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A Human Rights Approach to Understanding Provider Knowledge and Attitudes toward the Human Papillomavirus Vaccine in São Paulo, Brazil

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Abstract

A Human Rights Approach to Understanding Provider Knowledge and Attitudes toward the Human Papillomavirus Vaccine in São Paulo, Brazil

By Meredith H. Kruse, MSc

Background: In March 2014, the Brazilian Ministry of Health instituted a nationwide vaccination program that offers females a two-dose series of the quadrivalent HPV vaccine at no cost through Sistema Único de Saúde (Unified Health System or SUS). The vaccine, now fully integrated into the immunization calendar, is available to females through schools and SUS and excludes all males and females above the age of 13 from participation. However, Brazil's constitution dictates a right to health for the entire population.

Objective: To address to what extent human rights considerations influence the sexual and reproductive health care of all males and females over the age of 13 in Mauá, Brazil, specifically in terms of access to the HPV vaccine.

Methods: From May to August 2015, we conducted a cross-sectional study among health care providers in eight public health clinics located in the city of Mauá, a suburb of São Paulo, Brazil. Frequency analysis was conducted across the three main subject areas: knowledge, attitudes and access. Comparisons focused on response variance based on occupation.

Results: A total of 154 surveys were analyzed. Correct knowledge was relatively high among all providers, though there were some knowledge gaps. A majority reported it is medically effective to vaccinate females over the age of 13 (115/150 [77%]), females over the age of 13 should be vaccinated (126/150 [84%]), and they would vaccinate a female over the age of 13 (123/150 [82%]). Similar responses were reported for male vaccinations. A majority reported that Brazilians do not have equal access to health (120 [80%]) and the population exclusions of the HPV vaccination program limit an individual's right to health (108 [72%]).

Conclusions: Limiting access to the HPV vaccine infringes upon an individuals' right to health. The current economic and political climate in Brazil presents challenges to expand the vaccination program; however, it is Brazil's responsibility to anticipate what steps can be taken to assuage these barriers. The domestic production of the vaccine, additional education campaigns, and increased access will enable individuals to make their own decisions about their sexual and reproductive health and evoke their right to health.

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In memoriam, Veronica Kruse, Ruth Crowley, and Kathryn Kruse, who instilled in me a love for learning and inspire me to leave the world a better place.

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Chapter I: Introduction

Global Cancer Burden

The global burden of cancer incidence and mortality continues to increase at an unprecedented pace. In 2012, there were an estimated 14 million new cancer cases worldwide and 8.2 million cancer-related deaths [1]. These are expected to increase to 22 million cases per year and 13 million deaths per year over the next two decades [1]. The cancer burden is increasingly felt within low- and middle-income countries. Over 60% of cancer cases and 70% of cancer deaths occur in Africa, Asia, Central America and South America [1]. Unfortunately, this disproportionate burden is directly related to a lack of early detection and prevention methods and inadequate access to treatment.

Cervical cancer is the 4th most common cancer among women worldwide. Of the 527,624 cases of cervical cancer reported worldwide in 2012, a total of 45,008 were from South America[2]. Cervical cancer is also a leading cause of cancer mortality. In 2012, 265,672 deaths worldwide were attributed to cervical cancer, including 19,374 from South America [2].

Cervical Cancer Burden in Brazil

Brazil has a population of approximately 82 million women aged 15 years and older, all of whom are at risk for developing cervical cancer [2]. Approximately 5.4% of women in the general population are infected with human papillomavirus (HPV) types 16 or 18 infection [3]. These HPV strains are responsible for up to 70% of cervical cancer cases [4].

Cervical cancer rates in Brazil are among the highest in the world with correspondingly high mortality rates. In 2012, 18,503 cervical cancer cases (crude rate: 18.4 and age standardized risk [ASR] 16.3 per 100,000 population) were reported, followed by 8,414 cervical cancer deaths (crude rate: 8.3, ASR 7.3 per 100,000 population) [2]. Cervical cancer ranks as the 2nd leading

cause of cancer and 4th cause of cancer-related death among females in Brazil and 2nd most common cancer and cause of cancer death among women aged 15 to 44 in Brazil [2]. The Institutio Nacional de Câncer (the National Cancer Institute of Brazil or INCA) estimates in 2016, there will be 16,340 new cases of cervical cancer within the country, 2,120 cases (gross incidence rate of 9.50 per 100,000 population) within the state of São Paulo and 720 cases (gross incidence rate of 11.60 per 100,000 population) in the city of São Paulo [5].

These incidence and mortality rates are high, especially among younger women with low socioeconomic status; this is despite wide availability of gynecological screenings, such as the Papanicolaou (pap) smear and sexually transmitted infection (STI) tests, which can screen for HPV [3,6].

