	1	33	63824	27
27-42	11	(5)	3	(4)	2	7	-	-	2	15	-	-	8043	3
No prenatal care	12	(5)	2	2	-	-	-	-	-	-	-	-	3870	2

CHL: congenital hearing loss, CH: congenital hypothyroidism, CF: cystic fibrosis (CF), CAH: congenital adrenal hyperplasia, PKU: phenylketonuria; MCADD: medium-chain acyl-CoA dehydrogenase deficiency.

**Table 4.** Sex distribution of newborns diagnosed by the Newborn and Infant Screening Programme in Uruguay between 2010 and 2014.

Congenital Anomalies	Male	Female	Ambiguous sex	Total
Congenital hearing loss-CHL	144 (58%)	105 (42%)	0	249
Congenital hypothyroidism-CH	33 (37%)	55 (63%)	0	88
Cystic fibrosis-CF	17 (61%)	11 (39%)	0	28
Congenital adrenal hyperplasia*-CAH	4 (29%)	8 (57%)	2	14
Phenylketonuria-PKU	9 (69%)	4 (31%)	0	13
Medium-chain acyl CoA dehydrogenase deficiency-MCADD	1 (44%)	2 (66%)	0	3
Total newborn	122.251 (51%)	116.836 (49%)	2	

\* none of them presented saline depletion ("salt-wasting").

No sex data in 4 cases (2-CHL;1-CH; 1-CF).

**Table 5.** Risk factors related to congenital hearing loss (CHL).

Risk Factor	CHL				P value
	Yes		No		
	n	(%)	n	(%)	
Prematurity	98	(43)	21535	(9)	0.001
Uncontrolled Pregnancy	15	(6.5)	3855	(2)	0.001
Neonatal Depression	40	(18)	4965	(2)	0.001
Low educational Level (*)	85	(45)	27603	(12)	0.001

(\*) Only up to 6 years of schooling or fewer.

**Table 6.** Abnormalities associated with congenital hearing loss detected by Newborn and Infant Screening Programme in Uruguay and reported to National Registry of Birth Defects and Rare Diseases (2010-2014).

Syndromic and other abnormal findings	Number Cases	Type	Age at Death (days)
Congenital Hydrocephalus	3	SHLB	-
Extreme Congenital Hydrocephalus and porencephaly (Congenital cerebral cysts)	1	SHLU	521
Hydranencephaly	1	SHLB	134
Other reduction deformities of brain: Frontal hypoplasia	1	SHLB	-
Microcephaly	1	SHLB	-
Autistic Spectrum Disorder (ASD)	1	SHLB	-
Twin pregnancy, severe prematurity, connatal infection.	1	SHLB	16
Congenital Toxoplasmosis	1	SHLB	-
Severe microtia and congenital atresia of external auditory canal	1	SHLB	-
Down Syndrome	4	SHLB	260 (*)
Waardenburg Syndrome (WS)	1	SHLB	-
WS, type IV (with Hirschsprung Disease); Unilateral cryptorchidism	1	SHLU	-
Mucopolysaccharidosis Type I	1	SHLB	525
CHARGE Association	1	SHLB	-
Williams Syndrome	1	SHLB	-
Non Syndromic hearing loss	229	SHLB, SHLU	-

SHLB: Sensorineural hearing loss bilateral (ICD-10 H90.3); SHLU: Sensorineural hearing loss unilateral with unrestricted hearing on the contralateral side (ICD-10 H90.4); (\*) one case of Down Syndrome with congenital heart disease. CHARGE (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of Growth and development, and Ear abnormalities and deafness); -Not applicable. Total births between 2010 and 2014: 239,240.

## Discussion

The main objective of this study was to characterize the epidemiological profile of newborns from the National Newborn and Infant Screening Programme in Uruguay. The prevalence of the pathologies included in mandatory Programme in Uruguay (Table 1) was similar to the international literature, with the exception of MCADD for which a lower prevalence was observed (18), but the reason for this difference has yet to be determined. We believe that these similarities are explained by the contribution of a significant European ancestry. Hidalgo et al. [19] demonstrated a tri-hybrid model for the Uruguayan population with predominantly European genes (84.1%) and a more modest contribution from the Amerindian and African gene pools (10.4% and 5.6%, respectively). With regard to the coverage of prenatal care, the WHO Millennium Development Goals Report for 2014 states that more than 86.2% of pregnant women in the Americas region had four or more prenatal visits [20]. Uruguay is a privileged country, where the number of prenatal visits reported in this study was nine on average for all the births, including the ones with abnormal neonatal screening. However, only 66% of the mothers started prenatal visits in the first trimester, which means that at least 1/3 of the pregnant women missed the opportunity to prevent some congenital

