

Spatial Distribution of Congenital Disorders Diagnosed by the Newborn Screening Program in Ecuador

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Abstract

The newborn screening program in Ecuador has been operating since 2011 under the responsibility of the Ministry of Health. This program is centralized and diagnoses four diseases: congenital hypothyroidism, phenylketonuria, galactosemia, and congenital adrenal hyperplasia. This study aimed to assess the geographical distribution of newborn screening cases in Ecuador. Spatial analysis techniques were applied using the records of the National Newborn Screening Program with a congenital disease confirmed from January 2012 to December 2019. Morbidity rates per 100,000 were calculated by newborn screening disease detected and the province of birth, posteriorly, the map of its distribution was graphed and assessed using the QGIS 3.12 software. In total, 393 cases born confirmed between 2012 and 2019 were registered. The distribution of every disease tends to be different in all provinces in Ecuador; the spatial variation was significant and relative rates showed a higher incidence in some eastern provinces. In conclusion, we found a different distribution and rates of newborn screening disorders in Ecuador. The high incidence of congenital hypothyroidism, phenylketonuria, galactosemia, and congenital adrenal hyperplasia in some areas should be investigated, due could be related to ethnic, genetic, and cultural aspects of the population.

Keywords: spatial distribution, newborn screening, congenital disorders, Ecuador.

Introduction

The newborn screening (NBS) is a preventive health program for early identification of disorders that can hinder their normal development or cause premature death [1]. The aim of the NBS program is early detection of congenital disorders in newborns and start a treatment to prevent intellectual and physical disabilities and life-threatening complications [2]. The NBS has been in place for many years in each country; the number of diseases tested varies in every country and its health program. Also, there is no international standard of the disorders that be tested [3]. In Latin America, countries such as Cuba, Costa Rica, Uruguay, and Chile have a functional screening program for more than 20 years. In others, like Ecuador, the screening program has been working for a few years [4].

The Ecuadorian Ministry of Public Health (MPH), the government body in charge of public health matters, functions on national and local levels and is responsible for the NBS program. This program started in Ecuador in December 2011 with the diagnosis of four diseases: congenital hypothyroidism, phenylketonuria, galactosemia, and congenital adrenal hyperplasia [5]. Before 2011, the only screening disorder detected

in Ecuador was congenital hypothyroidism; however, this disorder was diagnosed in just a few local hospitals, and there was not a national screening program [6]. In 2009 and 2010, the country conducted a national study on disabilities. This study revealed that there were 68 687 people with intellectual disabilities in Ecuador and described congenital hypothyroidism as an important cause of disabilities [7]. On the other hand, the rates of phenylketonuria, galactosemia, and congenital adrenal

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hyperplasia were unknown, thus were included in the NBS due that their early diagnosis and treatment prevent intellectual disabilities and newborn deaths [5].

The NBS in Ecuador is a centralized program. The collection is made around the country in MPH health centers and hospitals. The screening program collects blood samples by heel-prick up to 8 days after birth. Posteriorly, the samples are spotted on FTA cards and sent to an MPH institution called located in Quito, which is in charge of the NBS. From 2011 until 2016, the samples were analyzed by fluorometry in the institution through a collaboration agreement between Cuba and Ecuador [5]. From 2017 to this day, the MPH send the samples to an external laboratory, where the analysis is performed by time-resolved fluoroimmunoassay [8]. A study conducted in 2014 about fluorometry technology, described a test specificity of 95.7% and VPP of 0,63% [9], and a research conducted in Colorado – United States about time-resolved fluoroimmunoassay in neonatal screening, described a specificity of 99% and VPP of 0,68% [10].