Human Papillomavirus (HPV)

HPV is a common sexually transmitted infection (STI) with over 190 different types that can infect the genital areas, mouth, and throat of both men and women [7]. It is contracted through sexual contact, most often during vaginal, anal, or oral sex, between partners, but can be transmitted through skin to skin contact. Largely asymptomatic, 70-90% of both low and high-risk HPV types resolve naturally within 1-2 years [3]. As a result, many individuals who have HPV do not realize they are infected and continue to spread the virus. However, persistent HPV infection, defined as the presence of HPV for a period of time (usually 6 months), that goes untreated can lead to more severe disease, such as cancer, and other negative health outcomes, such as genital warts [3].

The 12 high-risk HPV types with known associations to cancer in both males and females include HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 [7]. Within Brazil, 68.5% of cervical cancer cases are attributed to specific HPV-16/18 infections, while virtually all other cervical

cancer cases are linked to other strains of HPV infections [3]. HPV has also been linked with other anogenital cancers, including cancer of the anus, vulva, vagina, penis, and head and neck cancers, specifically oropharyngeal cancer [3].

HPV Vaccine

Currently, there are two prophylactic vaccines available in Brazil to prevent HPV infections: Cervarix™ and Gardasil™ [8]. Cervarix™, which is GlaxoSmithKline Biologicals' bivalent vaccine, protects against two strains of HPV (16 and 18) and is approved for use in females aged 9-25 to prevent against cervical cancer and pre-cancerous lesions [9]. Cervarix™ has not been studied in males [9]. Gardasil™, a quadrivalent vaccine from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., protects against four HPV strains (6, 11, 16, and 18) and is indicated for females and males aged 9-26 to prevent pre-cancerous lesions, cervical, vulvar, vaginal, and anal cancers caused by HPV types 16 and 18 and genital warts caused by HPV types 6 and 11 [10]. These vaccines both target the two main HPV strains (16 and 18) that are responsible for approximately 70% of cervical cancer cases worldwide and prevent over 95% of pre-cancerous cervical lesions caused by HPV-16/18 [4,7].

Merck Sharp & Dohme Corp. have also created a 9-valent vaccine, Gardasil 9™ which protects against nine strains of HPV (6, 11, 16, 18, 31, 33, 45, 52, and 58) that is available in the United States [11]. With this protection, the 9-valent vaccine has shown to prevent an additional 4.2% to 18.3% of cancers and 3,944 cases annually in the United States, which has the potential to show similar effects if implemented in other countries, like Brazil [11].

HPV vaccines are most effective when administered prior to becoming sexually active and possible exposure to HPV, as they do not treat existing infections [7]. The World Health Organization (WHO) and Pan American Health Organization (PAHO) recommend females aged

9-13 as the target vaccination group [7]. The bivalent and quadrivalent vaccines are administered through two or three injected doses; though both were originally licensed and marketed with a three-dose schedule, a two-dose schedule has been found to be non-inferior to three doses in females aged 9-14 [7]. The bivalent vaccine can be administered as a two-dose vaccine at 0 and 6 months for females aged 9-14 or a three-dose vaccine for females 15 and older administered at 0, 2, and 6 months [7]. The quadrivalent vaccine can be administered at 0 and 6 months or 0, 2, and 6 months, but females and males aged 14 and older should adhere to the three-dose schedule [7]. The bivalent vaccine has proven effectiveness for at least 9.4 years and on-going studies for the quadrivalent version show similar efficacy over time [12,13]. Studies show one month after the final dose of either HPV vaccine, nearly 100% of females aged 15-26 years old have detectable HPV antibody [14].

HPV Prevention

To avoid contracting HPV and risk developing HPV-related cancers, the WHO recommends routine administration of the HPV vaccine. Vaccination strategies are dependent upon health systems and cost effectiveness, but prioritize vaccinating the target population of females aged 9-13. Including females older than this age group is recommended only if feasible and does not jeopardize the resources intended for the target population and other cervical cancer screening programs. In low-resource settings, male vaccination is not prioritized, as again, precedence is placed on the vaccination of target females to ensure full coverage after each dose. For females younger than 15, a two-dose vaccination schedule with a 6-month interval between doses is recommended for both the bivalent and quadrivalent vaccines. For females older than 15 and individuals who are immunocompromised and/or HIV-positive, a three-dose vaccination schedule administered at 0, 1-2, and 6 months is recommended. [7].

The period between HPV infection and the progression to invasive cervical cancer is approximately 10 years [3]. Unfortunately, cervical cancer cases are often diagnosed once the cancer has progressed to such a point that treatment is very difficult. To prevent this, women are encouraged to regularly seek screenings for pre-cancerous cervical lesions and STIs so that they receive early treatment. In Brazil, the primary screening test used for cervical cancer screening is a pap smear, which is recommended for females aged 25-64 every three years after two consecutive annual negative tests [3].