anomalies due to environmental exposure. Maternal education data showed that a small number of women manage to complete high school, despite Uruguay's high rate of development. Aristimuño [21] mentioned that dropout from secondary school in Uruguay is a complex and persistent problem. There is evidence in the literature [22] that maternal education has a statistically significant impact on infant mortality. In Brazil, Victora et al. [23] reported that the years of maternal schooling were inversely associated with perinatal and infant mortality and infant hospital admissions in the first 20 months of life, along with three nutritional indicators (length for age and weight and weight/length ratio). Recent data from Italy showed lower socio-economic levels to be associated with adverse perinatal outcomes, such as prematurity, low birth weight, low Apgar scores and severe congenital anomalies [24]. However, there are no data in the literature comparing the impact of maternal education and abnormal neonatal screening results. Since 2011, the European Union has been trying to combat the absence of specific health policies for RDs, emphasizing the need for the establishment of a comprehensive strategy for Member States to support equity in providing access to prevention, diagnosis and care for patients with RDs [2]. Although Uruguay does not have specific policies on RDs, the PNPNL-type programmes that are in practice have that function. Taiwan, Brazil, the United

Kingdom and Germany have implemented similar neonatal screening programmes, with a variable number of RDs that are identified through mandatory screening. As the RD scenario continues to evolve differentially according to each local reality [25], the unification of organizations of patients and/or parents is key, both to develop best practices and to globalize the role of patients for the further development of programmes and policies. Very few registries of congenital anomalies in the world include the mandatory notification of pathologies that are diagnosed by the neonatal screening programme [26], as RND CER does in Uruguay. In the US, the Utah registry of CAs has begun a pilot plan to incorporate surveillance of metabolic abnormalities identified by newborn screening [27]. In the Americas region, Colombia has recently added CH to its congenital anomaly monitoring programme [28]. As reported by Howell et al. [29], approximately 12,500 newborn children in the US are diagnosed with 1 of 29 pathologies in the uniform screening panel each year; the five most common diagnoses are hearing loss, primary CHT, CF, sickle cell disease and MCADD; Uruguay shares this order of frequency for the first three pathologies. Few studies in the literature have evaluated the epidemiological characteristics of those babies born with pathologies detected by NBS programmes as a group. Some authors [30] consider the epidemiology of hearing loss in children and adolescents to be a field where there is a lack of standardization of information. Roberts et al. [31] observed a highest frequency of females in newborns with CH and a prevalence of 1.1% for associated congenital heart disease, both results coincident with our study. As reported by them there is little information on epidemiological data of NBS diseases such as CH and congenital anomalies in general [31]. As discussed by Howells et al. [29], the transmission of information from clinical services to the health system is the key to the adequate follow-up and management of the RDs patients. Despite the advances in health care in Uruguay [32–33], our results demonstrate that greater efforts should be devoted to improving maternal education, prenatal care and primary prevention of congenital anomalies. Full knowledge of this group of diseases will allow the monitoring of the occurrence of cases over time and will allow actions to be taken to improve health policies based on the health needs of the population.

## Conclusion

This is the first study evaluating the characteristics of newborns with abnormal screening in Uruguay. The detection of 399 cases of anomalies that can be significantly modified by early diagnosis and treatment reinforces the importance of PNP NL. There is sufficient evidence regarding national and international regulations that can be used to support the development of public policies related to disability and congenital anomalies. The same methodology of this study can be extended to evaluate other prevalent congenital anomalies. Our findings still open new

questions, for which several lines of research can be developed. Because these results may impact the planning of health services, data transmission between clinical care and public health systems is needed to improve both follow-up and management.

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## Ethics approval and consent to participate

This project was approved by the Research Ethics Committee under Opinion Number: 1.302.274. Plataforma Brasil <http://www.comite.iesc.ufrgs.br/>.

This article does not contain any studies on human or animal subjects.

## Authors' contributions

ML conceived the idea to write the paper. ML, MTS and LS-F wrote a draft version. The co-authors of this research critically reviewed the draft and provided suggestions for improvement. All authors read and approved the final manuscript.

## Declaration of Conflicting Interests

The author Mariela Larrandaburu declares there are no conflicts of interest.

## Supplementary Material

The following online material is available for this article:

**Table S1** - Distribution by birth Department of cases diagnosed by National Newborn and Infant Screening Programme in Uruguay from 2010 to 2014.

**Table S2** - Distribution of departments of maternal residence of cases diagnosed by National Newborn and Infant Screening Programme in Uruguay between 2010-2014.

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