Phenylketonuria, galactosemia, and congenital adrenal hyperplasia have an autosomal recessive Mendelian inheritance pattern. Phenylketonuria is caused by a mutation in the gene encoding phenylalanine hydroxylase (PAH), which catalyzes the hydroxylation of phenylalanine (Phe) generating tyrosine (Tyr) [11]. Galactosemia is caused by mutations of the genes encoding the Leloir pathway enzymes: galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT), and UDP-galactose 4-epimerase (GALE) [12]. In 90%-95% of cases, Congenital Adrenal Hyperplasia is caused by a mutation in the CYP21A2 gene; other less frequent are caused due to 17-alpha-hydroxylase deficiency, 3-beta-hydroxysteroid dehydrogenase deficiency, 11-beta-hydroxylase deficiency, and cytochrome P450 oxidoreductase deficiency [13]. Alternatively, congenital hypothyroidism has a complex etiology that can be divided into primary, secondary, or peripheral etiologies (85% is caused by Thyroid dysgenesis) [14].

Even though screening for metabolic disorders has been available through public health care for some years in Ecuador, there are no studies on rates and distribution of NBS disorders in the country, neither in public health records or medical literature. Geospatial studies are wide use in epidemiological studies; their purpose is to use tools that help analyze the spatial variability of diseases and health determinants in a geographic area [15]. This study described the spatial distribution of individuals with an inborn metabolic disease by using data from the Newborn Screening Program in Ecuador between 2012 and 2019.

Methods

Study area and population

This is an ecological study that used distribution and spatial analysis. This study was conducted in Ecuador, a country multiethnic located on the west coast of the northern South

American continent and which is divided into four regions with different climate conditions: The Pacific Coast Line (the Coast), Highlands (Andes mountains), Amazonia (eastern region) and Galapagos Islands. At the same time, these four regions are divided into 24 provinces.

Data collection

Dataset was taken from the registry of the national NBS program of the Ecuadorian Health Ministry between January 2012 and December 2019. This registry contains all data of tested patients and the data of positive case surveillance. The population characteristics, demographic distribution by provinces, and geographic files were obtained from the website of the “Instituto Nacional de Estadísticas y Censos”, which is the governing body of national statistics and responsible for generating official statistics of Ecuador.

Data analysis

We calculated the adjusted cumulative incidence of newborn screening disorders with the positive new cases during the study divided by the total of newborns with screening tests performed per 100 000 in every province. The spatial analysis unit used to prepare thematic maps was the provinces. We performed a spatial distribution of the NBS disorders tested. The spatial analysis and map modeling were conducted in the program QGIS 3.12.

Results

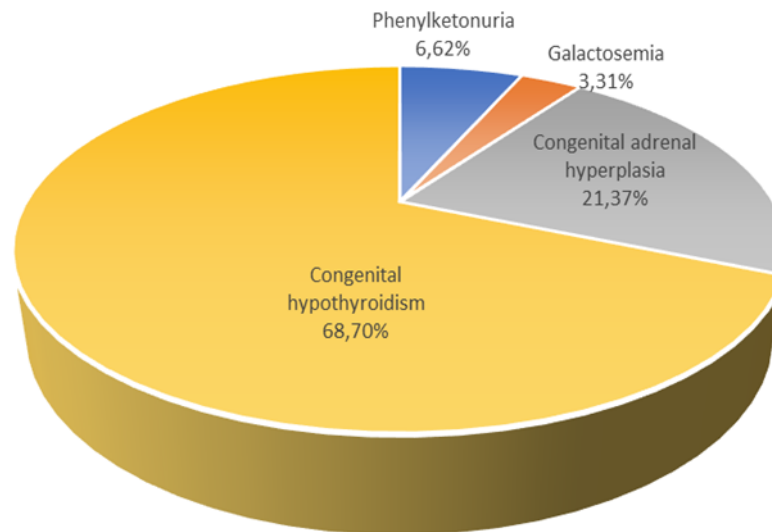
A total of 2 278 189 children were born in Ecuador between January 2012 and December 2019, of which 74.64% (1 700 440 children) were screened and registered in the Newborn Screening Program Database. Of these, 393 cases (0.02%) presented congenital disorders detected by the program. Congenital hypothyroidism was presented in most of the cases (270 cases, 68.70%), followed by congenital adrenal hyperplasia (84 cases; 21.37%), phenylketonuria (26 cases; 6.62%), and galactosemia (13 cases; 3.31%) (Figure 1).