HPV Vaccine Program Implementation in Brazil

In March 2014, the Brazilian Ministry of Health's Programa Nacional de Imunizações (National Immunization Program or PNI) instituted a nationwide initiative that offers females a three-dose series of the quadrivalent HPV vaccine, Gardasil™, at no cost through Sistema Único de Saúde (Unified Health System or SUS) [4]. The vaccine was initially to be administered at 0, 6 months, and 5 years. The original dosing schedule was based upon proven efficacy of a two dose schedule of 0 and 6 months with the addition of a reinforcement dose at 60 months for maintenance of a prolonged response against the virus [15]. The program began with the vaccination of females 11 to 13 years old in 2014; each consequent year, the age group lowers. In 2015, the targeted age included females 9 through 11 years old and in 2016, 9 year old females will be the focus [4]. The vaccine schedule and population eligibility was based upon the recommendation of the Technical Advisory Group on Immunization of the Pan American Health Organization (TAG / PAHO) and approved by the Comitê Técnico de Imunizações do Programa Nacional de Imunizações (Technical Committee of Immunization of the National Immunization Program or PNI) [15].

The vaccine, now fully integrated into the nationwide immunization calendar, is available to females through SUS and the school system, yet excludes all males and females above the age of 13 from participation. The populations ineligible for vaccination through the PNI must independently purchase the vaccine, which ranges from R$330 – R$440, and has an average cost of R$365.67 per dose of the two or three dose quadrivalent vaccine; a price often too high for the high-risk populations who otherwise do not have access or seek preventative services [16]. The first dosage reached 4.3 million females, approximately 87.3% of the target population, resulting in one of the greatest coverage levels for the HPV vaccine in the world [17].

In 2014, the Ministry of Health purchased 15 million doses of the Gardasil™ vaccine[17,18]. In order to finance a sustainable program, a Productive Development Partnership (PDP) was signed in 2013 between the Brazilian Ministry of Health, Butantan Institute in São Paulo and Merck, Sharp & Dohme Corp. to produce the vaccine domestically [18,19]. Over the next five years, 36 million doses of the vaccine will be purchased for a below market price of R$31.02 per dose, an investment of R$1.1 billion, after which point the technology transfer will be complete and vaccine production will take place in Brazil [17]. It is estimated the PDP will save the Brazilian government approximately USD$19.7 million [17].

As of January 2016, Brazil's Ministry of Health, in collaboration with recommendations from the Technical Committee of Immunization of the PNI, decided to reduce the number of HPV and infant pneumococcal vaccine doses in the PNI schedule [20]. Females, aged 9 to 14, will receive only two-doses of the HPV vaccine administered at 0 and 6 months, while females, aged 9-26, who are immunocompromised or HIV-positive will continue the three-dose series [20]. While the WHO recommendations do suggest limiting the HPV vaccine to a two-dose schedule in low resource settings due to evidence of non-inferiority, it is difficult to separate this policy change

from the current economic recession in Brazil. The efficacy of the vaccines will not be altered, but the change will save federal, state and municipal governments money in health budgets that are already strained in an economic recession and have spent a reported R$2.9 billion (USD$720 million) in 2015 to distribute 300 million vaccines nationwide [21].

Sistema Único de Saúde (Unified Health System or SUS)

Though the Brazilian HPV vaccination program focuses its delivery within the school systems, individuals are also able to receive the vaccine through SUS. Created in 1988, SUS is the Brazilian national health system which was established by the government as a response to the Federal Constitution of the Brazilian Republic's recognition of the right to health [22]. It is the responsibility of the government to provide universal health coverage to all citizens and SUS is the means through which this right can be achieved. SUS creates a system of decentralized governance that shares responsibility across federal, state and municipal levels [23].

SUS provides coverage to over 75% of the population and offers care through an array of different health facilities, including more than 6,000 hospitals and 60,000 unidade basica de saúde (basic health unit or UBS), the later as the main location of primary care service for citizens [24]. SUS services include free access to drugs, including cancer treatment and immunizations provided through PNI, health technology, prevention services, and performs general epidemiological surveillance. PNI vaccines are supplied through the Programa de Auto-Suficiência Nacional em Imunobiológicos (National Self-Sufficiency Program in Immunobiologicals or PASNI) that guarantees free access to vaccines, which in turn encourages high coverage rates [25].

A focus was placed on access to primary health care services in SUS through the introduction of the Programa Agentes Comunitários de Saúde (Community Health Agents

Program or PACS) and the Programa Saúde da Família (Family Health Program or PSF), which is a team of health care workers who make a concerted effort to reach the country's poorest and most isolated communities that may not ordinarily have or seek access to care [23,25]. The program began with a focus on maternal and child health services for high-risk populations, but now has evolved to focus on families and communities through a family healthcare team, which includes a doctor, nurse, auxiliary nurse, and 4-6 community health workers, who are assigned to a geographical location, similar to that of a school district, and are the main point of contact for health care services in SUS [25]. PSF reaches over 98 million people within 85% of the municipalities in Brazil and employs more than 33,000 healthcare teams and 236,000 community health workers [25].

