



## EDITORIAL

# Advancing and prioritizing research on oral clefts in Brazil<sup>☆,☆☆</sup>

## Avançando e priorizando a pesquisa sobre fissuras orais no Brasil

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Research on oral clefts has noticeably grown over the past two decades to cover its various aspects, including etiology, epidemiology, prevention, treatments, health services, and health and socioeconomic outcomes of patients and families. Researchers from multiple disciplines have joined efforts to investigate these complex areas. Brazil provides a unique setting for these studies for several reasons. As the largest country in South America, Brazil has a large number of newborns with oral clefts each year, crudely estimated between 2,900 and 4,400 births in 2011.\* Brazil also has one of the most diverse populations worldwide, making it particularly suited for genetic studies based on admixture mapping. Furthermore, Brazil has some of the largest centers specialized in treating oral clefts and craniofacial anomalies such as the Hospital de Reabilitação de Anomalias Craniofaciais (HRAC) or ‘Centrinho’ in Bauru, São Paulo and the Centro de Atendimento Integrado ao Fissurado Lábio-palatal (CAIF) in Curitiba, Paraná, among

others. Such centers provide a particularly appropriate setting for interventional studies related to prevention or treatment.

Research gaps and priorities for oral clefts have been identified in a Centers for Disease Control and Prevention (CDC) workshop.<sup>1</sup> These are useful for researchers in Brazil to consider and pursue. However, we identify here priorities that are particularly relevant to strengthening and expanding research on oral clefts in Brazil under four areas: epidemiological surveillance, research on environmental and genetic factors, outcome studies, and prevention.

### Epidemiological surveillance

Population-based surveillance of birth defects is essential for building the capacity of epidemiological research. Building a nationwide program is the most inclusive approach for identifying and tracking birth defects. However, such programs may be challenging to design and implement, particularly in large countries. In the absence of national programs, state-based programs provide a good substitute. Souza and Raskin<sup>2</sup> describe the currently available surveillance programs in Brazil. The program based on live birth certificates (declarations) is nationwide. However,

\*This is based on the author’s calculations with the following assumptions: crude birth rate of 15 per 1,000 population and a total population of 196,655,014 in 2011 (World Bank: <http://data.worldbank.org/indicator>), and a range of clefting incidence from 1.5/1,000 (Lopez-Camelo et al., 2010) to 1/1,010 (Souza and Raskin, 2012).

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<sup>\*\*</sup>See paper by Souza J et al. in pages 137–44.

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as highlighted by the authors, it has several limitations, including concerns about completeness and accuracy of description. Therefore, there is still a need for building population-based programs in Brazil. This is important for accurate estimation of the prevalence of oral clefts by type, and of the changes in trends over time. Clinic-based tracking, such as presented by Souza and Raskin,<sup>2</sup> is an alternative when population-based programs are not available. However, clinic-based approaches suffer from several well-known limitations, including case selection bias, which may significantly distort estimates, among others.

### Research on environmental and genetic factors

In addition to accurate epidemiological tracking, collecting rich data on environmental risk factors, collectively defined here to include maternal health (chronic conditions such as diabetes and obesity, and acute problems such as infections and medication use) and behavior (such as smoking, alcohol use, nutrition, and vitamin use), demographics, socioeconomic, and the physical environment (such as air quality and exposures to teratogens) for *population-based samples* is essential for research aimed at studying the contributions of these factors to the etiology of oral clefts. Similarly, collecting DNA from the *same* samples is essential for studies of genetic etiology including gene-environment interaction effects, which have been shown to contribute to oral clefts, such as between smoking and certain detoxification pathway genes.<sup>3</sup> Conducting this research specifically in the Brazilian population is important given the potential heterogeneity in the effects of environmental and genetic risk factors between populations, which would limit the generalizability of results on certain risk factors based on other populations.

It is also important to conduct research that can capture the causal effects of environmental risk factors, not just association, such as by applying genetic instrumental variables (or Mendelian randomization),<sup>4,8</sup> which provides another incentive for collecting the environmental and genetic data on the *same* population-based samples. This research requires collecting similar data on (ideally randomly selected) controls that are representative of the unaffected population. Given the likely challenges of systematically collecting environmental and genetic data on most of the population affected with oral clefts in a large country such as Brazil, an alternative would be a coordinated data collection across multiple state-based samples, as performed in the National Birth Defects Prevention Study in the United States.<sup>6</sup> While these studies can be conducted using clinic-based samples, the issues of limited generalizability and biased estimates due to sample selectivity may significantly reduce the value of research on environmental risk factors.

### Outcome studies

Another important research area is to understand the effects of oral clefts on the health and well-being of affected individuals and their families, both during childhood and adolescence and as adults. Such research is essential for identifying the needs of affected individuals and their families, as well as devising interventions to address these needs and improve the outcomes of affected families. Particular outcomes to consider are infant survival and health problems; effectiveness, quality, and cost of surgical, medical, dental, and behavioral treatments from infancy through early adulthood; access to these treatments; child and adolescent psychosocial status; child/adolescent academic achievement and long-term health (chronic health conditions, healthcare utilization, mortality risks); psychosocial wellbeing (mental health, social adaptation, marriage); economic performance (educational attainment, employment, income); and quality of life. It is also important to study the effect of having a child with oral clefts on the family's financial status, quality of life, and parental and sibling psychosocial wellbeing.