Overall, female cases predominated (61,06%), with a female/male ratio of 1.57 (Table 1). In the case of phenylketonuria and congenital adrenal hyperplasia, the cases registered were slightly higher in males. By contrast, congenital hypothyroidism was higher in female patients. In Galactosemia's cases was equitable for both genders.

The incidence of newborn disease screening in Ecuador was 23.10 per 100 000 newborns screened (95% CI: 17.77 to 28.45). The congenital hypothyroidism incidence rate was 15.88 per 100 000 neonates screened (95% CI: 12.80 to 18.96), the congenital adrenal hyperplasia incidence rate was 4.94 per 100 000 neonates screened (95% CI: 2.47 to 7.41), the phenylketonuria incidence rate was 1.53 per 100 000 neonates screened (95% CI: 0.78 to 2.28) and galactosemia incidence was 0.76 per 100 000 neonates screened (95% CI: 0.37 to 1.16).

Table 1. Cases by the Neonatal Screening Program classified by type of disorder and sex.

NBS Disorder	Number of cases	SEX		FEMALE - MALE RATIO
		FEMALE	MALE	
Phenylketonuria	26	10	16	0.63
Galactosemia	13	7	6	1.17
Congenital adrenal hyperplasia	84	38	46	0.83
Congenital hypothyroidism	270	185	85	2.18
Total	393	240	153	1.57

**Figure 1.** Cases diagnosed by the NBS Program between 2012 and 2019 in Ecuador.

Regarding the frequency by provinces, provinces with higher populations and births present a higher frequency of NBS cases. Guayas, Pichincha, and Manabí present a higher frequency of children with NBS-positive cases in phenylketonuria, galactosemia, and congenital hypothyroidism. Although, if we compare the congenital adrenal hyperplasia absolute frequency, it is higher in five provinces with lower births than Manabí (Azuay, Loja, Imbabura, Cañar, and Chimborazo).

During its first year of operation (2012), the NBS program detected 66 cases. In 2013, the year with the highest registration, cases detected increased to 80, a marked increase in the cases of congenital hypothyroidism and adrenal hyperplasia were observed. The number of new cases registered each year decreased in 2015 and 2016. Posteriorly to these years, the program increased the frequency of detected cases (Figure 2).

Figure 3 shows that the eastern and southern provinces of Ecuador presented the highest newborn disease incidence in the country. In the eastern region, the provinces of Pastaza, Morona Santiago, and Sucumbios obtained a cumulative incidence larger than 30.5 per 100 000 live births. In the Andes Mountains region, the highest incidence was in Loja, followed by the provinces of

Cotopaxi, Cañar, and Azuay. On the other hand, El Oro was the province with the highest incidence in the Pacific Coast Line. Among the 24 provinces, Morona Santiago and Pastaza got the main cumulative incidence rate (50.25 and 50.22 per 100 000 neonates, respectively). There were no cases of NBS disorder in the Galapagos Islands.

Figure 4 shows that the incidence rate of the different disorders diagnosed by the NBS program varies between provinces. Phenylketonuria was registered in 11 provinces, being Cotopaxi, Andes Mountains, which presented the highest incidence rate. Only 7 provinces reported galactosemia, with the highest rate reported in Morona Santiago, Amazonia. On the other hand, 19 provinces reported positive cases of congenital adrenal hyperplasia, the highest incidence rate was registered in the province of Cañar. However, the provinces of Loja, Imbabura, Carchi, and Pastaza achieved significant rates compared to the rest of the provinces. Regarding congenital hypothyroidism, it was reported in 21/24 provinces (not presented in Zamora Chinchipe and Galapagos). The highest rates for this disease were found in Morona Santiago and Pastaza; both provinces of the Amazon region.