Mauá, Brazil

Our research focuses on the attitudes and beliefs of health care providers, often members of the PSF, who interact with parents and patients of reproductive age and work in SUS managed clinics within the city of Mauá. There are a total of 23 clinics and 1 hospital, among other health facilities, in the city [26].

Mauá is located in the ABC region of São Paulo, an industrial area composed of 7 cities: Santo André, São Bernardo do Campo, São Caetano do Sul, Diadema, Mauá**,** Ribeirão Pires and Rio Grande da Serra. Mauá is the 11th largest city in the state of São Paulo. It is home to one of the largest industrial parks in the country and has two economic development zones, highlighting the city's industrial based economy. Despite this growth potential, Mauá lacks sufficient urban planning, infrastructural development and financing to adequately provide a high quality of life for its residents. [26].

The city of Mauá is home to approximately 425,169 inhabitants and 125,369 households. Nearly 70% of the population depends on SUS for health care services. Mauá has an annual budget per capita of approximately R$1,000.00 to provide health care, education, employment and other social services. Though efforts have been made to encourage education of the population and the development of the workforce, Mauá has the 10th poorest per capita in the state with a per capita income of R$583.61. Of the 7 cities in the ABC region, Mauá ranks 6th with a Human Development Index (HDI) of 0.781. [26].

In 2015, the Ministry of Health's Sistema de Informação do Programa Nacional de Imunizaçõe (National Immunization Program Information System or SI-PNI) reported a total of 8,202 doses of the first HPV dose administered in Mauá within an estimated population of 10,550 eligible females of all age groups (overall coverage of 77.7%) [27]. This is a decrease in reported coverage from 2014 (10,956 doses among 10,680 eligible females, 102.6% coverage) [27]. It is of note to mention the discrepancy between the total number of eligible participants in 2014 and the total number of doses administered may be the result of providing the vaccine to individuals not initially accounted for in the original population estimates.

Receipt of the second dose in 2015 showed another decrease in coverage from 2014. In 2015, 6,139 doses were administered to an eligible population of 10,785 females in Mauá (overall coverage of 56.9%) [27]. In 2014, higher levels of vaccine up-take were reported for the second dose (7,496 doses among 10,683 eligible females, 70.2% coverage) [27]. This study seeks to understand more about how provider knowledge and opinions may influence the administration of the HPV vaccine in a low-income city, such as Mauá.

Current HPV Vaccine Program Outcomes in Brazil

The Brazilian HPV vaccine campaign has the potential to produce great public health impacts for the future. Demarteau, Breuer, and Standaert's study shows when incorporating HPV vaccine (with 80% coverage) and retaining the same level of screenings as pre-vaccination (50% participation in Brazil), combined with screenings every 5 years thereafter, would equate to lower cervical cancer rates under the same budget used prior to program implementation [28].

Unfortunately, though high coverage rates were reported after the first dose in 2014, coverage declined in 2015 [17,27]. In 2015, the state of São Paulo administered 762,610 doses of dose one to females aged 9-11 (952,705 eligible females, 80.1% coverage). Nationwide in Brazil, overall coverage was 69.6% among 9-11 year olds (4,897,795 eligible females, 3,406,988 doses); specifically, 87.3% among 9 year olds (1,590,611 eligible females, 1,388,071 doses), 72.6% among 10 year olds (1,623,598 eligible females, 1,177,937 doses), and 50% among 11 year olds (1,683,586 eligible females, 840,980 doses). In 2014, the state of São Paulo administered 1,096,123 doses of dose one to 953,778 eligible females (114.9% coverage) and 5,345,722 doses nationwide (4,954,906 eligible females, 107.9% coverage). [27].

The second HPV dose administered in 2015 saw similar declines in uptake as depicted in Mauá, when compared to coverage from dose one in both 2014 and 2015 and dose two in 2014. In 2015, the state of São Paulo administered 587,206 vaccines of dose two to females aged 9-12 (969,992 eligible females, 60.5% coverage). In Brazil, overall coverage was 41.4% among 9 years olds (795,305 eligible females, 328,958 doses), 41.9% coverage among 10 year olds (1,634,401 eligible females, 684,060 doses), 47.6% coverage among 11 year olds (1,683,586 eligible females, 801,446 doses), and 42.2% coverage among 12 year olds (861,720 eligible, 363,585 doses). Among all females aged 9-12, total coverage was 43.8% (4,975,013 eligible

females, 2,178,049 doses). In 2014, the state of São Paulo administered 676,472 doses of dose two to 956,453 eligible females (70.7% coverage) and 3,189,515 doses nationwide (4,974,454 eligible females, 64.1% coverage). [27].

