# Screening for oral cancer during a flu vaccination campaign:

# A Brazilian strategy

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## DEDICATION

I dedicate this project to my late father, Sh. Amarjeet Singh whose struggles were a continuous source of inspiration.

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LIST OF ABBREVIATIONS

Oral cancer (OC)

Oropharyngeal carcinoma (OPC)

Age standardised incidence (ASI)

Age standardised mortality (ASM)

Potentially malignant disorders (PMODs)

Leukoplakia (LE)

Lichen planus (LP)

Lichenoid lesions (LL)

Oral erythroplakia (OE)

Oral submucous fibrosis (OSF)

Proliferative verrucous leukoplakia (PVL)

Oral erythroplaki (OE)

Actinic Cheilitis (AC)

World Health Organization (WHO)

# PREFACE

This project follows the manuscript-based style of the thesis. According to McGill University standards, the manuscript incorporated in the thesis should be logically coherent and should have a centralized theme. The manuscript in this research describes and evaluate the coverage of an oral cancer screening program in São Paulo, Brazil, which is organized every year in October, along with an influenza vaccination campaign. We provided the introduction and literature review on the epidemiology and screening programs on oral cancer. After discussing the previous knowledge, we present the study objectives followed by the methodology, and the manuscript. The last chapter of this dissertation presents the summary of results and addresses the methodological concerns and recommendations for future investigation on the subject. The manuscript included in this work has various writers and their contribution is mentioned below.

## CONTRIBUTION OF AUTHORS

Harsh Vardhan Singh Arora, Masters' Candidate, Faculty of Dentistry - McGill University, Montreal, Quebec, Canada: Contributed to the development of the objective of the investigation, carried out statistical analysis, and wrote the manuscript.

Sreenath Arekunnath Madathil, Assistant professor, Faculty of Dentistry - McGill University, Montreal, Quebec, Canada: Contributed to the objective of the study, the design of statistical analysis, reviewed and contributed to manuscript writing.

Belinda Nicolau, Professor, Faculty of Dentistry - McGill University, Montreal, Quebec, Canada: Contributed to the objective and design of the study and reviewed and contributed to manuscript writing.

ABSTRACT

**Background**

Oral (OC) and oropharyngeal (OPC) squamous cell carcinoma are among the top ten malignancies worldwide accounting for a significant burden of disease among all cancers. An estimated 354,864 and 92,887 new cases of OC and OPC, respectively occurred worldwide in 2018. The incidence of these cancers in Brazil is very high; a total of 14,700 OC cases and 4,629 OPC cases were reported in the country in 2018. These numbers represent almost half of these cancers in Latin America and Caribbean countries. These devastating diseases have a low survival rates (~50% 5-year survival) and it is often diagnosed at advanced stages. However, when OC and OPC are diagnosed at an early stage, the 5-year survival rates improve substantially. Screening programs help the identification of OC and OPC at early stages, however, due to the relatively low incidence of these cancers, the implementation of population screening is questionable. Therefore, alternatives strategies to screen for these diseases are necessary.

**Objective**

To describe an innovative population oral cancer screening strategy program implemented in São Paulo, Brazil. In addition, we describe the coverage of this program in the municipalities in the state of São Paulo from 2015-2019 and the detection of oral lesions during the same period.

**Methods**

Since 2001 the Secretary of Health of São Paulo state in Brazil implemented an on oral screening program that takes places every year during the national vaccination campaign against influenza. The program provides the population with an oral health screening that is conducted by trained dentists and includes an assessment of oral lesions. When a lesion is detected, it is classified into

low or high-risk. However, for this project, we analysed only the presence or absence of an oral lesion using a database from 2015-2019. To obtain geographic information and population size, we linked this database to the Brazilian Institute of Geography and Statistics. After an extensive data cleaning, we used descriptive statistics to evaluate the coverage of the program according to municipalities and age groups. In addition, we map the coverage using the results of reporting cities along with the geographic data in R-software.

**Results**

There are 645 municipalities in the state of São Paulo, Brazil, from which approximately 50% to 60% of them have data available. Furthermore, most of the data are available for the elderly (above 60 years). While looking into the screening coverage, we have found ~2% coverage across all age groups for the state. When taking a closer look at age, the younger age group (20-<60 years old) shows less coverage than the older. Also, there is a significant variation in the coverage among municipalities, as is illustrated by the maps. It is evident from the spatial presentation that some municipalities performed more screening than others; these trends seem consistent over the 5-year period. The number of oral lesions decreased from 2015-2019 with a slight decrease in 2016 and 2018 for the whole state.

**Conclusion**

In summary, there is a notable variation in the screening coverage and the number of oral lesions among cross municipalities of the state of São Paulo. It is advised to health authorities to increase the screening coverage. Further, individual-level data are needed to better understand the reasons for significant variation in coverage.

RÉSUMÉ

**Contexte**

Le carcinome épidermoïde buccal (CO) et oropharyngé (CPO) figurent parmi les dix principales tumeurs malignes dans le monde, ce qui représente une charge de morbidité importante parmi tous les cancers. On estime que 354 864 et 92 887 nouveaux cas de CO et de CPO, respectivement, sont apparus dans le monde en 2018. L'incidence de ces cancers au Brésil est très élevée ; un total de 14 700 cas de CO et 4 629 cas de CPO ont été signalés dans le pays en 2018. Ces chiffres représentent près de la moitié de ces cancers dans les pays d'Amérique latine et des Caraïbes. Ces maladies dévastatrices ont un faible taux de survie (~50% survie à 5 ans), est souvent diagnostiquée à des stades avancés. Cependant, si le diagnostic de CO et de CPO est précoce, le taux de survie à 5 ans s'améliore considérablement. Les programmes de dépistage permettent d'identifier les CO et les CPO à un stade précoce, mais la mise en œuvre du dépistage dans la population est discutable en raison de l'incidence relativement faible de ces cancers. Il est donc nécessaire de mettre en place des stratégies alternatives de dépistage de ces maladies.

**Objectif**

Décrire un programme novateur de stratégie de dépistage du cancer buccal dans la population mis en œuvre à São Paulo, au Brésil. En outre, nous décrivons la couverture de ce programme dans les municipalités de l'état de São Paulo de 2015 à 2019, et les tendances des lésions buccales au cours de cette même période.

**Méthodes**

Depuis 2001, le secrétaire à la santé de l'état de São Paulo au Brésil a mis en place un programme de dépistage oral qui a lieu chaque année pendant la campagne nationale de vaccination contre la grippe. Le programme propose à la population un dépistage de la santé bucco-dentaire qui est effectué par des dentistes en formation et comprend l'évaluation des lésions bucco-dentaires. La présence de lésions buccales est évaluée et lorsqu'une lésion est détectée, elle est catégorisée : à risque faible ou à risque élevé. Pour ce projet, nous avons analysé la présence et l'absence d'une lésion buccale en utilisant une base de données de 2015 à 2019. Pour obtenir des informations géographiques et la taille de la population, nous avons relié cette base de données à celle de l'Institut brésilien de géographie et de statistique. Après un nettoyage approfondi des données, nous avons utilisé des statistiques descriptives pour évaluer la couverture du programme en fonction des municipalités et des groupes d'âge. En outre, nous avons cartographié la couverture en utilisant les résultats des villes déclarantes ainsi que les données géographiques dans le logiciel R.

**Résultats**

Il y a 645 municipalités dans l'état de São Paulo, au Brésil, dont environ 50 à 60 % disposent de données. En outre, la plupart des données sont disponibles pour les personnes âgées (plus de 60 ans). En examinant la couverture du dépistage, nous avons trouvé une couverture d'environ 2 % dans toutes les tranches d'âge pour l'état. Cependant, lorsque nous zoomons sur la couverture par catégories d'âge, la tranche d'âge la plus jeune (20 à moins de 60 ans) présente une couverture moindre que la plus âgée. De plus, les cartes montrent une variation significative de la couverture entre les municipalités. Il ressort de la présentation spatiale que certaines

municipalités ont effectuée plus de projections que d'autres et que celles-ci semblent être constantes sur la période de cinq ans. Le nombre de lésions buccales a diminué entre 2015 et 2019, avec une légère baisse en 2016 et 2018 pour l'ensemble de l'état.

**Conclusion**

Il existe une variation notable dans la couverture du dépistage et le nombre de lésions buccales entre les municipalités de l'état de São Paulo. Il est conseillé aux autorités sanitaires d'augmenter la couverture du dépistage. Il est également nécessaire de disposer de données au niveau individuel afin d'examiner de près les raisons des variations importantes de la couverture.

# 1. INTRODUCTION

Oral (OC) and oropharyngeal (OPC) squamous cell carcinoma are among the top ten malignancies worldwide (1) accounting for a significant burden of disease among all cancers (2). According to 2018 statistics, an estimated 354,864 OC cases and 92,887 OPC cases; and 177,384 OC deaths and 51,005 OPC deaths occurred worldwide. Unfortunately, these cancers represent a growing problem in several regions of the world including Brazil. In 2018, 14,700 and 4,629 new cases of OC and OPC were reported in Brazil, respectively. These numbers represent almost half of these cancers in Latin America and Caribbean countries (3). Moreover, among the 26 Brazilian states, the state of São Paulo has one of the highest age standardised incidence (ASI) and mortality (ASM) rates for OC (12.17 and 3.09 per 100,000 for men and women, respectively) (4, 5).

OC and OPC are devastating diseases with low 5-year survival rates (approximately 50%), and are often diagnosed at advanced stages (6). This low survival is mainly attributable to late detection. Indeed, due to the aggressive behavior of these cancers, the early-stage diagnosis is vital for improving survival (7). For example, while the survival rates for early stage OC are approximately 93%, these rates drop significantly to 38% for advanced stages, and 20% for metastatic disease (8).

OC and OPC can arise from potentially malignant disorders (PMODs) of oral cavity and pharynx and up to 51% of these group of chronic lesions have a degree of dysplasia at time of presentation (9). Therefore, direct efforts toward prevention and early detection is a promising preventive strategy.

Taking the opportunity of the annual influenza-vaccination campaign, the state of São Paulo has performed an oral health screening program that includes the assessment of oral lesions since 2001. This screening program has shown to organise network of patient care and to encourage oral health care professional to screen for oral cancer; however, a detailed coverage of the screened population across the municipalities of the state of São Paulo has not been performed (10). Moreover, the incidence of oral lesions in São Paulo has not been evaluated since 2015.

Therefore, the aim of this thesis is to describe this innovative oral cancer screening program and evaluate the program's coverage across the municipalities of the state of São Paulo from 2015-2019. Also, we examine the detection rates of oral lesions among those who were screened, during this period. By evaluating the coverage of this program, this work provides vital information for the planning of public health strategies for the state of São Paulo.

# 2. LITERATURE REVIEW

This section presents an epidemiological overview of oral cancer and PMODs, followed by a description of oral cancer screening programs.

## 2.1 Oral cancer

### 2.1.1 Definition

Oral cancers are defined as malignancies that arise in the lip and oral cavity—including base of the tongue, gum, floor of the mouth, and palate—which corresponds to the International Classification of Diseases, 10$^{th}$ revision [ICD-10: C00-C06, C09, C10, C14] (11). We also discuss cancer of the tonsils and other parts of oropharynx (OPC) as these cancers are increasing in incidence (ICD: C09, C10). Most of these malignancies (~90%) are squamous cell in origin (12).

### 2.1.2 Oral cancer: global incidence and mortality with special reference to Brazil

OC and OPC squamous cell carcinoma are among the top ten malignancies worldwide (1) accounting for a significant disease burden (2). In 2018, 354,864 and 92,887 new cases, 177,384 and 51,005 deaths of OC and OPC, respectively, were reported worldwide (13). The age-standardized incidence rates were of ≥ 0.76 (age group: 20-39 years), ≥ 10.0 (age group: 40-59 years), and ≥ 27.7 (age group: 60 and above) in the world for both sexes in 2018, with higher incidence among males (14). While OC and OPC are more common in the older age group, the literature shows an increase in the incidence of these cancers among the younger age group (15, 16). Lip, OC and OPC contribute to 3.8% of all cancer cases, which is estimated to rise by 62% in 2035 worldwide (17). The number of cases are astronomical in countries such as Australia

(specifically for lip cancer), Asia (India, Pakistan, Taiwan), North America, Europe (Hungry, Slovakia, Germany) and Latin America (Brazil, Uruguay, and Puerto Rico) (12, 17, 18).

Brazil has the highest incidence rates for OC and OPC among South American males. The incidence of these cancers varies widely among Brazilian regions: the southeast region reports the highest number of cases (61%), followed by the northeast (19%), south (15%), central-western (3%), and northern (2%) regions(19). The state of São Paulo located in the southwest region reported the highest number of cases among males in Brazil, ranging from 10.38/100,000 in 1998–2002 to 9.14/100,000 in 2003–2007. Brasilia, Cuiaba, and Goiania are among other states with high incidence (19). It is important to highlight that this project describes an oral cancer screening program in São Paulo, Brazil (20, 21), where the incidence of these cancers is one of the highest in the world.

**2.1.3 Oral cancer survival**

OC and OPC mortality rate are high with the five-year survival rate approximately 50% around the world (12). The five-year survival rate of OC and OPC for Brazil as country was 51.7% and 45%, respectively from 2001–2012. However, a considerable variation is the overall survival is observed in the different Brazilian states (22). While the five-year survival of OC patients remains mostly unchanged (50%) in the last decades, OPC survival rates have improved from 37% to 49%. Survival after diagnosis of OC is mainly dependent on the stage at the time of diagnosis. The probability of survival decreases when the cancer is diagnosed at an advanced stage; while the survival rates for early stage OC are approximately 93%, these rates drop significantly to 38% for

advanced stages, and 20% for metastatic disease (8). In Brazil, almost 90% of OC are diagnosed at later stages, leading to a low survival rate (12, 22).