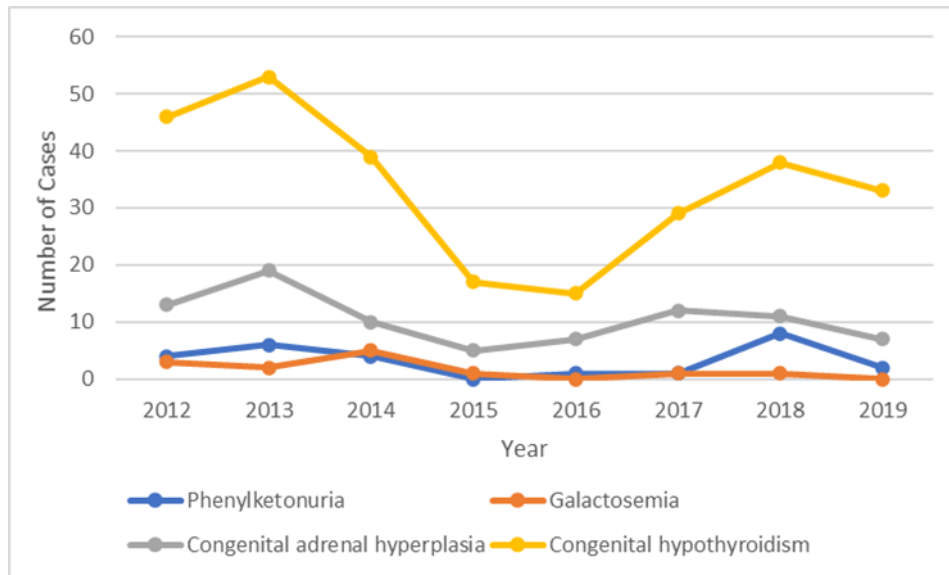


Figure 2. Cases diagnosed by the NBS Program distributed by years in Ecuador, 2012–2019.