As evident in the fluctuation of vaccine coverage rates, the PNI HPV program is not without challenges. Knowledge regarding the HPV vaccine is not consistent. In a qualitative study conducted in a São Paulo, Brazil shortly after the Brazilian HPV campaign was implemented, parental knowledge of the HPV vaccine was found to be low, though this did not influence whether eligible females were vaccinated [29]. In Rio de Janeiro, a similar cross-sectional study in 2014 analyzed the knowledge of HPV among female and male students aged 10-20 who have had contact with the Brazilian HPV campaign [30]. Knowledge of HPV as a virus and means of transition were shockingly low (0.4% and 32%, respectively), indicating an overwhelming knowledge gap within the very population who receives the vaccine [30]. However, there were still relatively high vaccination rates; the state of Rio de Janeiro administered 389,433 doses of dose one to 374,707 eligible females (103.9% coverage) and 219,875 doses of dose two to 375,726 eligible females (58.5% coverage) in 2014 [27]. Both of these studies signify a lack of education regarding the vaccine within the Brazilian context, but also suggest vaccination compliance is not influenced by this knowledge gap. This dichotomy is an issue that needs to be reconciled by policy makers through better communication campaigns.

Participation in the school-based HPV vaccine program in Brazil is also not required; those who do not want to participate can refuse. However, as described in São Paulo's informe ténico (technical report for implementation) on HPV, which is adapted from the Guia Práctico (federal technical report for providers) and Operacionalização da Implantação da Vacina HPV (federal HPV implementation plan), parental authorization and presence is not required for the

vaccine to be administered [15]. Therefore, if a parent does not want their daughter to receive the vaccine, they must complete a Termo de Recusa (refusal form) that must be signed and returned to the school prior to vaccination [15]. As an opt-out program, the likelihood of parental permission to be revoked is limited, thus facilitating high vaccination rates; however, this method of authorization can lead to inconsistent or inaccurate communication and a lack of knowledge of the vaccine and purpose for vaccination.

Finally, the PNI strategy does not allow access to the HPV vaccine through SUS for interested patients outside of the sex and age target; though these individuals can receive the vaccine if independently purchased [17]. This issue is the focus of our research.

Human Rights Impact

Article 6 of the Brazilian Constitution details a distinct right to health for all individuals regardless of sex, age, or socioeconomic status through SUS, enforceable through article 196, which states, “Health is a right of all and a duty of the State and shall be guaranteed by means of social and economic policies aimed at reducing the risk of illness and other hazards and at the universal and equal access to actions and services for its promotion, protection and recovery” [22].

In addition, Brazil is a strong advocate for human rights and non-discrimination in the global arena and has both signed and ratified numerous international human rights treaties, which support target populations that are the subject of our research. These treaties include: International Convention on the Elimination of all Forms of Racial Discrimination, ratified in 1968; International Covenant on Economic, Social and Cultural Rights, ratified in 1992; Convention on the Elimination of all Forms of Discrimination against Women, ratified in 1984; and Contention on the Rights of the Child, ratified in 1990. Though a signatory, Brazil does not sufficiently report on the country’s progress toward adhering to their right to health

commitments and unfortunately, this lack of reporting may highlight a larger political strategy which seeks to emphasize the country's global standing rather than enforce human rights and eliminate disparities [31].

With the right to health as the foundation upon which SUS was created, the Brazilian government has a constitutional responsibility to protect the rights of its citizens and create policies that allow equal access to health. Currently, however, the HPV vaccine eligibility policies exclude a large population of individuals who are still at risk of contracting HPV and potentially cervical cancer, among other preventable cancers and diseases. While this decision was largely based upon cost effectiveness, the concept of herd immunity (boys do not need vaccinated because they will be indirectly protected by females), and WHO recommendations, it still presents a conflict of conscience and pocketbook [15]. The primary goal of the PNI strategy is to prevent cervical cancer; yet, by eliminating males and females over the age of 13 from participating in the program and receiving targeted health messages, these populations effectively receive limited or no access to important health information that can influence their decisions to seek alternative means to receive the vaccine.

Objectives and Aims

The **objective** of this study is to address to what extent human rights considerations influence the sexual and reproductive health care of all males and females over the age of 13 in Mauá, Brazil, specifically in terms of access to the HPV vaccine. Included in this objective are several **aims**:

1) To assess the level of clinical knowledge health care providers have regarding the HPV vaccine;

2) To understand health care providers' attitudes toward the Brazilian HPV vaccine program's eligibility requirements; and
3) To examine the influence of health care providers' interpretation of the Brazilian constitutional right to health and the association with their attitudes toward the Brazilian HPV vaccine program's eligibility requirements.