### 2.1.4 Oral cancer risk factors

The main risk factors for OC and OPC are age, sex, alcohol drinking, smoking tobacco, and diet (23) and, for a subset of these cancers, human papilloma virus (HPV) (24). Data from the National Institutes of Health, in the USA, demonstrates that older people are more likely to develop OC and OPC, whereas recent literature suggests the incidence of these diseases is increasing in younger ages (25). Additionally, male sex shows greater risk to develop OC and OPC irrespective age. Tobacco smoking, alcohol drinking, and their joint effect are well established risk factors for these cancers (26). In addition, diet also plays a role in the enhancement of OC risk. While the nutrients in the food vary with geographical factors, diets rich in fruits and vegetables is considered a protective factor against OC and OPC (27).

## 2.2 Oral precancerous lesions

### 2.2.1 Definition

Oral precancerous lesions are tissue changes affecting the oral mucosa, that may turn cancerous—the WHO termed it as potentially malignant oral disorders (PMODs) in 2005 (28). Recently, the PMODs have been termed as potentially premalignant oral epithelial lesions (PPOELs) for both clinical and histological malignant dysplasia (28). The different types of PMODs are oral leukoplakia (OL), erythroplakia, lichen planus (LP), oral submucous fibrosis (OSMF), actinic cheilitis (AC), and other inflammatory lesions in oral cavity (29, 30).

### 2.2.2. Prevalence and Incidence of PMODs

It is essential to discuss the epidemiology of PMODs as PMODs precede the oral squamous cell carcinoma, the most common type of OC (31). As discussed above, the survival of the patient is dependent on the stage of the cancer diagnosis. It is estimated that less than 20% of people will die when OC is diagnosed at earlier stages; however, there is a substantial increase in mortality (more than 60%) and decreased in 5-year survival rates when these cancers are diagnosed at later stages (32). Table 2:1 displays the results of recent systematic reviews on the prevalence of various PMODs.

The incidence and prevalence of PMODs vary widely worldwide depending on socio-demographic characteristics of the population and the exposure to carcinogens. Moreover, studies used different clinical definition of PMODs which, in turn, lead to a considerable variation of the incidence and prevalence of these lesions.

Findings from two systematic reviews reported an overall prevalence of PMODs worldwide of 7.9% (95% CI: 4.9-11.5) (33) and 4.47% (95% CI: 2.43-7.08) (29) while the prevalence of leukoplakia, the most common of PMODs, ranged from 0.89% (95% CI: 0.38-2.05) to 4.1% (95% CI: 1.98-6.97) (29). The prevalence rates vary across the world; Asia (10.54%, 95% CI: 4.60-18.55) and South America (3.93%, 95% CI: 2.43-5.77)—where Brazil is located—, reporting the highest prevalence (29). A high incidence of oral lichen planus in South America is reported by population (1.39%, 95% CI: 0.58%-3.28%) and clinical studies (3.18%, 95% CI: 0.97%-9.95%). The high prevalence of oral lichen planus in Brazil (6.04%) compared to India (0.02%) can be attributed to

the climate, behavioural habits, eating styles, frequent cigarette smoking, and alcohol usage in Brazil (34). However, India has a high prevalence of leukoplakia (range = 0.2% to 5.2%) and oral submucous fibrosis (range = 0.03% to 3.2%). The fact that India is the second-largest consumer of tobacco products after China, and the habits of paan chewing may explain the high prevalence of these lesions in the country (35).

**Table 2.1 Prevalence of oral lesions: results from systematic review & meta-analysis**

| Authors | Year | Studies | Prevalence %(95%CI) |
|---|---|---|---|
| **Locca *et al.* (33)** | 2020 | 92 Studies | PMODs 7.9 (95% CI: 4.9-11.5)<br>LP 1.4 (99% CI: 0.9-1.9)<br>LE 9.5 (99% CI: 5.9-14.0)<br>OLL 3.8 (99% CI: 1.6-7.0)<br>OSF 5.2 (99% CI: 2.9-8.0)<br>OE 33.1 (99% CI: 13.6-56.1)<br>PVL 49.5 (99% CI: 26.7-72.4) |
| **Li *et al.* (34)** | 2020 | 46 Studies | LP 0.89 (95% CI: 0.38-2.05) |
| **Mello *et al.* (29)** | 2018 | 22 Studies | PMODs 4.4 (95% CI: 2.4-7.1)<br>OSF 4.9 (95% CI: 2.2-8.6)<br>LP 4.1 (95% CI: 1.98-6.97) |
| **Petti *et al.* (36)** | 2003 | 23 Studies | LP 1.4 (95% CI: 1.4-1.5) |

The differences in the prevalence and incidence of PMODs from the systematic review may be attributed to different study designs including, for example, retrospective, cross-sectional, and systematic review/meta-analysis. The population's demographic characteristics, time, and methods used to calculate the prevalence can also contribute to the variability. Apart from this, inclusion and exclusion criteria may also lead to the differences in study results.

### 2.2.3. Age, sex, and ethnicity

Overall, PMODs are more often observed middle aged individuals. However, some lesions (e.g., leukoplakia) have been diagnosed among adolescents and young adults (15- 24 years old) (37). This age distribution may be explained by earlier exposure to carcinogens and lifestyle differences. For example, the habit of chewing betel quid or smokeless tobacco, which is common in developing countries (e.g., Bangladesh, India), may lead to the development of PMODs 5 to 10 years earlier than in more developed countries where these lesions usually occur in middle age (38).

Ethnicity is another factor that may influence the incidence of these lesions. For example, the prevalence of PMODs among different ethnic groups living in Malaysia varies substantially; while the Chinese living in Malaysia had the lowest prevalence of PMODs, the Indian living in the same country had the highest prevalence (39). It is hard to disentangle the effects of ethnicity as ethnic diversity among Southeast Asian countries is linked to different behaviors (e.g., smoking and chewing habits).

Males are predominantly more affected than females. However, the distribution of PMODs among males and females varies according to smoking habits and geographical area (36). Also, some PMODs (e.g., lichen planus) are more common females(36).

### 2.2.4 PMODs risk factors

There are diverse risk factors that account for the development of PMODs; alcohol, tobacco smoking and chewing habits are the principal risk factors. Also, there is growing evidence for the role of HPV in the ætiology of these lesions. For example, while most oral lesions (e.g., leukoplakia, erythroplakia, oral lichen planus) are associated with smoking and alcohol habits, oral submucous fibrosis are associated with history of areca nut chewing (40). Apart from this, several types of oral dysplasia are idiopathic and may not have any risk factors.

## 2.3 Screening Programs

There are three main levels of public health strategies. Primary prevention aims to discourage known risk factors in order to prevent the occurrence of these diseases. For example, campaigns that discourage smoking to prevent chronic diseases including OC and OPC. Secondary prevention aims to detect disease at an early stage in order to reduce morbidity and mortality. Tertiary prevention tries to decrease the deleterious effects of the disease.

Screening programs are a form of secondary prevention (41) as they aim to identify the disease before it manifests its clinical symptoms (42). Screening programs are defined as "*the process by which a practitioner evaluates an asymptomatic patient to determine if he or she is likely or unlikely to have a potentially-malignant or malignant lesion*" (Page e3)(43). Screening programs may help considerably in reducing mortality and morbidity for some malignancies because they increase the chances of detecting certain cancers earlier, when they might be easier to treat (13, 44). The guidelines for screening recommendations are based on drawbacks and

benefits of the intervention (45). The most cost-effective screening programs not only identify the most at risk populations but also inform these populations of the program's existence and treat those presenting abnormalities. This differs from opportunistic screening, which is offered by a doctor or health professional. Contrasting to an organized screening program, opportunistic screening may not be checked or monitored. There are different types of screening strategies, namely population-based and targeted groups (46). While population-based screens the entire population, the targeted groups is a selective strategy which tests only the community at risk (44, 47, 48).

The following questions are important: How should we screen for a specific disease? if so, should we screen high-risk groups or the whole population? For some malignancies, population-based screening is recommended, but for others, only high-risk individuals are advised to be screened. Testing the entire community requires many more resources than focusing on the smaller high-risk groups. Ultimately, policymakers decide on the strategy for screening. Even after determining the high-risk group for screening, the more profound question that needs to be answered is if the benefit trickles down only to an economically wealthier society or the actual individuals at risk (49). The former question is vital as OC and OPC are socially pattern, that is, people belonging to lower economic sectors of society has higher risk of disease and less access to care(50).

The WHO's report, "Principles and Practice of Screening for Disease" written by Drs. Wilson and Jungner, in 1968, provides a framework to guide population-based screening decisions and presents 10 principles to evaluate screening programs:

“1. The condition should be an important health problem.

2. There should be an accepted treatment for patients with recognized disease.

3. Facilities for diagnosis and treatment should be available.

4. There should be a recognizable latent or early symptomatic state.

5. There should be a suitable test or examination.

6. The test should be acceptable to the population.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.

8. There should be an agreed-upon policy on whom to treat as patients.

9. The cost of case-finding (diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care.

10. Case-finding should be a continuing process and not a “once and for all” project.” (51)

Screening is always a debatable topic, primarily when the balance between adverse effects and benefits are not precise in the scientific literature. Screening, if done regularly, sometimes gives the false feeling of being protected. However, it is advantageous if treating the targeted disease at earlier stages is more effective than treatments at later stages. The WHO’s recommendations for screening stresses the view that it should be done when clear scientific evidence of its benefits is available in the literature. Before introducing the screening in the public domain, it is also essential to check the reliability of the test in question. If the test itself gives more false positives than true positives, it does more harm than good. Sometimes, screening presents a false sense of improvement in survival of the disease, while individuals do not survive

longer; this is known as lead-time bias. They simply receive the information on diagnosis earlier and before the clear presence of symptoms (52).

**2.4 Oral cancer screening programs**

OC is one of the leading causes of morbidity among all carcinomas worldwide (45). Currently, opportunistic screening (45, 53) is the mode of choice for detecting cancer in its earlier stages. However, there is growing evidence that supports population-based approaches from the studies in India (9, 32, 54-56).

OC screening is usually performed by visual examination of the oral cavity. In addition, various oral examination diagnostic adjuncts have been suggested in response to the rising incidence of these cancers and in order to improve health professional's ability to detect malignant changes early, e.g., tissue staining (e.g., toludine blue), brush cytology (e.g., oral CDx), and visualization adjunct (e.g., VELscope). However, the use of these tools to screen OC can only be justified if the prevalence of OC and both the specificity and the sensitivity of tests to detect OC precursors are high. Indeed, studies on the effectiveness of OC screening programs using the diagnostic adjuncts discussed above are no more effective than the visual exam (57). Therefore, it has been suggested to adopt the simpler method of oral-visual examination for screening OC as it can detect the presence of OC and improve the survival to a great extent.

However, the question on whether to perform population-based OC screening is still debatable. The United States Preventive Services Task Force suggests that there is insufficient

evidence for the benefit of OC screening. They suggest that adopting the oral screening as part of the complete head and neck examination during a periodic health check up and reporting any departure from normal structures would decrease the risk (58).

Our literature search did not discover much about the effectiveness of OC screening programs. The need for population-based screening is only suggested in a randomized controlled trial in Kerala, India. However, this study had some limitations; for example, the screening by non-medical staff may have resulted in low sensitivity (67%) and the compliance rate among the screened group was 59%. The study focused on population with high incidence of OC and could not justify the screening in low incidence communities. Moreover, there are no details on random assignments and concealments (59). Therefore, researchers are of the view to screen only high-risk patients opportunistically in a clinical setting (60). Alternatively, screening high-risk groups may be a potentially more cost-effective strategy, specifically those who do not or cannot access health care systems, since high-risk groups may include those who do not have regular check-up visits with health professionals (54). Despite the potential benefits of detecting OC at an early stage, population-based screening is not endorsed (59). Although population-based screening is not supported, there are studies conducting population screenings for high-risk individuals.

Table 2.2. presents the coverage of two oral cancer screening programs conducted in Taiwan (61) *al.* and in Tokonama city, Japan (62)**.** For example, a study in Taiwan screened high-risk populations (i.e., those with habits of cigarette smoking and/or betel quid chewing)18 years and older. This study covered 55.1% of the population under investigation and highlights the

advantages of visual oral examinations for detecting pre-cancerous oral lesions and reducing OC incidence (an average positive predictive value of 61%). The findings also showed a 21% reduction in stage III or IV OC with a 13% higher survival rate in the screened group. The screened group had a hazard-ratio of 0.88, whereas the non-screened group had 0.96 after adjustments. Finally, the authors suggest a need for longer screening intervals for lesions such as leukoplakia which has a longer dwelling time, but a shorter screening interval than other PMODs such as erythroplakia, erythro-leukoplakia, and submucous fibrosis.

**Table 2.2 Studies describing Oral Cancer Screening Programs.**

| Author | Year | Patients | Design | Population coverage |
|---|---|---|---|---|
| **Chuang SL *et al.* (61)** | 2017 | 2 334 299 | Prospective | 55.1% for high-risk population |
| **Nagao T *et al.* (62)** | 2003 | 6 705 | Prospective | 26% total population |

The study by Nagao *et al.* (62), the first study from an industrialized country (Tokoname city, Japan) on OC screening in a target population, showed a high compliance among middle age groups with female predominance. This study also reiterates that the people who are at greater risk are less likely to show up for screening. The authors conclude that free OC screenings help improve the attendance rates among high-risk individuals, which helps detect invasive pre-malignancies at an earlier stage and thus, further adds to public health benefit.

The alarming rise in the number of OC cases around the world suggests a need for more research in the prevention of these cancers. While a significant number of studies in the field of OC

prevention have been conducted in the US, India, and the UK, much less has been done in other countries such as Brazil, Hong Kong, and European countries (63).