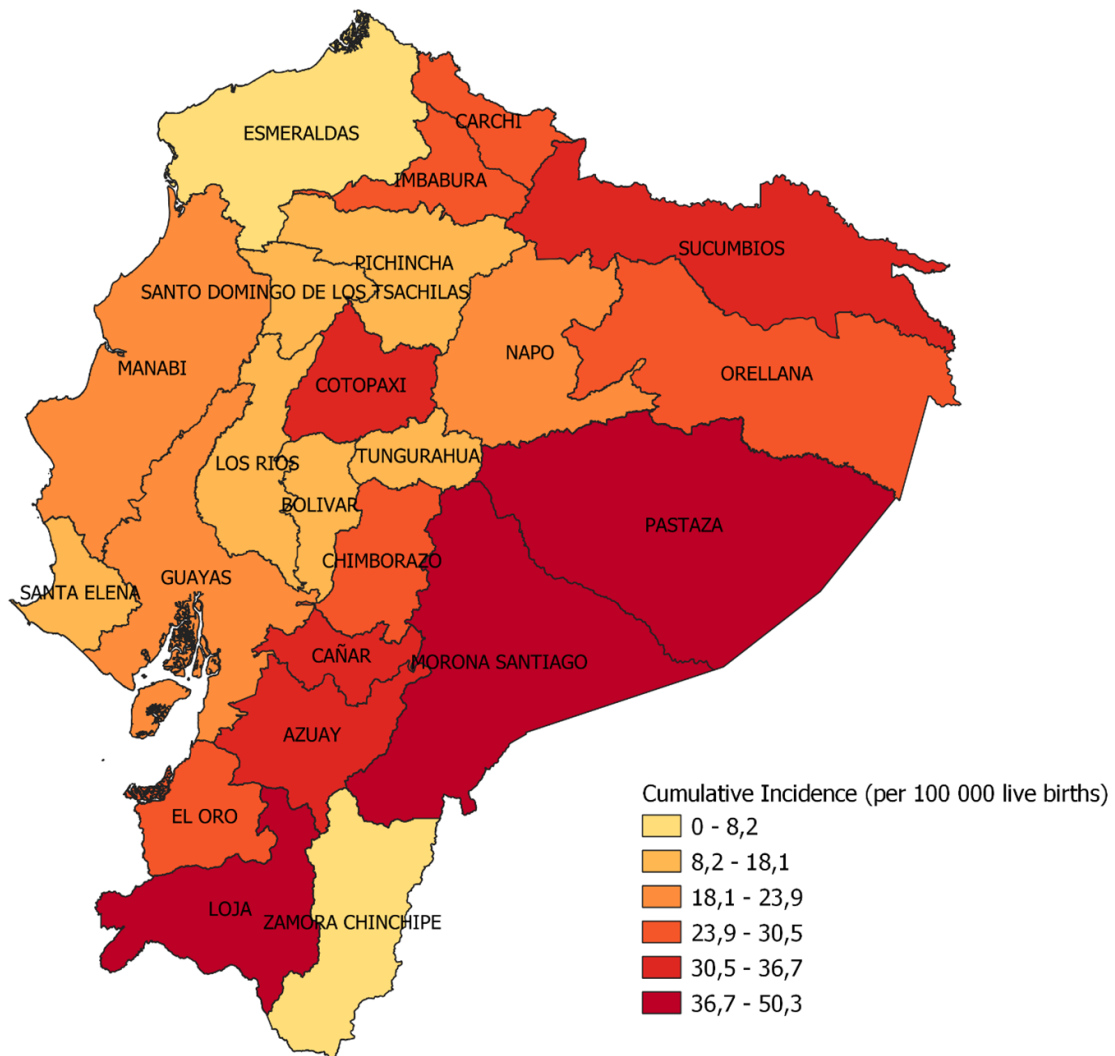


Figure 3. Spatial distribution of newborn screening disorders diagnosed in Ecuador, 2012 – 2019.