Brazil is a model of how low- and middle-income countries (LMICs) may introduce and implement universal health coverage [23]. The creation of SUS is great achievement for the Brazilian government, which sought to promote social justice and diminish inequalities within the population through creating universal health care [32]. However, with this recognition and accolade comes great responsibility.

SUS is not without fault; with limited resources and underfunding among other complaints, the system can fall short of meeting its purpose to provide health care access for all individuals [23]. SUS has a large workforce of health care employees, yet the need for services often exceeds the capacity of the workforce and as a result, facilities are overcrowded with long wait times [24]. To accommodate the population, additional funding is needed. Currently, SUS is supported at the federal, state and municipal level. Approximately 9.7% of the Brazil's gross domestic product was attributed to healthcare costs in 2013, placing Brazil 31st in the world for health expenditures [33]. At the state level, governments are required to allocate a minimum of 12% of their budget to health spending; yet, less than half of the 26 states comply [24]. In contrast, municipalities must attribute 15% of their budget to health, which is met by 98% of the municipalities [24]. Despite the participation at the municipal level, financial resources within SUS are severely lacking and insufficient to support universal health coverage. To achieve this goal,

approximately USD$73 billion are needed to sustain SUS, which is an increase of more than USD$100 per capita [24].

The result of these challenges and deficiencies are large disparities in access and care provided to the population. The HPV vaccine implementation program and limited eligibility requirements highlights this inequity, which leads to the greater concern of how these policies jeopardize the Brazilian constitutional right to health. As an example for other countries seeking to implement universal health care, it is crucial for the Brazilian government to consider how their vaccine implementation policies can negatively affect health care services received by at-risk populations within their country and globally.

The HPV vaccine has recently become a mainstream vaccine that is either incorporated into existing immunization schedules or is offered to individuals of reproductive age through pilot or established programs as a first line of defense against the spread of HPV and consequent development of cervical cancer and other preventable cancers or diseases. To date, the focus of research has largely highlighted program implementation and cost-effectiveness of administering the vaccine in certain locations and to target populations. What lacks is a thorough analysis of how the vaccine implementation programs, specifically the eligibility requirements, influence an individual's right to health, either positively or negatively. Our research seeks to begin this necessary and overdue conversation.

Chapter II: Literature Review

The quadrivalent and bivalent human papillomavirus (HPV) vaccines, Gardasil™ and Cervarix™ , were first introduced in the United States in 2006 and 2009, respectively [9,10]. In 2006, the quadrivalent vaccine was approved in Brazil, followed by the bivalent in 2008 [34,35]. Since their release, the quadrivalent and bivalent vaccines have been licensed in over 100 countries, and of these, 53 have incorporated the HPV vaccine into their national immunization programs, with many other countries currently piloting or planning pilot demonstration projects in the future [36]. Within Latin America, Argentina, Brazil, Colombia, Paraguay, Peru, Suriname, Trinidad and Tobago, and Uruguay have national HPV vaccine programs [36].

Though each country has its own implementation strategy and target population for vaccination, they all share the common goal of introducing the HPV vaccine as a strategy to prevent the spread of HPV and cervical cancer. Who, where, when and why the vaccine is delivered have been issues of great interest over the past decade, as cervical cancer incidence and mortality rates continue to increase globally, while implementation of the HPV vaccine as a nationwide program has shown to be a successful means of protecting against the virus, evident through declines in HPV prevalence, as seen in the United States, and other negative health outcomes, such as incidence rates of genital warts, as seen in Australia [37-39]. Here we describe the current state of HPV vaccination and address these issues.

HPV Trends – Who? Target Population

The question of who to vaccine against HPV has been a topic of continuous debate, as both males and females are susceptible to the virus and its health effects. Current literature focuses largely on recommendations related to the cost-effectiveness and acceptability of incorporating males into HPV vaccination programs. The World Health Organization (WHO)

recommends that vaccination programs target females aged 9-13 and vaccination of females above this age range as a secondary target population, so long as resources are not diverted from the target population or other cervical cancer screening programs [7]. The WHO does not recommend the vaccination of males in resource-constrained settings and again emphasizes the need for adequate resources to be directed toward vaccinating the target population of females 9-13 in order to reach levels of high coverage [7]. In contrast, the United States Advisory Committee on Immunization Practices (ACIP) supports routine HPV vaccination for females and males at age 11 or 12, and more specifically for females aged 13-26 and males 13-21 or 26 in high-risk populations, such as men who have sex with men or immunocompromised individuals, who have not previously received the vaccine [40]. However, these recommendations have been staggered; in 2006, females were recommended to receive the HPV vaccine as part of a routine vaccination schedule, while males were not included until 2011 [12]. ACIP also notes including males in the vaccination schedule is more cost-effective when all HPV-related health outcomes are accessed and female vaccination coverage is low [12].