As mentioned earlier, São Paulo, Brazil has the highest number of cases of OC, and an OC population screening is in place since 2001. This program takes advantage of influenza vaccination period that happens every year to screening for OC. Table 2.3 summarizes the results of previous studies evaluating this program. These studies calculated coverage by dividing number of people who underwent OC screening by the number of people vaccinated. Their results show an increase in OC screening among vaccinated individuals and a decrease for the suspicious oral lesions. Though this program initially targeted people who were 60 years and over, to strengthen the oral cancer prevention startegy in the state and in light of this program's success, it was expanded to include anyone aged 18 or over (64).

This previous analysis of the screening program in São Paulo details the number of cities that held the screening program, the number of people screened in all the municipalities, and the number of suspicious cases of lesions among those vaccinated for influenza (H1N1) by municipality from 2001-2009. However, no details on the individual municipality is discussed and results were only reported for those 60 years and over. My project expands this work by presenting a detailed description of the screening program from 2015 to 2019, including all the age categories screened (age groups: 20-39, 40-59 and, 60 and above).

**Table 2.3 Summary of oral cancer screening program among vaccinated individuals age 60 years & above in São Paulo, Brazil.**

| Year | Participating municipalities | No. people screened | Soft tissue changes (64) | | % Suspicious cases**(10) | % Coverage |
|---|---|---|---|---|---|---|
| | | | No. of People | % | | |
| **2001** | 334 | 90 886 | 7 028 | 7.8 | 28 | 4.1 |
| **2002** | 434 | 142 774 | 13 801 | 9.7 | 10 | 6.4 |
| **2003** | 512 | 226 540 | 18 059 | 8.0 | 8 | 8.8 |
| **2004** | 490 | 238 087 | 20 270 | 8.5 | 9 | 8.7 |
| **2005** | 317 | 253 648 | 22 939 | 9.0 | 9 | 10.8 |
| **2006** | 509 | 360 760 | 30 481 | 8.4 | 8 | 12 |
| **2007** | 503 | 435 971 | 34 481 | 7.9 | 8 | 15 |
| **2008** | 539 | 480 607 | 24 280 | 5.0 | 5 | 16 |
| **2009** | 551 | 629 613 | 28 401 | 4.5 | 5 | 18 |

0 Individual with healthy soft tissue
1 People with soft tissue changes without suspicion of malignancy (changes not listed in code 2)
2 High risk-individuals with oral lesions such as white (leukoplakia) or red (erythroplakia) plaques, actinic cheilitis, mouth ulcers of over two weeks' duration, oral lesions of rapid growth, (Exophytic and endophytic) *(64)*
**Suspicious cases among those screened (10, 65)

**2.5 Conclusion of the literature review: Rationale**

OC and OPC are one of the top ten cancers in the world with a substantial burden among all cancers globally. Brazil has one of the highest incidences of these cancers in the world. The most

common and severe malignancies usually arise from PMODs, such as: oral leukoplakia, oral erythroplakia, oral submucous fibrosis, oral lichen planus, and actinic cheilitis (29).

The most important risk factors for PMOLs include tobacco smoking, alcohol consumption, and their combined effects. Further, there is growing epidemiological evidence supporting an aetiologic role for human papillomaviruses (HPV) for a subset of PMODs. However, the knowledge of these risk factors is of little benefit to patients once cancer has developed, as five-year survival rates have remained unchanged for the past decade at less than 50%.

Late diagnosis of OC and OPC is a major problem as a diagnosis at a late stage requires aggressive treatment that lowers survival rates (66). As a result, screening is suggested as the solution to detect OC and OPC at preliminary stages. Screening, diagnosing, and following PMODs could capture OC and OPC cases at earlier stages, thus, reducing its burden on public health resources. Studies from countries with a high incidence of these diseases, such as India and Taiwan, have suggested the effectiveness of OC screening programs. However, these studies have some limitations and there is not yet a consensus on the efficacy of these programs. Consequently, national governments have not adopted these screening programs given insufficient justification for their implementation (67). Screening high-risk groups may be a potentially more cost-effective strategy, specifically for those who do not or cannot access health care systems. Similarly, screening PMODs along with other health check ups, referred to as opportunistic screening, is highly recommended for early detection of PMODs, OC and OPC (55, 56).

The state of São Paulo in Brazil, in partnership with municipalities and health organizations, developed a cancer prevention program that co-occurs with the national vaccination campaign against influenza every year in October. Furthermore, oral examinations, including the screening of oral lesions, were also offered during the vaccination campaign. While this program has been evaluated between 2001-2009, the actual coverage of the program is not reported according to the population of the municipality (the past studies only evaluated the percentage of those screening among those attending the vaccination day). Also, their analysis included only subjects 60 years old and over. My project expands this work by presenting a detailed description of the screening program from 2015 to 2019, including all age categories screened (aged 60 years and above, and those aged20 to 59 years). These results are indispensable for planning public health strategies for São Paulo and may provide a valuable example of a population screening for OC that is cost effective.

# 3. STUDY OBJECTIVES

The overall aim of our study is to describe an OC screening program in the municipalities of the state São Paulo, Brazil from 2015 to 2019. The specific aims are to:

- Tabulate the number of participating municipalities in the screening program according to age groups from 2015-2019.
- Determine the overall coverage of the screening program according to age groups across the state of São Paulo, Brazil, from 2015 to 2019.
- Map the coverage of the screening program for the age categories across municipalities of São Paulo, Brazil, from 2015-2019.
- Graph the time trend for the coverage of the screening program according to age categories and the percent of oral lesions among those screened from 2015-2019.

# 4. METHODS

## 4.1 Study Design

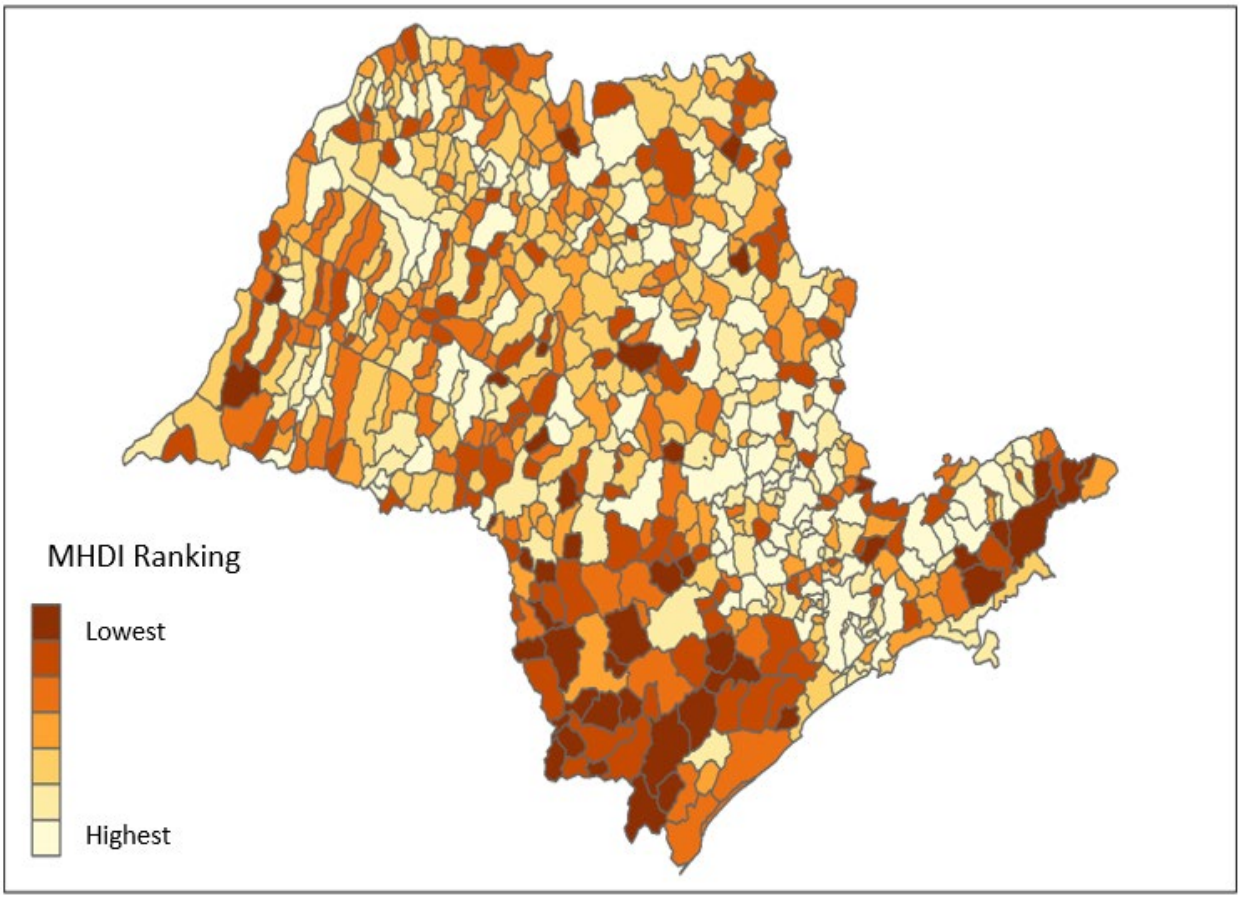
Since 2001 the government of São Paulo state in Brazil have been collecting data on the oral health clinical examination during the national vaccination campaign against influenza for the elderly in primary health care centers. This cross-sectional study uses these data to evaluate coverage of this program across the municipalities and the trends in the incidence of oral lesions.

A cross-sectional design collects information on the population at a given point in time. It is like viewing the community in a snapshot. Researchers use these studies for descriptive or analytical purposes (41). It is always advised to be cautious when using them for analytical purpose because the results are correlational rather than causal. Cross-sectional descriptive studies cover time, place, and person which is ideal for public health strategies for several reasons. One reason is that this design allows insights into the extent and pattern of public health problem in time as precise as months, in location as precise as which towns, municipalities, or neighbourhoods, and in demographic groups. Cross-sectional study design can also provide a detailed description of the health of a population using tables, graphs, and maps and identify areas or groups within the population with high rates of disease. This information can be used for making public health strategies and also to generate important information on the causes of the disease, which in turn may lead to testable hypotheses (68).

## 4.2 Study Setting

Among the 27 states in Brazil, São Paulo has one of the highest scores in the human development index (MHDI= 0.700 and 0.799); MHDI considers longevity-life expectancy at birth, education,

**Figure 4. 1 Map of São Paulo presenting Human Development Index.**




and per capita monthly income, with a population of 41 million (2010 Census) and population density of 166.23 people/km², most of the state of São Paulo's population lives in urban (~95%) areas with a roughly equal proportion of males to females. This state, one of the wealthiest in Brazil, had an average per capita income of R$ 1,084.46 in 2010. The state showed an improvement in the Gini index (an instrument for calculating income concentration) from 1991 to 2010, probably reflecting a decrease in income disparity between poor and prosperous groups of the population. In addition, a substantial increase in population levels of education has been observed between 1991 and 2010 in São Paulo.

Despite these favourable economic indicators, the state has the highest incidence of oral cancer (69) in Brazil, and the country itself is counted as a high incidence of oral cancer worldwide (4). To address the burden of oral cancer, the state of São Paulo started an oral cancer screening program in 2001. This screening program takes advantage of the vaccination campaign to cover the maximum people.

**4.3 Data Sources**

The Secretary of Health of the state of São Paulo (SES-SP), in partnership with municipalities and organizations linked to the health system, initiated a prevention and early diagnosis of oral cancer program in 2001. It was officially launched during the III Health Review Cycle Bucal, event promoted by SES-SP in March 2001.

This prevention program, which had the support of the Oncocentro Foundation of São Paulo from 2005 to 2012 (7), co-occurs with the national vaccination campaign against influenza for the elderly. It usually happens in October of each year in the primary health care and community centers located in the municipalities of the state of São Paulo.

In addition to immunization and preventive activities that encourages self-care and the self-examination of the oral cavity, the program includes a clinical examination of the oral cavity. In its initial stages the program was offered only to the elderly population (age 60 years and older), however, since 2015, it is opened to other age groups (65). The link between the consolidated campaign of influenza vaccination and oral health prevention program is well

accepted, and the oral clinical examination is performed with ease and without constraints to 69% of those examined (64).

The development of this program involved several steps including: (i) the development of printed material to guide municipalities on how to: conduct the campaign, to identify codes and criteria to be used and to provide guidance for data entry; (ii) training of professionals; (iii) development of educational material; (iv) performing the clinical exams; (v) conducting educational orientation groups for the elderly about self-care and self-examinations; (vi) establishment of referral flows; (vii) practical training based on the review of individuals who presented some soft tissue changes together with the specialist in the health unit; (viii) expansion of the number of services directed to the oral diagnosis (Centers of Dental Specialties, CEOs) (9).

The training of dentist and dental assistants involved in this initiative was carried out in local or regional levels. In places where resources were available, the training involved practical activities. During the training sessions, the codes and criteria be used for examining teeth, need of a prothesis, and soft tissue's lesions were taught. In addition, instructions on how to fill out the forms, carry out educational activities and how to perform referrals were given. Calibration of professionals during training sessions were not performed. According to Morita et al. (70), approximately 10,000 professionals across the state participated in the 2009 campaign.

### 4.3.1 Data collection procedures

As aforementioned, oral health professionals collect the data during the influenza-vaccination campaign, following specific guidelines as outlined below.