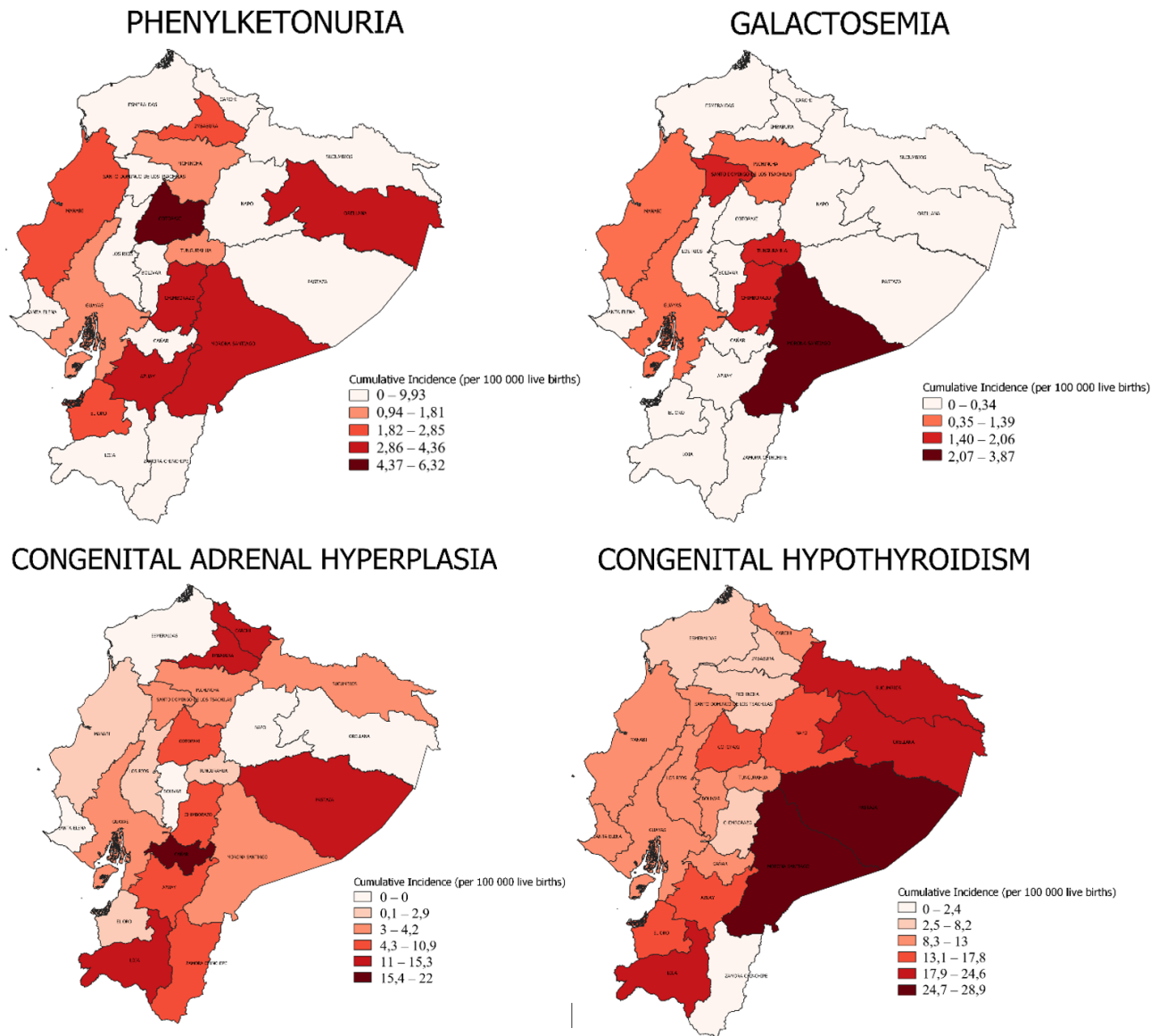


Figure 4. Spatial distribution of newborn screening disorders diagnosed in Ecuador by type disorder, 2012 – 2019.

Discussion

This study describes the rate and geographical distribution of the four metabolic disorders of the NBS program in Ecuador. We found that the incidence rate of phenylketonuria in Ecuador was lower than the world average described by Shoraka (6.00 per 100 000 live births) [16]. Borrajo described an incidence in Latin America between 1.90 and 6.61 per 100 000 live births [17]. Comparatively, the Ecuadorian cumulative rate in the last 8 years was slightly lower (1.53 per 100 000 live births). On the other hand, we found relatively higher incidences in provinces such as in Cotopaxi, which obtained an incidence of 6.32 per 100 000 live births, the highest rate in Ecuador. Galactosemia rate in Ecuador was almost half of the worldwide incidence (1.66 to 2.5 per 100 000 live births) [18], however, in Morona Santiago the incidence rate was higher (3.86 per 100 000 live births).

Congenital hypothyroidism occurs in 1/3000 to 1/4000 worldwide (25 – 33 cases per 100 000 live births [19]). However, the average rate in Latin America reaches 36.01 per 100,000 live births [17]. In reference, a higher incidence of congenital hypothyroidism in the Hispanic population compared to other ethnic groups has been reported [20, 21]. In this study, we found rates in provinces such as Morona Santiago, Pastaza, and Loja with rates of 28.85, 26.77, and 24.62, respectively. These incidence rates were the highest in Ecuador, however, were lower than the Latin American average.

Congenital adrenal hyperplasia occurs in 6,67 to 7,69 per 100 000 live births around the world [22]. Overall, the Ecuadorian rate was lower. However, 9 provinces obtained higher rates than the world average: Cañar (22.03 per 100 000 live births), Imbabura (15.31 per 100 000 live births), Loja (14.43 per 100 000 live births), Pastaza (14.38 per 100 000 live births), Carchi

(12.62 per 100 000 live births), Azuay (10.88 per 100 000 live births), Chimborazo (10.27 per 100 000 live births), Cotopaxi (8.43 per 100 000 live births) and Zamora Chinchipe (8.23 per 100 000 live births).

Phenylketonuria, galactosemia, and congenital adrenal hyperplasia frequencies should be similar in males and females due they are autosomal recessive disorders [23]. This is in line with what was observed in our cohort of cases of these disorders. In the case of congenital adrenal hyperplasia, it is known that a female-male ratio increases in places without an NBS program, this is due to unrecognized male deaths as a consequence of poor diagnosis and treatment [23]. In this study, a similar sex ratio of congenital adrenal hyperplasia with a slight predominance of male cases was observed, this could indicate a timely execution in the diagnosis of congenital adrenal hyperplasia by the NBS program in Ecuador. Regarding congenital hypothyroidism, female cases exceeded male cases by more than 100%, this is similar to international rates that describe a higher incidence of the disease in women [21].