Health Outcomes

The medical need for vaccinating males and females is not contested. It is scientifically proven that males are carriers of HPV and can also experience negative health effects from the virus, such as anal, penile and oropharyngeal cancers, and genital warts, furthering the justification for including males in HPV vaccination strategies [3,41]. While genital warts do not lead to mortality, incidence rates are increasing [41]. In addition to the psychological stigma associated with the disease, treatment for genital warts can be both costly and time consuming, which places an undue economic burden on patients and health systems that could easily be alleviated through HPV vaccinations [41]. In Australia, the incidence rates and consequent

treatment of genital warts in both males and females has declined since the introduction of the country's nationwide HPV program in 2007 [38,39]. In the United States, Elbasha and Dasbach present mathematical population modeling of public data sources to show that a vaccination program including both males and females would decrease the number of cases of genital warts by 5,146,000, cancer cases by 116,000 and cancer deaths by 40,000 [42].

Cost-Effectiveness

However, in low- and middle-income countries, the issue of cost-effectiveness for vaccinating both males and females takes priority and can have conflicting results. Cost-effectiveness analyses are integral components of HPV immunization program planning and implementation and must consider, among many other things, what outcomes ought to be measured and how this information should be relayed to inform policy [43].

Chesson, Ekwueme, Saraiya, Dunne, and Markowitz's cost-effectiveness analysis of male vaccinations in the United States is dependent upon the coverage of female vaccination [44]. When there is low female vaccination coverage, adding male vaccination has an incremental cost per quality-adjusted life year (QALY) gained of $23,600; this increases to $184,300 per QALY gained with high female vaccination coverage [44]. However, increasing coverage of female vaccinations was found to be more cost-effective than including males in the coverage [44].

A similar modeling approach was conducted in Brazil focusing on HPV-16 and -18 [45]. Assuming 90% coverage rates and lifelong protection from the virus after vaccination, vaccinating only females reduced the cancer risk by 63%, increasing to 67% when males were included in the vaccination [45]. Assuming a cost of USD$50 per vaccination, vaccinating only females showed USD$200 per year of life saved (YLS) and USD$810-1,860 YLS for males

dependent upon coverage levels, clearly proving the cost-effectiveness of a female only program in a resource-strained setting [45].

In contrast, through cost-benefit analyses and modeling, Garland suggests routine vaccination of 12 year old females with catch-up vaccines for 12-24 year olds is the most cost-effective strategy, while adding males aged 9-26 would be the most effective strategy for preventing disease [46]. This type of vaccination program, including both females and males, has the potential to reduce HPV 16 infection by 88-94% in females and 68-82% in males by 2050 [46].

Resources in Brazil are limited and as a result, studies have been conducted to evaluate the cost-effectiveness of HPV vaccinations compared to population screening [47-49]. In 2006, the annual direct costs for prevention and treatment of cervical cancer were estimated to reach USD$538,709,332; 77% of which was spent on screening, 10% on pre-cancerous lesions and 13% on treatment of cervical cancer [50]. With these already outstanding costs, introducing the HPV vaccine through PNI has placed a strain on Sistema Único de Saúde (Unified Health System or SUS) and increased the costs of cervical cancer prevention temporarily, but will have future benefits for disease prevention, especially in a country with low rates of pap testing [47].

Social Acceptability

Acceptability of vaccinating different genders and populations has also been acknowledged as a factor in HPV vaccine program implementation. In general, parental perceptions of the HPV vaccine for males were positive with moderate willingness to vaccine, especially if they perceived high levels of vaccine effectiveness and anticipated regret for not pursuing vaccination if their son later developed a HPV infection [51,52]. A vaccine that prevents diseases related to the HPV virus, including genital warts and cervical cancer, was found to have the greatest acceptability and served as a motivator for vaccination [53,54].

Male attitudes toward the vaccine can vary drastically. Knowledge about the vaccine is generally low, suggesting the need for further education and awareness within this population [52,53]. Males were more inclined to receive the vaccine if they perceived vaccine acceptance from their peers or anticipated regret for not receiving the vaccine if they became infected in the future [51]. Of interest is the perceived severity of disease among males who are shown to be more willing to receive the vaccine when it is marketed as preventing cancer in addition to genital warts, as opposed to simply preventing genital warts alone [55]. In studies conducted with male university students, acceptability of the HPV vaccine was high, but much lower within a representative population sample of males, perhaps reflective of different knowledge levels and awareness of the vaccine [53,56]. Potential side effects, efficacy, safety and cost were all issues that influenced a male's decision making, with cost being a primary concern for those who had the greatest intention to receive the vaccine [56].