Oral health data collection procedures comprise of several stages. First, all patients attending the vaccination program is invited for the oral health examination. Those who accept the invitation are asked to sign a consent form and fill out a registration form (Form 1, Appendix 9) which contains date, municipality, health examination unit, information on if the participant is the part of the campaign, name of participant, and their signatures. After filling this form and obtaining consent, the participants take part on health education activities, including distributing educational material that highlights the importance of avoiding risk health behaviors (e.g., smoking and alcohol habits), instructions on proper oral hygiene and the oral health examination. Subsequently, the dentists carry out an oral health exam using a specific form designed for this objective (Form 2, Appendix 9) using a wood tongue depressor. The clinical exams follow the sequence detailed in Form 2, which starts with the evaluation of soft tissue including presence of oral lesions (Table 5.1), describe the criteria for oral lesion), followed by dental treatment needs, and oral prosthesis needs (no need, one complete denture, two complete dentures, one partial denture, two partial dentures, one complete denture, and one partial denture). Information on health care unit, municipality, the name of the dentist, date of data collection, participant being the part of a vaccination program (Yes/No), name and address (including phone number) of the patient, age (collected in age groups >=60, 40-59, 20-39) are also collected in this form. At the end of the vaccination period, each dentist compiles these individual data in one single summary

table. For example, one dentist performed 30 oral exams in which 3 of them had 1 oral lesions, 5 of them hade dental caries, and 15 of them were in the age group 60 years over. These aggregated data, that is, 3 oral lesions, 5 dental caries and 15 people in the age group age group 60 years and over, are then sent to the coordinator of the health centers in their respective municipalities. Each coordinator inputs this information an online platform (Moodle program) that is password protected.

### 4.3.2 Oral lesions data

Participants, in whom oral lesions are detected, are referred to an oral pathologist specialist or a dentist with specific training in oral pathology. To facilitate the referral and re-examination of the suspected lesion, the screening team schedules the participant's appointment with the specialist and provide them with a list of documents necessary for their appointment.

In summary, the screening team fill out a third form containing data for all those in whom an oral lesion is detected (name, date of screening, location of the lesion, contact phone, medical card number) (Form 3, Appendix 9). The participants leave the center with an appointment scheduled. A copy of Form 3 is kept in the health center and another copy is sent to the specialist. To keep record of those who attend the appointment, the specialists send back the names of those who did not attend the appointment so that the health center can contact the participants to reschedule the appointment and probe for the reason for non-attendance. Participants have the freedom to abandon the program, however, it was advised to keep the abandonment to the minimum.

**Table 4.1 Diagnostic criterion for the oral lesions**

| Classification | Code | Criteria |
|---|---|---|
| No risk | 0 | individuals without any oral lesions |
| Low risk | 1 | individuals with abnormal tissue which do not have the lesions described in criteria 2 |
| High risk | 2 | Individual with soft tissue changes with suspected malignancy: painless ulcers with more than 14 days of evolution, with raised edges and slightly hardened base or not; white or blackish lesions with ulcerated areas; reddish lesions with more than 14 days of evolution, with defined contours and clear limits suggesting erythroplakia; rapidly growing vegetative lesions (papules, nodules), smooth, granular, verrucous or ulcerated. |

Form 4 is filled out (Form 4, Appendix 9) when participants, who had oral lesions that required further intervention as determined by the specialists. Form 4 has information on the individuals with suspected lesions with explicit knowledge on the type of lesions, treatment given or referral of cases, date conclusion, date of appointment, referral (tertiary prevention going to the hospital cancer cases).

In advanced scenarios where biopsies and anatomopathological examinations confirm the diagnose of oral cancer, Form 5 (Appendix 9) is completed. This form collected information on several domains of exposures including behavioural (e.g., smoking and alcohol habits, exposure to sun), socio-demographic (e.g., data of birth, sex, occupation education level), clinical and pathological information (histological type, date biopsy).

Although we have described above all steps of data collection, this project uses the data from (Form 2, Appendix 9) to calculate the screening coverage and the number of suspected cases in the municipalities of the state of São Paulo from 2015-19.

### 4.4 Statistical Analysis

Our first step in the data analysis was to prepare the database. We search for inconsistences in the database and try to solve the problems by contacting the Secretary of Health of the state of São Paulo. Subsequently, we linked this database to the Brazilian Institute of Geography to obtain geographic information and population size of each municipality in the State of São Paulo. Once obtained, the databases were prepared and cleaned. Subsequently we evaluated the number (%) of missing values and calculated the overall coverage by dividing the total number of people screened by the total population of each municipality; these data are publicly available on government portal (71). Similarly, the overall percentage of participants who had one or more oral lesion(s) was calculated out of total number of screening. Furthermore, the average coverage screening with 95% confidence intervals (CI) across municipalities each year were plotted. We also tabulated the coverage of screening with 95% CI according to age groups. Using the data from municipalities that had data for the whole period from 2015 to 2019, we plotted time trends coverage according to age groups. Lastly, to explore the spatial patterns in coverage, maps with shaded areas according to coverage were created for each year from 2015 to 2019 stratified by age groups.

# 5. RESULTS: MANUSCRIPT

## Description of an oral cancer screening program in São Paulo, Brazil from 2015-2019

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Abstract

**Objective:** To describe the coverage of influenza vaccination-campaign-based oral cancer screening programs in the municipalities of the state of São Paulo, Brazil, during the five-year screenings campaign (2015-19) among various age categories (20 to below 60 years and 60 years and above). **Methods:** We used the oral lesions database (2015-19) from the Secretary of Health of São Paulo state, Brazil. Each participating municipality is expected to transmit the tabulated data to this central hub. The oral lesions were categorized based on the risk of cancer into no, low and high-risk lesions. We further linked this database to the Brazilian Institute of Geography and Statistics to obtain population size by age categories and municipality. Coverage by age group and years of the program are estimated as binary proportions and explored spatially using maps. **Results:** The state of São Paulo, Brazil, has 645 municipalities, of which only approximately 50% to 60% transmitted data to the central hub. Most of the data were available for the elderly (above 60 years) compared to the younger age group (20 to below 60 years). On an average, the coverage rates were low (~2%) across all age groups. Coverage was relatively higher among the older age group. The spatial exploration uncovered a considerable geographical variation in coverage. It was also noted that some municipalities screened more than its capacity due to people's freedom to screen outside their municipality. Lastly, the average number of suspicious oral lesions among screened decreased from 2015-19. **Conclusions:** We provide a comprehensive analysis of the screening program in the State of Sao Paulo, Brazil. These data can be used to improve the outcomes of these programs.

## Introduction

Oral squamous cell carcinoma (OSCCs), including cancers of oral cavity and oropharynx, are among the top ten malignancies worldwide (1) accounting for a significant burden of disease among all cancers (2). An estimated 447,751 new cases with 228,389 deaths of Oral cancers (OCs) occurred worldwide in 2018 (1). Unfortunately, OCs represent a growing problem in several regions of the world including Brazil which reported 14,700 new cases in 2018. These numbers represent almost half of these cancers in Latin America and Caribbean countries (3). Moreover, the state of São Paulo has one of the highest age standardised incidence (ASI) and mortality (ASM) rates for OC (12.17 and 3.09 per 100,000 for men and women, respectively) among all 26 Brazilian states (4, 5).

OCs are devastating diseases with numerous functional, aesthetic, and psychological consequences and a low probability of survival (5-year survival rates approximately 50%). This low survival rates is mainly attributable to late detection and advanced stages at diagnosis(6). Indeed, due to the aggressive behavior of these cancers, the early-stage diagnosis is vital for improving survival (7). For example, while the survival rates for early stage OC are approximately 93%, these rates drop significantly to 38% for advanced stages, and 20% for metastatic disease (8).

OCs can arise from potentially malignant disorders (PMODs) of the oral cavity and pharynx (29). Up to 51% of these groups of chronic lesions have a degree of dysplasia at the presentation (9).

Therefore, direct efforts toward prevention and early detection is a promising effective prevention strategy.

A variety of secondary prevention strategies have been reported to improve the detection of cancers at an early stage to stop its progression, thus preventing death and substantially improving quality of life. However, the cost effectiveness of oral cancer screening is still debatable with considerable uncertainty in several issues (45). Visual examination by the health professional is easy to perform, acceptable, affordable and provides the specificity and sensitivity to justify using it as a screening test. However, we still do not adequately understand the natural history of oral premalignancies. In addition, the identification of pre-malignant lesions in some areas of the oral cavity are difficult to achieve. Therefore, there remains a controversy about whether early detection through screening program is an appropriate strategy (57, 58). Studies conducted in Kerala, India (9, 32, 54-56) and Taiwan (18, 61) have suggested the adoption OCs population screening. However, a Cochrane review notably concluded that the available evidence is insufficient to justify a population-based screening program (59). A similar conclusion was made by the US Preventive Services Task Force (58). Nevertheless, others have argued that targeted screening should be implemented in spite of weak evidence because of the positive impact of early intervention (58). Opportunistic OCs screening is an option to deal with the cost-effectiveness problems (45). However, high-risk groups may include those who do not have access to regular health check-up visits (67). Therefore, there is a need to find alternative solutions to improve the detection of early oral lesions that are inclusive and cost effective. The government the state of São Paulo in Brazil developed and implemented an oral health screening which includes the assessment of PMODs, that may be cost effective. This screening program in

place since 2001 (72), takes advantage of the influenza-vaccination campaign. Although there is some evidence that the program stimulates and organize a network of patient care and encourage oral health care professionals to screen for OCs, a detailed evaluation of program coverage across the municipalities of the state of São Paulo has not been performed (10) neither the detection of oral lesions has not reported. We describe the coverage of the OCs screening program across the municipalities of the state of São Paulo and examine the proportion of oral lesion detected from 2015-2019, a period from which electronic data base is available.

## Methods

This cross-sectional study uses secondary data from an oral health screening program, which included assessment of oral lesions. The program developed and implemented by the State Government of São Paulo takes advantage of the national vaccination campaign against influenza to invite people to take part of the screening. Although the program is in place since 2001, an organized online database is available only since 2015. Therefore, in this project, we use data from 2015-2019.

Health professional specially trained for this program conduct a clinical oral examination following strict criteria. First, individuals attending the vaccination period are invited for an oral health exam. Those who accept the invitation are asked to sign a consent form and fill out a registration form. After filling this form and obtaining consent, the participants take part in health education activities, including reading educational material that highlights the importance of avoiding risky health behaviors (e.g., smoking and alcohol drinking habits) and oral hygiene

instructions. Subsequently, the dentists carry out an oral health exam using a wood tongue depressor followed by a sequence based on an oral examination form specially designed to record the data. The exams start with the evaluation of soft tissue including presence of oral lesions using a criterion described in Table 6.1, followed by dental treatment needs. Information on health care unit, municipality, the name of the dentist, date of data collection, participant being part of a vaccination program (Yes/No), name and address (including phone number) of the patient, age (groups >=60, 40-59, 20-39) are also collected in this form. Participants with oral lesions are referred to an oral pathologist specialist.

At the end of a vaccination cycle, each dentist compiles these individual data into a summary table. For example, one dentist performed 30 oral exams in which 3 of them had an oral lesion, 5 of them had dental caries, and 15 of them were in the age group 60 years over. These aggregate data are then sent to the coordinator of the health centers in their respective municipalities. Each coordinator inputs this information into an online platform (Moodle program) that is password protected.

**Table 5. 1 Criterion to classify oral lesions.**

| Classification | Code | Criteria |
|---|---|---|
| No risk | 0 | individuals without any oral lesions |
| Low risk | 1 | individuals with abnormal tissue which do not have the lesions described in criteria 2 |
| High risk | 2 | Individual with soft tissue changes with suspected malignancy: painless ulcers with more than 14 days of evolution, with raised edges and slightly hardened base or not; white or blackish lesions with ulcerated areas; reddish lesions with more than 14 days of evolution, with defined contours and clear limits suggesting erythroplakia; rapidly growing vegetative lesions (papules, nodules), smooth, granular, verrucous or ulcerated. |

*Data analysis:* Once we obtained the databases, our first step was to prepare the databases and cleaning the data. Subsequently we evaluate the number (%) of missing values and calculated the overall coverage by dividing the total number of people screened by the total population of each municipality, data is publicly available on government portal (71). Similarly, the overall percentage of participants who had one or more oral lesion(s) was calculated out of total number of screening. Furthermore, the average coverage screening with 95% confidence intervals (CI) across municipalities each year were plotted. We also tabulated the coverage of screening with 95% CI according to age groups. Using the data from municipalities that had data for the whole period from 2015 to 2019, we plotted time trends coverage according to age groups. Lastly, to explore the spatial patterns in coverage, maps with shaded areas according to coverage were created for each year from 2015 to 2019 stratified by age groups. All the analyses are performed using r-software (version 3.5.2 (2018-12-20))

Results

All 645 municipalities of São Paulo state participated in the oral cancer screening program. However, data from a substantial number of municipalities were not available, with missing values ranging from 35% to 49% (Table 5.2). The reasons for missing values are either because the municipality fail to report the data, or they did not participate in the screening in given years. Only for 137 municipalities had data for all the years from 2015 to 2019.

**Table 5. 2 Description of data from 645 health care centers from São Paulo, Brazil.**

| Year | Total no: of municipalities n=645 | | Data by age group | | | |
|---|---|---|---|---|---|---|
| | Any data available | Missing* | 20-59 years | | 60 years & above | |
| | | | Available | Missing* | Available | Missing* |
| 2015 | 361(55%) | 284(45%) | 323 | 38 | 360 | 1 |
| 2016 | 424(65%) | 221(35%) | 363 | 61 | 416 | 8 |
| 2017 | 404(62%) | 241(38%) | 368 | 36 | 403 | 1 |
| 2018 | 324(51%) | 321(49%) | 309 | 15 | 324 | 0 |
| 2019 | 388(60%) | 257(40%) | 372 | 16 | 388 | 0 |

*Missing = No screening performed / Not reported

Table 5.3 shows the overall coverage of screening with 95% confidence intervals (CI) for all age groups. Overall, the coverage was low ranging from 1.69% to 2.54%. The time trend in coverage is presented in Figure 5.1, using the data from 137 municipalities for which data were available from 2015-2019. Although, coverage seems to have improved on average, the overlap in 95% confidence intervals reflect that this difference is not meaningful. Interestingly, when we plotted the maps (Figure 5.2), the coverage ranged from <5% up to 40% among the municipalities, with almost the same municipalities offering the highest coverage across the years. It is also worth noting the coverage percentage is very much heterogeneous in the municipalities; the municipalities with smaller population sizes had higher coverage than larger ones.