Three of the four diseases examined, except for congenital adrenal hyperplasia, are below the world average. These low rates need special attention because they could spell a deficiency in the program. It is important to compare the coverage of the program in different provinces to find the causes that make it difficult to achieve the planned coverage [24]. Another important part of the program involves knowing the different stages of the analysis: pre-analytical (collection, sending, and receiving of samples), analytical (analysis laboratory), and post-analytical (report of results, the initiation of the intervention, and confirmation of the diagnosis). All these stages require adequate time and quality control [25].

Currently, there is no description of false-negative cases in the national NBS program in Ecuador, however, there are differences in coverage, which is evidenced in the lack of case detection in some provinces. For example, if we compare the congenital hypothyroidism detected in the eastern provinces, Zamora Chinchipe detected a very low number of cases. This implies that the NBS program no the same quality in all the provinces. It is important to improve the epidemiological surveillance system that collects patients who are diagnosed outside of the neonatal metabolic screening and gather data of cases that escape the diagnosis of neonatal screening [26]. However, for subsequent studies, it is important to continually evaluate and search for the best diagnostic option and the best tools for improving program efficiency.

Variations in the frequency of cases of the same disease in regions different is an example of the complexity of its population and genetic diversity [27]. There are many factors related to the etiology of congenital hypothyroidism (multifactorial disorder). However, dietary iodine deficiency is the leading cause of congenital hypothyroidism around the world [28]. In Ecuador, Fierro et al., described in the year 1970 a high prevalence of cretinism in communities of the Andes due to iodine deficiency in the diet [29]. Although there is no information on the behavior of congenital hypothyroidism in the eastern provinces in the

literature, we suggest that the possible cause of the high prevalence of congenital hypothyroidism is due to characteristics of the diet of these communities like goitrogenic food consumption and insufficient use of iodized salt in the diet [30].

Another possible explanation for a higher rate in some provinces than others is the genetic composition. Phenylketonuria, galactosemia, and congenital adrenal hyperplasia have an autosomal recessive inheritance pattern and occur with increased frequency in the offspring of consanguineous marriages [31], or populations where an original "founder mutation" occurs and is subsequently propagated throughout the population in future generations [32].

Ecuador is a country with a mixture of different ethnicities and cultures. Zambrano et al. published an ancestry analysis in the Ecuadorian population, this study explained the Ecuadorian genetic composition as a mixture of three ancestors: Native Americans, European and African descendants in a different proportion. Native American ancestry is the principal in all regions, more than 51%. European and African ancestry were in a lower proportion and vary in different regions of the country (there is a major African genetic composition of the Coast compare in the Highlands and Amazonia [33]). Some communities could present a higher rate of specific NBS disorders in some provinces, while in other communities, the rates are low, it could be the product of ethnic and geographical differences in gene polymorphisms.

Consanguinity is also an important factor that increases the probability of inheritance of a recessive mutation in a homozygous state [31]. The prevalence rate of consanguinity in people with disabilities was 0.31 per 1000 people in Ecuador [34]. Lardoet et al. described that the provinces with were Loja and Cañar were the provinces with a higher rate of consanguinity in people with disabilities [7]. In this study, Cañar incidence rate of congenital adrenal hyperplasia tripled the world average rates and Loja incidence rate was more than double for the same disease. This extremely high rate could be the result of pathogenic polymorphisms, therefore, studies are needed to identify genetic risk factors in these populations. This information could help to identify some factors that generate a different distribution of the incidence rates of innate metabolic disorders and improve the NBS program in Ecuador.

Conclusions

Newborn screening disorder rates differ between types of disorder and provinces in Ecuador. In some provinces, the incidence rate is lower than the world average while in some cases the incidence is higher. We suggest that the lower rates are due to NBS program quality differences and the higher rates are primarily due to the impact of ethnicity and consanguinity in the country. This study provides recent epidemiological data of the NBS disorders in Ecuador; this information is useful to those providing and planning services for patients with an inherited metabolic disorder.

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Declaration of conflict of interest

The authors declare no conflict of interest.

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