Several previous studies have evaluated some of these outcomes using data from developed countries;<sup>9-15</sup> more research is still needed for several of these outcomes, especially using robust designs and large population-based samples from less developed countries, as it is unclear to what extent these outcomes are generalizable. The outcomes of affected individuals and their families may vary with several factors including individual- and household-level effects (e.g. parental socioeconomic status), neighborhood-level characteristics (e.g. quality of schools, availability and quality of health professionals with experience in treating patients with oral clefts, and social networks and support), and country-level factors (e.g. characteristics of the healthcare system and policies related to healthcare coverage, and access to and quality of healthcare services). Since these factors vary widely between countries, population-specific studies may be needed to comprehensively assess the needs of affected individuals and families in Brazil and to develop policies and interventions to address these needs. Without these, it is unclear how the results from studies in other populations, such as those related to child behavioral health,<sup>9,11</sup> long-term mortality,<sup>10</sup> and hospitalization use<sup>12</sup> of affected individuals apply to Brazil.

As in the case of studies of etiologic risk factors, outcome studies also require coordinated large-scale data collection efforts that are population-based, can accurately measure several outcomes, and are designed to capture long-term outcomes. Some countries with universal health insurance systems such as Denmark have administrative population-based registries for healthcare services use, income/employment, educational attainment, and several other social and economic indicators that can be linked and used for research studies, providing a great resource for health services research and socioeconomic outcome studies, particularly for studying long-term outcomes.<sup>12</sup> Such resources are currently unavailable for Brazil, and it is unclear whether they can be developed in the near future. In the absence

<sup>6</sup>The National Birth Defects Prevention Study: <http://www.nbdps.org/>

of these, an alternative is conducting surveys of affected individuals (including adults), their unaffected family members, and representative controls of the unaffected population. Of course, such studies would ideally include a representative sample of the affected population and their families, which would depend on the availability of nationally representative population-based registries of affected individuals.

In addition to identifying the effects of oral clefts on health and well-being, research is also needed to identify treatments and interventions that reduce cleft co-morbidities and health risks and improve the outcomes of affected individuals. These studies can have an interventional or observational design. One example is an interventional multi-site study that evaluated the effects of early systematic pediatric care on neonatal mortality and hospitalizations in a sample of infants born with oral clefts in several South American countries, in collaboration with the Latin American Collaborative Study of Congenital Anomalies (ECLAMC).<sup>16,17</sup> Another example is an observational study that analyzed data routinely collected by ECLAMC in their surveillance program for congenital anomalies to evaluate how the effects of prenatal care on birth weight vary between infants with and without oral clefts, since affected individuals are born at lower birth weights than unaffected ones.<sup>18,19</sup> Additional studies are particularly needed to evaluate the effects of household and neighborhood characteristics on the health, psychosocial wellbeing, education, and economic achievement of affected individuals.

## Prevention

Identifying preventive interventions for common birth defects is a long-established goal worldwide. The most successful example is preventing neural tube defects (NTDs) by folic acid supplementation and fortification programs. Folic acid has also been suggested to reduce both oral cleft occurrence and recurrence (i.e. having a second affected child or a first affected child for affected mothers), but the evidence is still mixed,<sup>20</sup> as it is based on observational studies or interventional studies that were not randomized and blinded. Souza and Raskin<sup>2</sup> report a reduction in their clinic-based prevalence of oral clefts after the folic acid fortification program was implemented in Brazil. However, since that study was clinic-based, it may not accurately estimate the prevalence of oral clefts in the population. Therefore, their analysis should be viewed as descriptive, and their results should be considered with caution. Other vitamins/nutrients besides folate, such as vitamin B6,<sup>21</sup> have also been suggested to play a role, although the evidence is still controversial. Therefore, randomized double-blinded clinical trials (RCTs) that can test vitamin/supplement effects in a large enough sample of at risk-women are particularly needed to detect moderate risk changes. Since primary occurrence of oral clefts is relatively rare, conducting RCTs for occurrence may be challenging and cost-prohibitive, as it requires a very large sample.<sup>20</sup> RCTs are more particularly suited for recurrence, which may be at least 30 times as common

as primary occurrence.<sup>22</sup> Brazil is particularly suited for these clinical trials since it has several large clinics specialized in cleft/craniofacial care that can serve as sites for recruitment and intervention.

An example of one RCT is the Oral Cleft Prevention Program (OCP), which was developed to test the effect of a high dose of folic acid (4 mg) taken daily preconception and during the first three months of pregnancy on recurrence of oral clefts relative to a low dose (0.4 mg).<sup>23-25</sup> The OCP recruited women at-risk of cleft recurrence in several sites in Brazil, but recruitment was suspended in 2009 due to lower than expected rates of recruitment, retention, and pregnancy. However, the OCP established a unique collaborative research infrastructure among some of the largest cleft/craniofacial clinics in Brazil that can be considered for future interventional studies and provided important preliminary data on effectiveness and safety of high dose folic acid.<sup>24,25</sup>

## Conclusion

Nationwide efforts are needed in Brazil for building the capacity for research on major common birth defects, including oral clefts. Brazil is particularly suited for leading research in several areas, including environmental and genetic factors and prevention. Furthermore, since it is unclear whether the findings on health and well-being of affected individuals from specific settings apply to other countries - especially when generalizing results from developed countries to less developed ones - understanding the health and socioeconomic well-being of affected individuals and their families in Brazil both in the short and long term is important in order to identify needs and develop interventions for reducing oral cleft-related disparities, and maximizing the well-being of affected individuals and their families.

## Conflicts of interest

The author has no conflicts of interest to declare.

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