**Table 5. 3 Coverage of the screening program for all age groups (20 years old & above).**

| Year | All age (20 years old & above) | | | |
|---|---|---|---|---|
| | Data available Municipalities | Screened population | Total population | % Coverage (95% C.I) |
| 2015 | 322 | 408 171 | 19 346 936 | 2.11% (2.1 - 2.22) |
| 2016 | 361 | 392 885 | 23 269 650 | 1.69% (1.68 - 1.7) |
| 2017 | 367 | 447 685 | 22 393 517 | 2.00% (1.99 - 2.1) |
| 2018 | 309 | 417 092 | 21 059 334 | 1.98% (1.97 - 1.99) |
| 2019 | 388 | 618 258 | 24 30 0418 | 2.54% (2.53 - 2.55) |

**Figure 5. 1 Time trend in coverage of the screening for all age groups (20 years old & above) from 2015-19 (137 municipalities).**

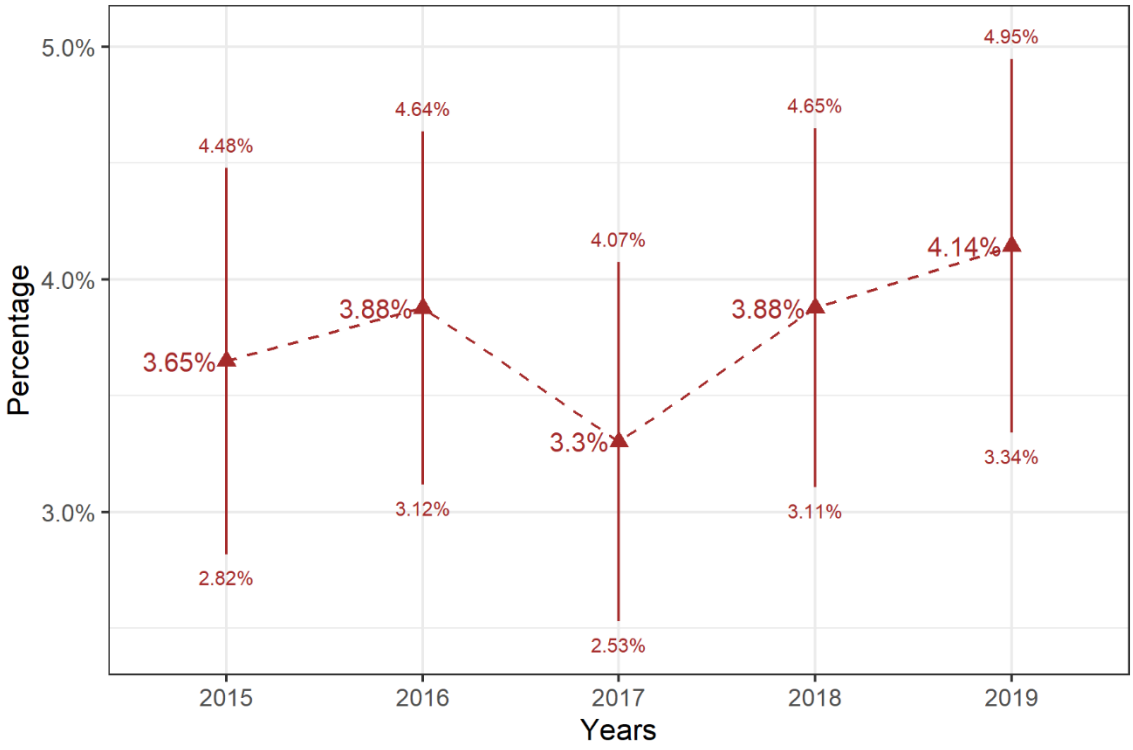


**Figure 5. 2 Spatial patterns of coverage of screening in the State of São Paulo for all age groups (age 20 years & above) from 2015 to 2019.**

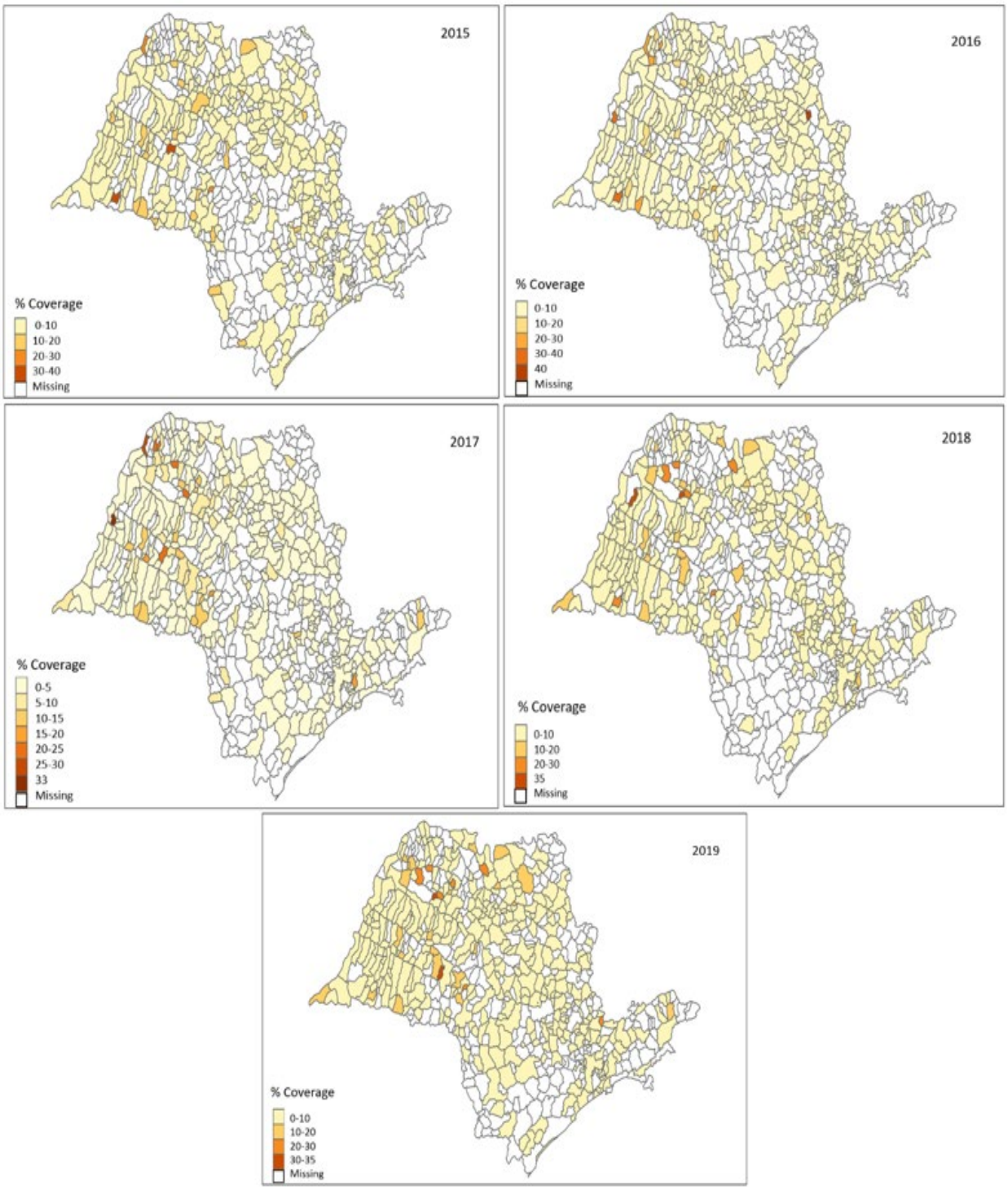
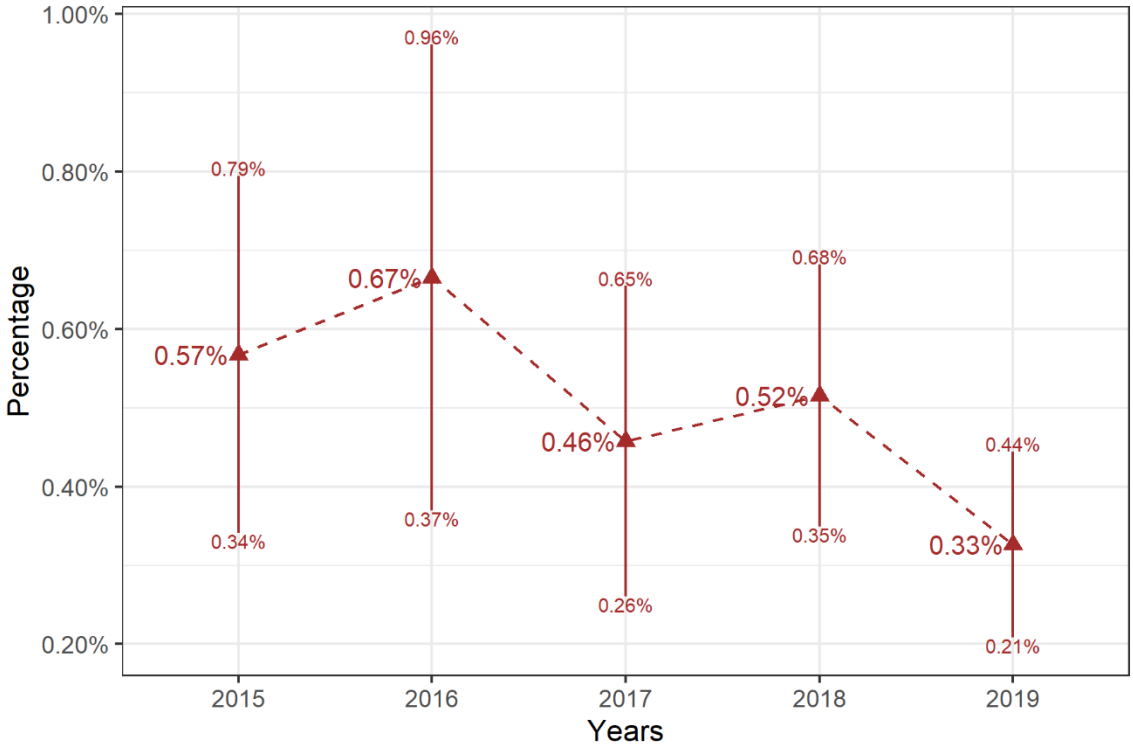


Table 5.4 presents the percentage of screened participants who had at least one oral lesion suspicious of oral cancer among all age groups from 2015 to 2019. Overall, this percentage was very low and ranged from 0.28% to 0.50% from 2015 to 2019. The time trend in percentage of screened participants who had at least one oral lesion suspicious of oral cancer is presented in Figure 5.3. Although in later years in the period the average proportion of participants with oral lesion reduced, the change is less than one percent.

**Table 5. 4 Percent of screened participants with at least one oral lesion suspicious of oral cancer among all age groups from 2015 to 2019.**

| Year | Data available Municipalities | Suspects among Screened | Total No of people screened | % Suspects |
|---|---|---|---|---|
| **2015** | 322 | 1 710 | 408 200 | 0.42% (0.4 - 0.44) |
| **2016** | 361 | 1 948 | 392 885 | 0.50% (0.47 - 0.52) |
| **2017** | 367 | 1 839 | 447 685 | 0.41% (0.39 - 0.43) |
| **2018** | 309 | 1 384 | 417 092 | 0.33% (0.31 - 0.35) |
| **2019** | 372 | 1 723 | 618 258 | 0.28% (0.27- 0.29) |

**Figure 5. 3 Time trends in percent of screened participants with at least one oral lesion among all age groups from 2015 to 2019 (137 municipalities).**




Coverage details stratified by age groups are presented in Table 5.5 and Figures 5.4, 5.5 & 5.6. Coverage among 60 years and above age group was higher compared to below 60 years in all years. The time trends from 2015-19 indicates no prominent change in coverage in both age groups (Figure 5.4, 5.5). Some municipalities showed more coverage than their capacity e.g., municipalities like Arco-Íris (109%) and Estrela do Norte (101%) in 2015; Estrela do Norte (106%) in 2016. Participants had the liberty to go to any municipality for vaccination and this may explain the over coverage. Also, Figures 6.5 and 6.6 show the same trend as in the age categories combined with slight variations.

**Coverage and suspicious lesion % for whole state of São Palo (All age groups)**

**Table 5. 5 Coverage of the screening program stratified by age groups from 2015 to 2019.**

| Year | 20 to below 60 years | | 60 years & above | |
|---|---|---|---|---|
| | Data available Municipalities | % Coverage | Data available Municipalities | % Coverage |
| 2015 | 323 | 0.50% (0.49 - 0.51) | 360 | 9.55% (9.52 - 9.58) |
| 2016 | 363 | 0.46% (0.45 - 0.46) | 416 | 7.92% (7.89 - 7.94) |
| 2017 | 368 | 0.76% (0.75 - 0.77) | 403 | 7.25% (7.22 - 7.27) |
| 2018 | 309 | 0.83% (0.82 - 0.84) | 324 | 6.55% (6.53 -6.58) |
| 2019 | 372 | 1.00% (1 - 1.009) | 388 | 8.59% (8.57 - 8.62) |

**Figure 5. 4 Time trends in coverage of screening program among 20 to below 60 years of age from 2015-19 (137 municipalities).**

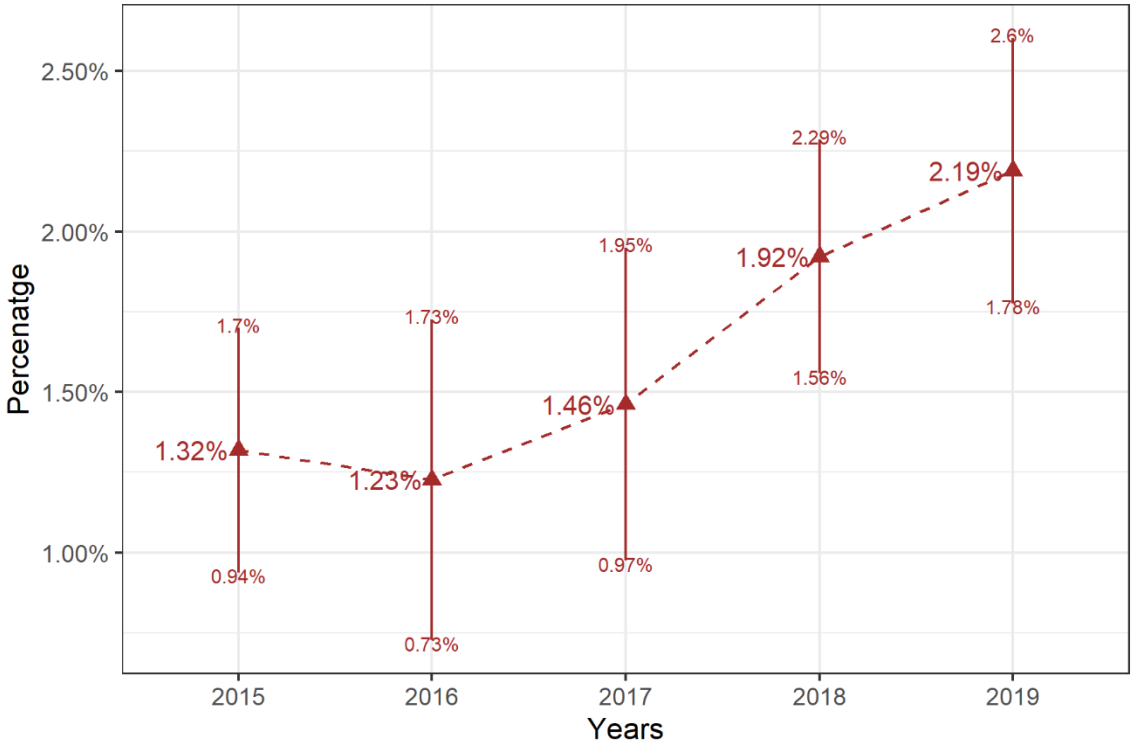


**Figure 5. 5 Time trends in coverage of screening program among 60 years and above from 2015-19 (171 municipalities).**

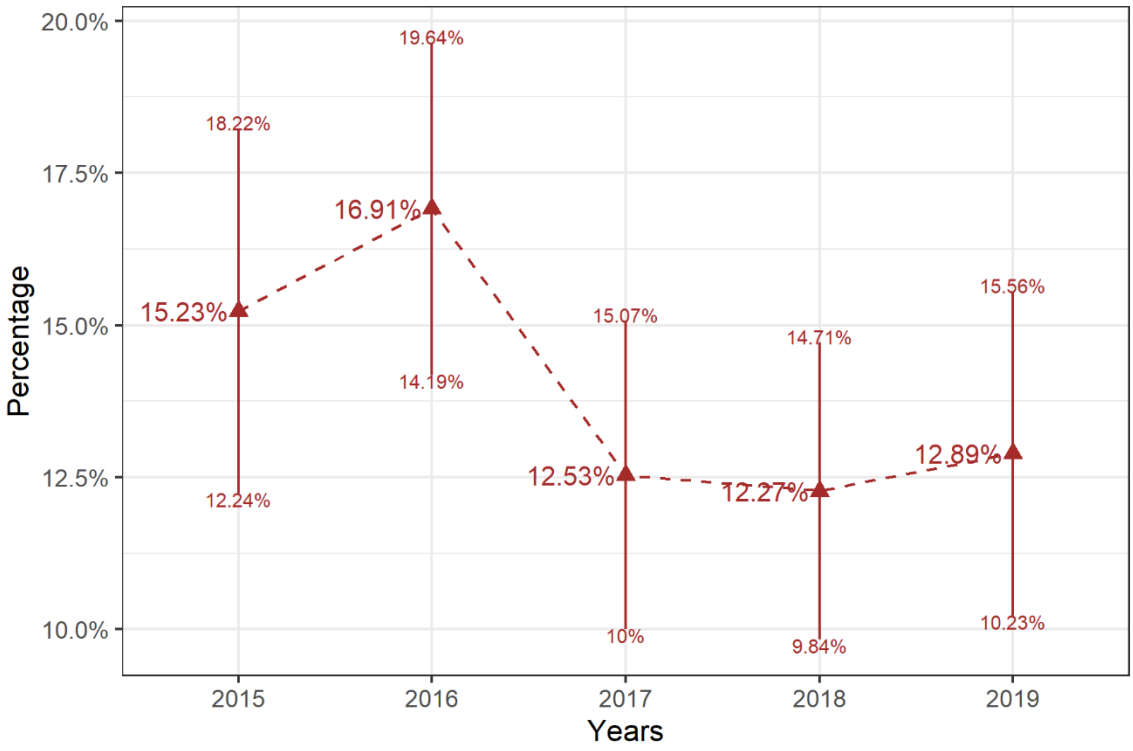


**Figure 5. 6 Spatial patterns of coverage of screening among participants with 20 to 59 years of age from 2015 to 2019**

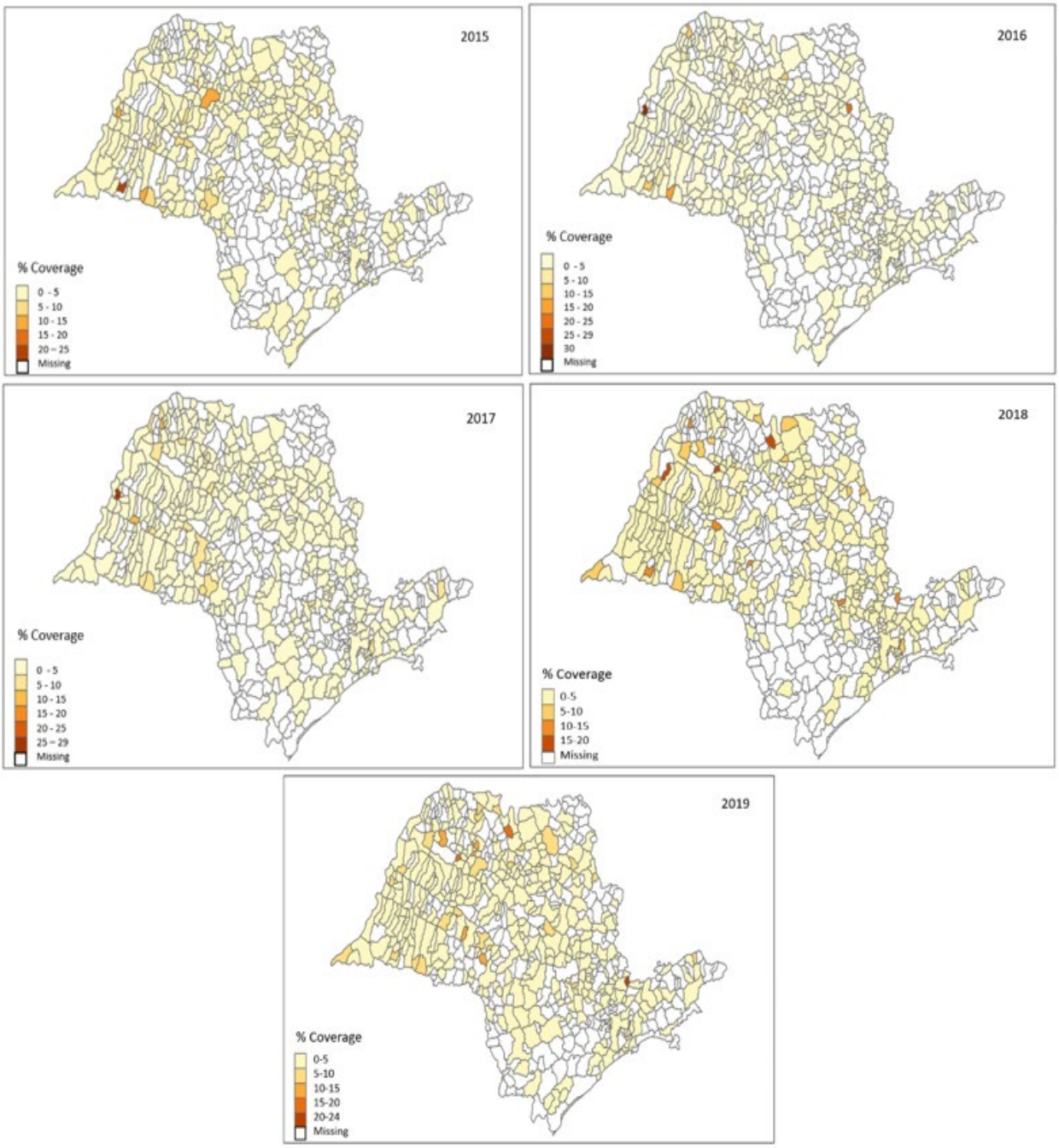
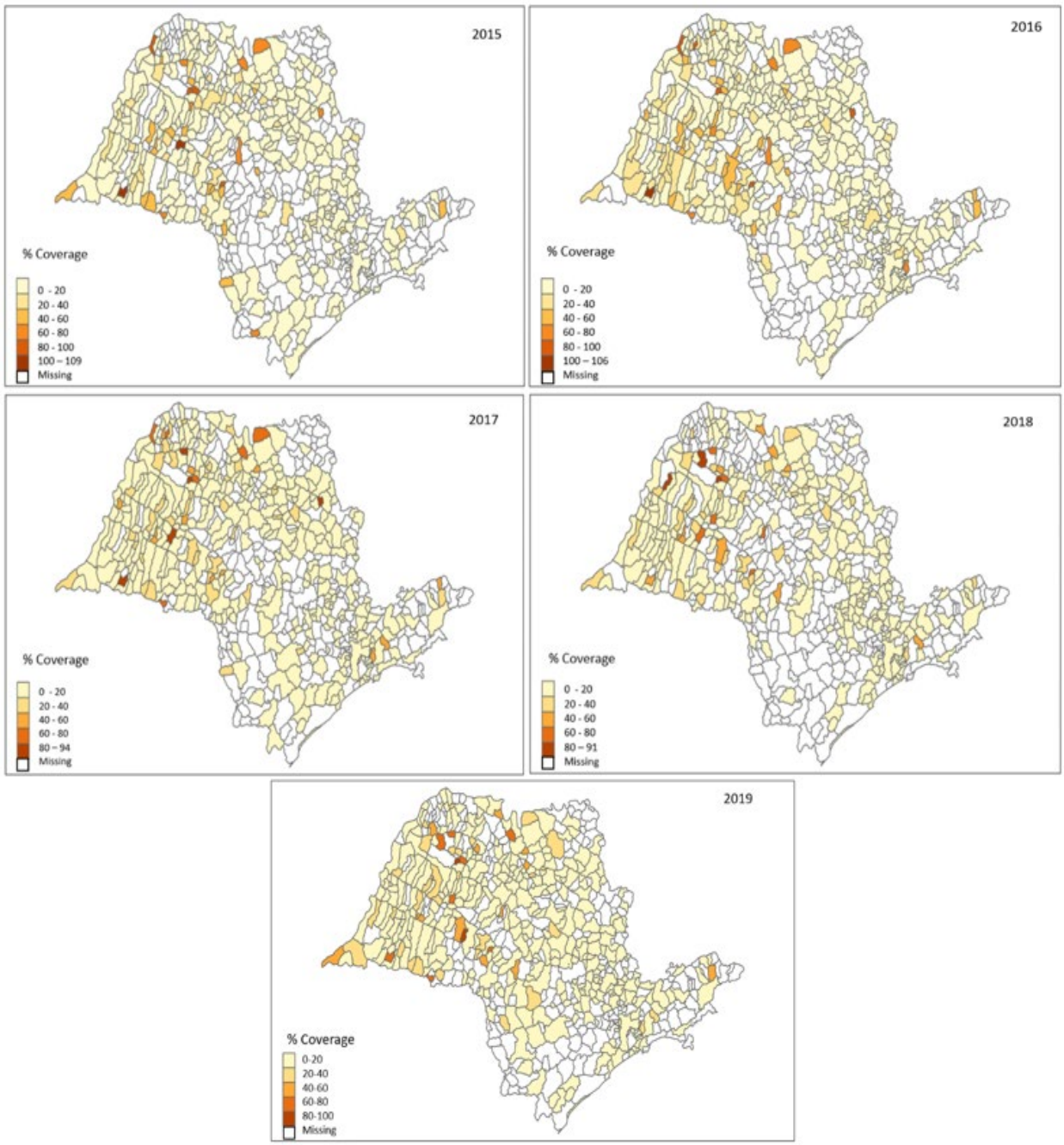


**Figure 5. 7 Spatial patterns of coverage of screening among participants with more than 60 years of age from 2015 to 2019.**



## Discussion

The overall objective of this research project is to describe the coverage of a screening program in the State of São Paulo, Brazil, and the number of suspected oral lesions in a five-year period 2015-19. Our results revealed an inadequate coverage (~2%) for the state of São Paulo, Brazil with a considerable variation in the coverage among the municipalities and between young and elderly population. Possible variations may be explained by the size and funding availability to run the program across São Paulo state municipalities (73). Although previous studies using these databases (2001-09) suggest that the strategy is working satisfactory, the methodology used by this previous evaluation is different than the ones used in our study (10, 64, 65).

The results of this study should be considered in relation to its limitations. First, there was a lack of information on some crucial variables such as sex, the number of people coming for influenza vaccination. Due to this missing information, we are unable to compare the studies with other screening programs. For example, it well known that males have a higher probability of developing oral cancer than females, but we cannot conduct such analysis in our data. While previous data (from 2001-2009) had information on people who underwent screening among vaccinated, this was not available for the period of 2015-2019. Despite the database limitations, we tried our best to describe data in each possible way using graphical and spatial presentation.

The information in electronic databases is more pronounced, especially in administrative databases as ours (41, 75). We used a central database from the Secretary of Health of São Paulo state, Brazil. We found that most of the data are available for the age group 60 years and older.

The missing information on other age groups is suggestive of possible information bias in the study. For example, our results show that the coverage is higher among the older ages groups; this may be because of the missing information on other age categories.

Another challenge was the missing data. The constitution of Sao Paulo gives special provision to the state municipalities that enables them to choose to send/not send the data (74), resulting in missing data from many municipalities, with missing values fluctuating from 35% to 49% (Table 6.1). Only 137 towns had data for all the years from 2015 to 2019. However, we believe that the missing values were not a result of a systematic error. The data were missing because some municipalities' health authorities did not send the information to central coordination, or the cities did not have sufficient funds to encompass the screening program. This issue could be considered a case of MCAR (Missing completely at random (MCAR)-when the likelihood of being missing is the same for all subjects, i.e., there is nothing systematic in place that makes some information more likely to be absent than others. And has the benefit/presumption that the data is unbiased.) and we consider the impact would be insignificant on our conclusions.

We provide a comprehensive analysis of the screening program in the State of Sao Paulo, Brazil. These data can be used to improve the outcomes of these programs. Future research should evaluate the reasons for the low coverage in some municipalities in the state of Sao Paulo.

# 6. DISCUSSION

This chapter addresses a comprehensive view of our results, its consistency with other studies in the literature, along with strengths, and limitations of this work. Lastly, it presents the future research tracks and conclusions.

## 6.1 Summary of Results

The overall objective of this research project is to describe the coverage of a screening program in the state of São Paulo, Brazil, and the number of suspected oral lesions in a five-year period 2015-2019. Our results revealed an inadequate coverage (~2%) for the state of São Paulo, Brazil with a considerable variation in the coverage among the municipalities and between young and elderly population. Possible variations may be explained by the size and funding availability to run the program across the municipalites of the state of São Paulo (73). Although previous studies using these databases (2001-2009) suggest that the strategy is working satisfactory, the methodology used by this previous evaluation is different than the ones used in our study (10, 64, 65).

## 6.2 Methodological reflections

### 6.2.1 Study design

We used the reported cross-sectional data from the oral cancer screening program of the state of São Paulo, Brazil. Secondary prevention via screening is an effective strategy for early detection of oral cancer in a community (41). The strategy in the state of São Paulo takes advantage of vaccination period to screen for oral cancer. Dentists perform an oral-visual

examination of oral lesion which is a gold standard method to detect precancerous lesions in primary health centers (46, 76).

While this is innovative screening strategy may increase the access to the population making it more cost effective, people who respond to vaccination campaign may have not necessarily be those who are at risk of oral cancer. Indeed, although the flu vaccination coverage is high in Brazil and in São Paulo State, previous studies in the Brazilian population shows that absent interaction with health services (77); skin colour, those with lower educational are less responsive to attend vaccination programs.  seem to negatively affect vaccine uptake.

**6.2.2 Unmeasured variables**

Missing information is one of the major challenges we faced in this project. Besides, missing information in electronic databases are more pronounced, especially in administrative databases as ours (41, 75). We used a central database from the Secretary of Health of São Paulo state, Brazil. We found that most of the data are available for the age group 60 years and older. The missing information on other age groups is suggestive of possible information bias in the study. For example, our results show that the coverage is higher among the older ages groups; this may be because of the missing information on other age categories.

Another problem with the study is the lack of information on some crucial variables such as sex, the number of people coming for influenza vaccination. Due to this missing information, we are unable to compare the studies with other screening programs. For example, it well known that

males have a higher probability of developing oral cancer than females, but we cannot conduct such analysis in our data. While previous data (from 2001-2009) has information on people who underwent screening among vaccinated, this was not available for the period of 2015-2019. Despite the database's limitations, we tried our best to describe data each possible way using graphical and spatial presentation.

### 6.3.3 Missing data

Missing data was one of the challenges when conducting this project. Missing data affects the representativeness of the sample; and can cause bias in the estimation of parameters. Therefore, substantially affecting the validity of the study.

Missing data have been classified three types based on the pattern of missing data(78). Missing completely at random (MCAR) is when the probability of being missing is the same for all cases, i.e., there is nothing systematic in place that makes some information to be more likely to be missing than other. MCAR has the advantage/assumption that the data is unbiased.

Missing at random (MAR), which is a more realistic assumption, is when there is a systematic relationship between the probability of missing values and the set of observed data but is not related to the missing data. In other words, the missing data is conditional on another variable. For example, if women are more likely to hide their weight than men, weight is a MAR. These data are not MCAR; however, we know the sex and if we assume MCAR within sex, then the data are MAR.

Missing not at random (MNAR) is when there is a relationship between the probability of a value to be missing and its values. For example, those most ill are more like to drop out of a study or wealthy people are more likely do not report their income. This type of missing data is "non-ignorable" because the missing data mechanism itself must be modeled as you deal with the missing data. MNAR is the most complex case. Strategies to handle MNAR includes identification of the causes of missingness and to carry out sensitive what-if analyses to verify the how the findings hold under different scenarios.

Another problem in our study are the missing values. Data were not available from substantial number of municipalities, with missing values ranging from 35% to 49% (Table 6.1). The reasons for missing values are either because the municipality failed to report the data, or they did not participate in the screening in the given years. Only 137 municipalities had data for all the years from 2015 to 2019. However, we believe that the missing values were not a result of a systematic error. The data were missing because the health authorities of some municipalities did not send the information to central coordination or the municipalities did not have enough money to run the screening program. This issue could be considered as a case of MCAR and we believe the impact would be minimal on our results.

### 6.3.4 Future research directions

The previous studies recommend opportunistic screening over population-based studies to screen oral cancer among older high-risk male-population. Nevertheless, the growing evidence of an increase in OC incidence in the young population demanded the extension of screening to other age groups.

This study investigated the coverage of an innovative screening strategy. We faced major challenges and make the following recommendations to improve the quality of information collected and therefore the program. First, there is a need to discuss and examine the health care centers' functioning with regards to the screening program. Due to notable variations in the size of the municipalities, it is challenging to compare cities. Furthermore, the data on sex, and the number of people coming for vaccination is also needed to analyze uptake and determine the latest trends.

# 7. CONCLUSION

The subsequent inferences could be extracted from the results exhibited in the thesis.

- About 50-65% of the municipalities send the data to the central system, and the elderly population is screened more than the younger.
- The overall coverage of the state of São Paulo is approximately 2%; however, the time trend across municipalities (sending data consistently from 2015-19) has a range of up to 3%. Moreover, the mapping represents the heterogeneous coverage over the years varies up to 40%.
- The percentage of suspects is decreasing over time for whole state, nevertheless, the time trend showed spikes in 2016 and 2018.
- The overall percentage of screening coverage is less for the younger (~1%) to older age cluster (~9%) over the state. The younger population showed an increasing time trend, whereas the elderly coverage is almost stable over the years with a spike in 2017.
- The Spatial-temporal trend also dispensed interesting information about the screening that some municipalities screened more than its capacity owing to its size.

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Form 1

**PREVENÇÃO E DIAGNÓSTICO PRECOCE DO CÂNCER BUCAL**

**FICHA 02**

**Mês/Ano_____/___**

**DRS_____ Município _____Dentista _____**

**Unidade de Saúde/ local do exame_____ Campanha ( ) sim ( ) não**

| | Nome do paciente | Idade | Avaliação dos tecidos moles (0,1,2) | Necessita de tratamento odontológico? sim/não | Necess.de prótese | Assinatura |
|---|---|---|---|---|---|---|
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |

**Idade**

| | |
|---|---|
| ≥ 60 | |
| 40 a 59 | |
| 20 a 39 | |
| TOTAL | |

**Tecidos moles**

| | |
|---|---|
| 0 (zero) | |
| 1 (um) | |
| 2 (dois) | |
| Total | |

**Necessidades dentárias**

| | |
|---|---|
| Sim | |
| Não | |
| Total | |

**Necessidade**

| | | |
|---|---|---|
| Não necessita | 0 | |
| 1 PT | 1 | |
| 2 PT | 2 | |
| 1 PPR | 3 | |
| 2 PPR | 4 | |
| 1 PT + 1PPR | 5 | |
| Total | - | |

PREVENTION AND EARLY DIAGNOSIS OF ORAL CANCER

DOCUMENT 02

**Month / Year _____/____**

**DRS_____ Municipality _____ Dentist _____**

**Health Unit/ examination site_____ Campaign (_) yes ( ) no**

| | Patient's name | Age | Soft tissue assessment (0,1,2) | Do you need dental treatment? yes/no | Need for prosthesis | Signature |
|---|---|---|---|---|---|---|
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |

**Age**

| | |
|---|---|
| ≥ 60 | |
| 40 a 59 | |
| 20 a 39 | |
| TOTAL | |

**Soft tissues**

| | |
|---|---|
| 0 (Zero) | |
| 1 (One) | |
| 2 (Two) | |
| Total | |

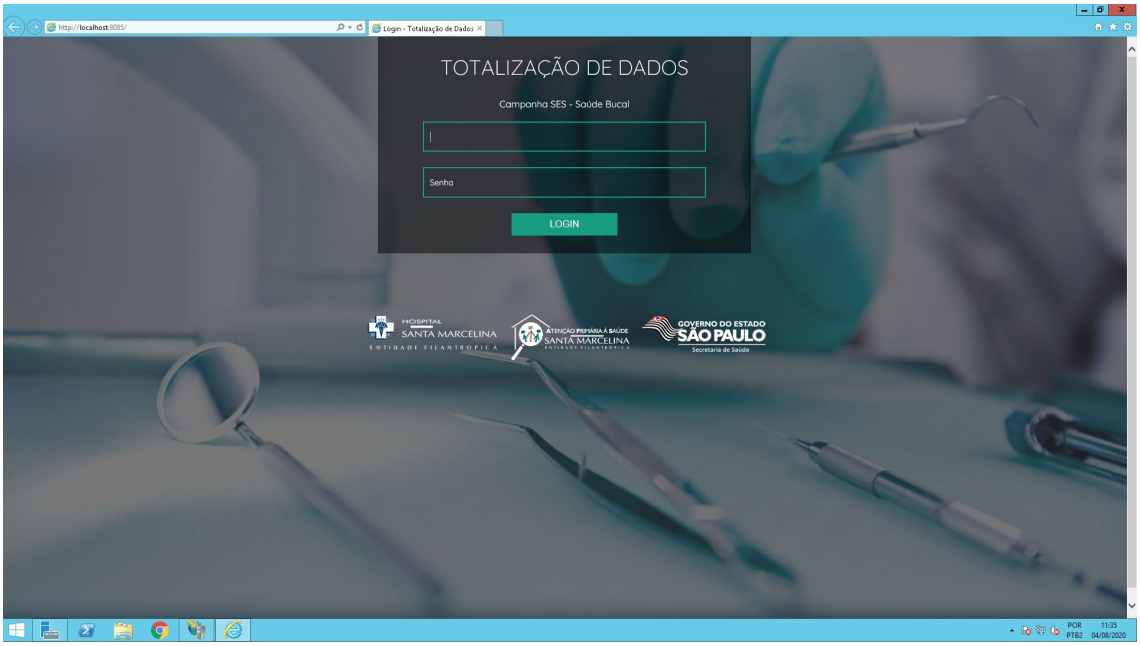
**Dental needs**

| | |
|---|---|
| Yes | |
| No | |
| Total | |

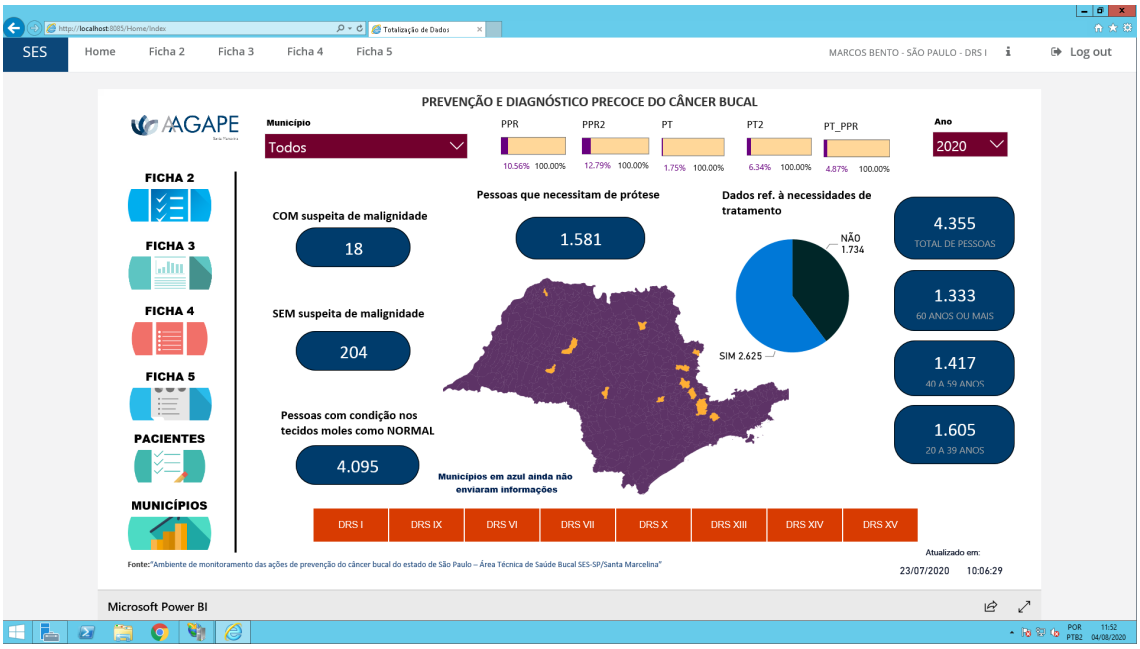
**Need**

| | | |
|---|---|---|
| No Need | 0 | |
| 1 Complete denture | 1 | |
| 2 Complete dentures | 2 | |
| 1 Partial denture | 3 | |
| 2 Partial dentures | 4 | |
| 1 Partial denture + 1 Complete denture | 5 | |
| Total | - | |

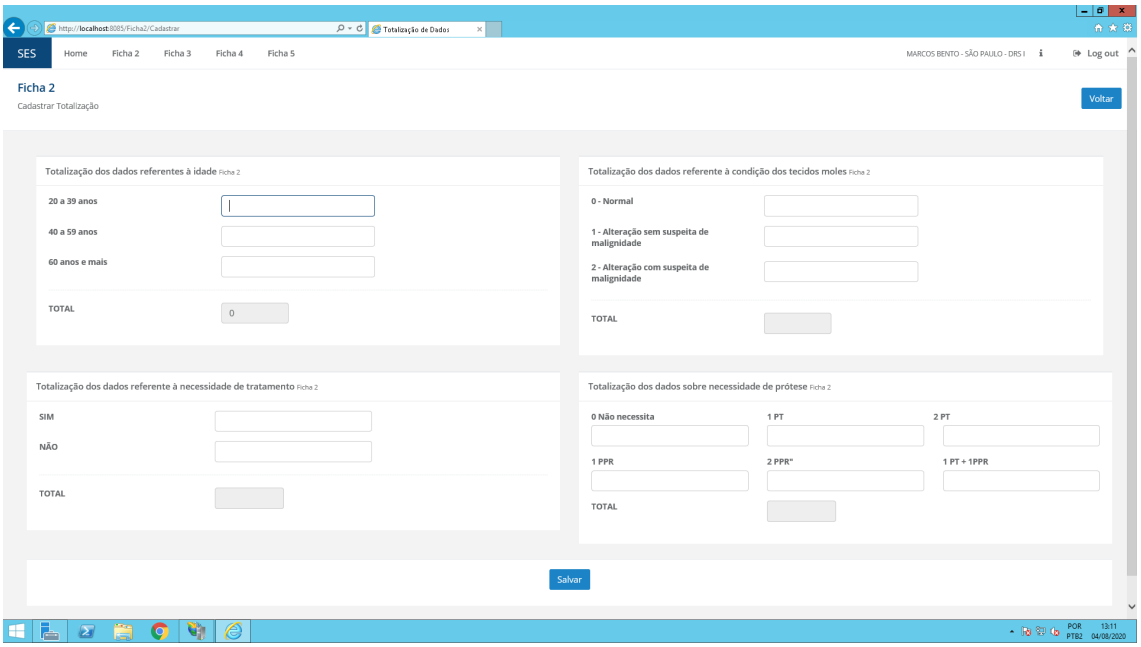
Access to data environment Municipal Coordinators of Oral Health (1)



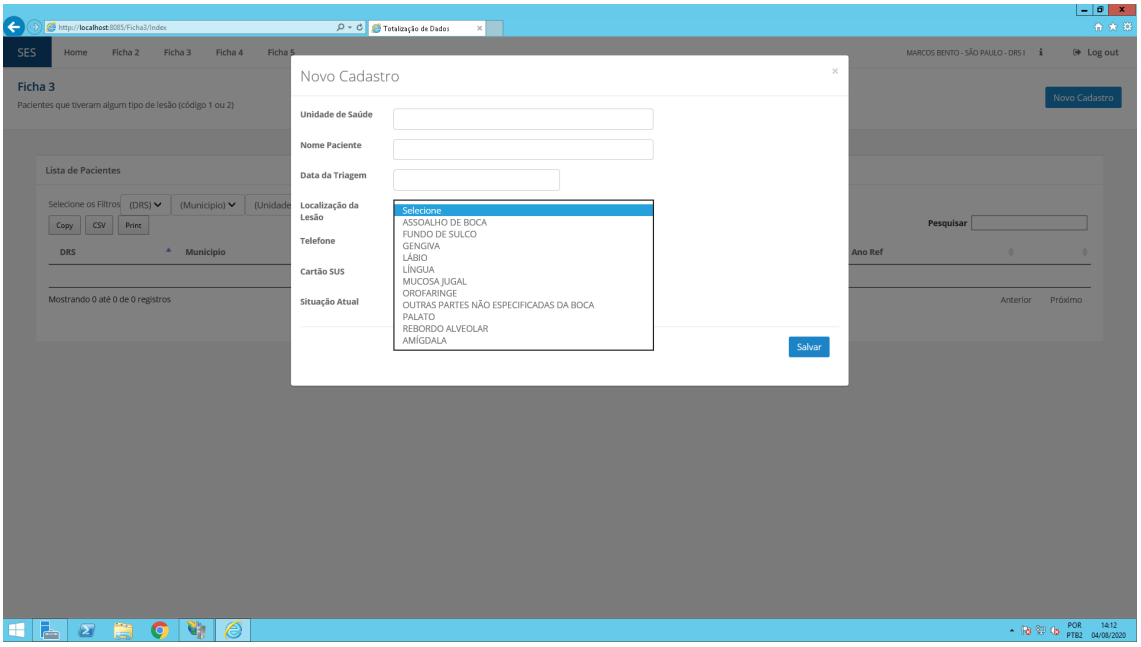

Consolidated data information (2)



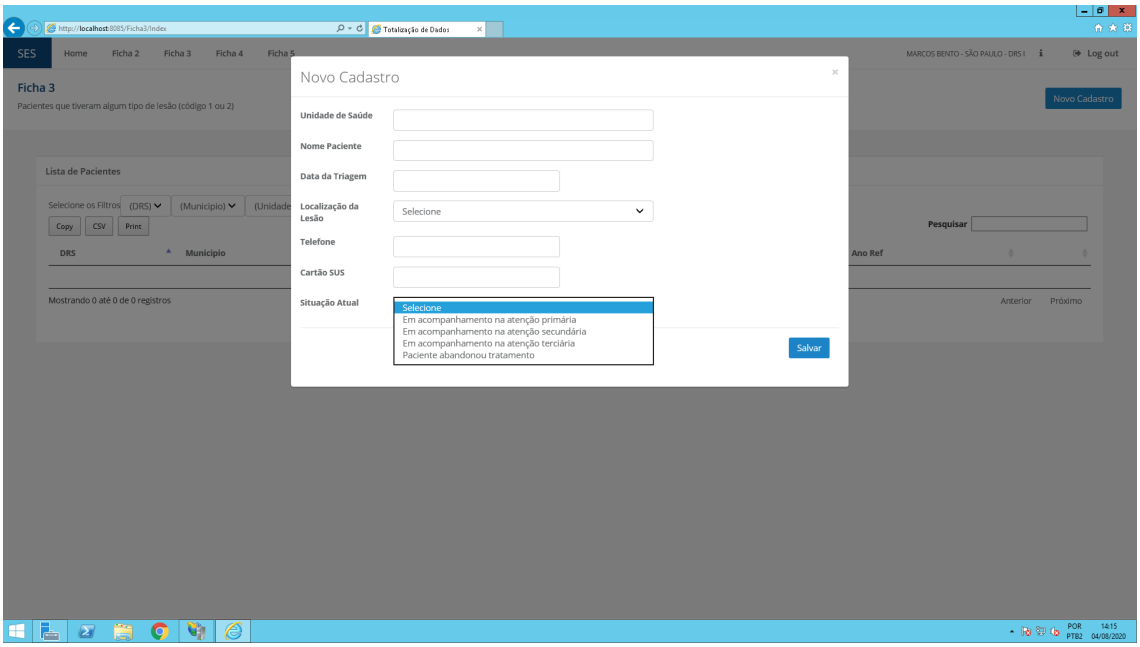

Form 2 - Screening



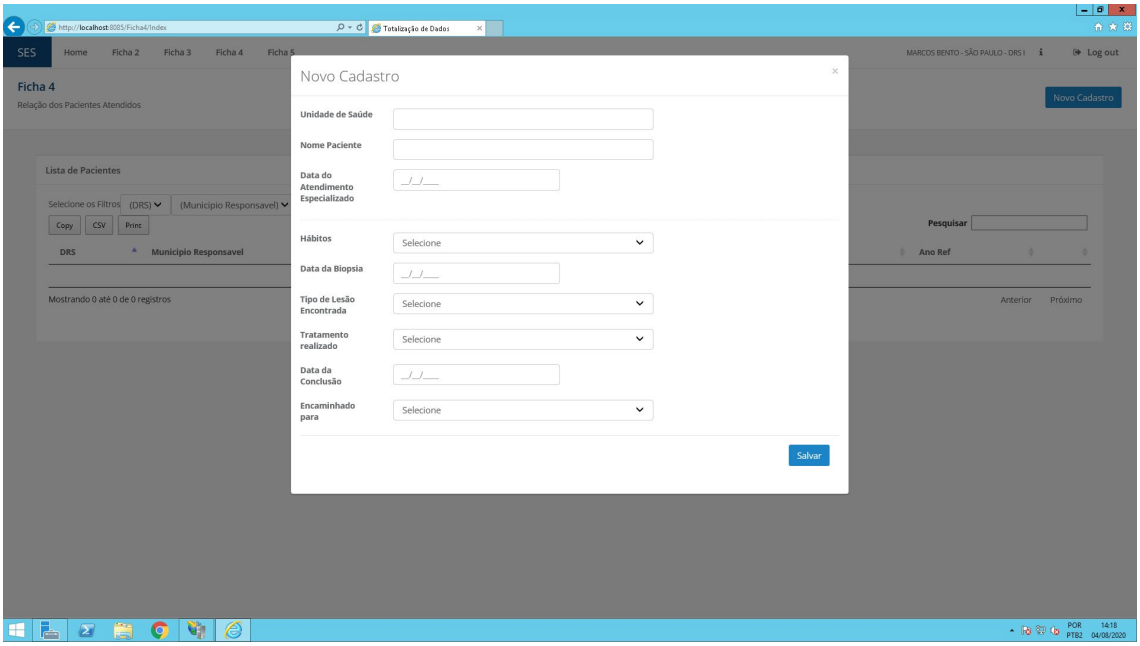

Form 3 - highlighting the “Injury Location” field



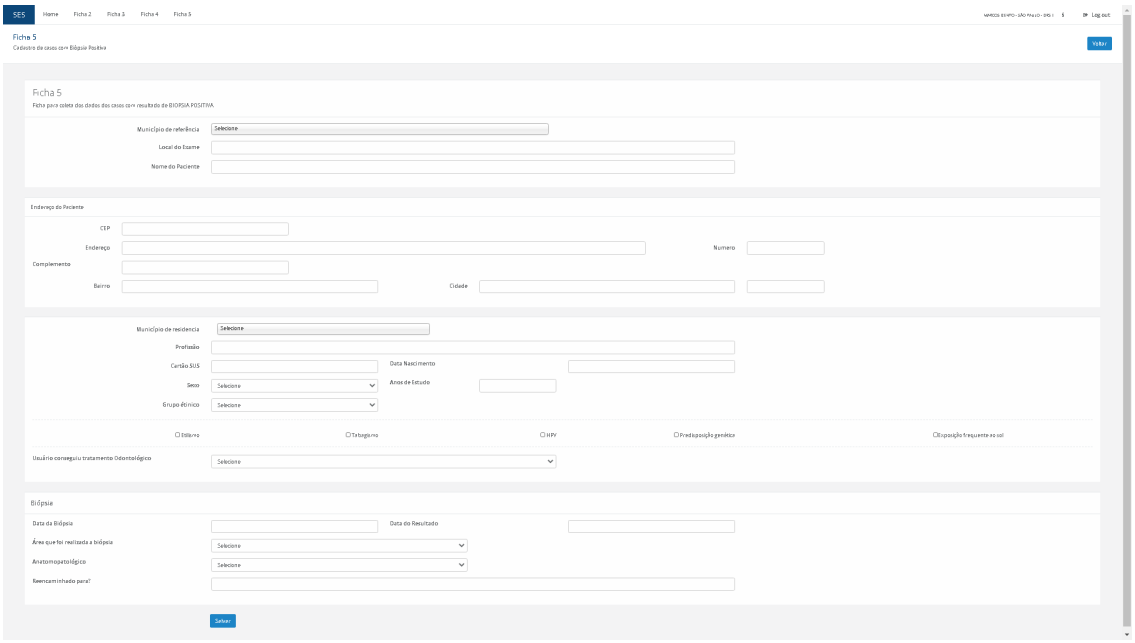

Form 3, highlighting the “Current situation” field. This field shows the status of patient monitoring in the local health system.


Novo Cadastro
Unidade de Saúde
Nome Paciente
Data da Triagem
Localização da Lesão
Selecione
Telefone
Cartão SUS
Situação Atual
Selecione
Em acompanhamento na atenção primária
Em acompanhamento na atenção secundária
Em acompanhamento na atenção terciária
Paciente abandonou tratamento
Salvar

Form 4


Novo Cadastro
Unidade de Saúde
Nome Paciente
Data do Atendimento Especializado
Hábitos
Selecione
Data da Biopsia
Tipo de Lesão Encontrada
Tratamento realizado
Data da Conclusão
Encaminhado para
Salvar

Form 5


SES
Home
Ficha 2
Ficha 3
Ficha 4
Ficha 5
Log out
Ficha 5
Cadastro de casos com Biópsia Positiva
Voltar
Ficha 5
Ficha para coleta dos dados dos casos com resultado de BIOPSIA POSITIVA
Município de referência
Selecione
Local do Exame
Nome do Paciente
Endereço do Paciente
CEP
Endereço
Numero
Complemento
Bairro
Cidade
Município de residencia
Selecione
Profissão
Cartão SUS
Data Nascimento
Sexo
Selecione
Anos de Estudo
Grupo Étnico
Selecione
Etilismo
Tabagismo
HPV
Predisposição genética
Exposição frequente ao sol
Usuário conseguiu tratamento Odontológico
Selecione
Biópsia
Data da Biópsia
Data do Resultado
Área que foi realizada a biópsia
Selecione
Anatomopatológico
Selecione
Reencaminhado para?
Salvar