Over all, there is a general sense of acceptability for vaccinating both males and females among providers when the vaccine is thought to be effective and there is a high likelihood of HPV infection, though there is a preference for female vaccinations [52,53]. In a United States based study of 2,714 pediatricians and family practitioners who primarily vaccinate females, 63.9% would vaccinate males aged 11-12, 93.4% would vaccinate males aged 13-18, and 92.7% would vaccinate males aged 19-26 [57]. A physician's recommendation of the vaccine is the largest motivator for receiving the vaccine and increases the likelihood of vaccine completion, while a lack of recommendation can serve as a barrier for patient and parent acceptability; other barriers include logistical challenges and concerns about vaccine efficacy and safety [58-60].

Acceptability is generally high among patients, parents and providers; perceived barriers, such as efficacy and safety, can be remedied through public health campaigns that promote

awareness and positive attitudes toward the HPV vaccine and provider recommendations [61]. But among policy makers with varying priorities and limited resources, the question of who should receive the HPV vaccine is a continual discussion – what is the most cost-effective way to achieve high coverage and who is most likely to accept the vaccine? Current literature provides analysis and modeling to aid policy makers in their decision making, but what is not considered is the individual patient and his or her own desire for vaccination or their right to access this health intervention.

HPV Trends – Where? Vaccine Location

Each country that implements an HPV vaccination program has the discretion as to where the vaccine will be administered. The WHO recommends delivery of the HPV vaccine through an array of means including outreach campaigns, health facilities, or school-based strategies [7]. The decision of how to implement the vaccine program should consider the specific country's infrastructure, cost-effectiveness, sustainability and means through which the highest possible coverage can be achieved among the most vulnerable populations who are less likely to have access to screening or other cervical cancer prevention methods as an adult [7].

In the United States, the vaccine is recommended as part of an adolescent's immunization schedule and can be a school entrance requirement depending on each individual state's vaccine policies, though is rarely required [40,62]. The vaccine is administered to patients in health provider offices but has had very low coverage rates since the vaccine was introduced. In 2010, only 30% of females 13-15 years old completed the entire three-dose HPV vaccination [63]. Though by 2014, this had increased to 69.3% (±2.4) completion of the three-dose HPV series among females and 57.8% (±3.0) among males, which is a statistically significant increase from 2013 [64].

In contrast, the Australian national HPV program, which has also incorporated the vaccine into their standard immunization schedule, provides the vaccine without cost to males and females aged 12-13 through a school-based system and successfully achieved 71% coverage in 2012 [65,66]. Other low- and middle-income countries, such as Indonesia, Malaysia, Sri Lanka and Tunisia, have also implemented successful school-based HPV vaccination programs and serve as a model for other countries considering similar programs [67]. Rwanda is another example of success. In 2011, Rwanda reached a 93.23% coverage rate through establishing a public-private community partnership with Merck Sharp Dohme Corp. to ensure effective vaccine delivery through a school-based vaccination program that targeted females in 6th grade [68]. A notable strength of this program was the involvement of the community who identified females who were absent from school or not enrolled in school so that they were also able to receive the vaccine [68,69].

School-based programs are not without challenges, however. Obstacles of the school-based approach include school absenteeism, reaching individuals who are not enrolled in school and the ability for schools to facilitate and manage the program through appropriate personnel and documentation [69]. However, if these issues can be overcome, as shown in the example of Rwanda, and age-based services, such as nutritional education, are also integrated into the program, then school-based immunizations can provide a unique opportunity to reach adolescents who might not ordinarily seek or have access to these services [67,69].

To assess the vaccination uptake and completion rates of a school-based program in Brazil, Fregnani et al., conducted a demonstrative study of an HPV vaccination program in Barretos, an affluent city in the state of São Paulo, prior to the introduction of the Brazilian PNI program [70]. Participants included females enrolled in 6th or 7th grade in both private and public

schools; of the 1,574 eligible females, 1,513 agreed to participate [70]. During the study, the quadrivalent HPV vaccine was offered at 0, 2 and 6 months; an uptake rate of 87.5% was found for the first dose, 86.3% for the second, and 85.0% for the third [70].

Critical to the success of Fregnani's demonstrative study were two key factors: 1) the collaboration of the health and school systems and 2) the scheduling of each dose. First, to introduce the Barretos project, parents and guardians were invited to attend a meeting to answer any questions approximately one week prior to the vaccination. While similar school-based informational meetings are a part of the PNI HPV strategy, whether or not these sessions occur is inconsistent. In addition, in the study, if students were unable to receive the vaccine on the designated day at school, the vaccine was made available at a local hospital for future vaccination. Within PNI, the vaccine is also available to all individuals at unidade basica de saúde (basic health unit or UBS), but this information may not be accurately relayed to parents or patients with the same clarity as used in the study. Finally, it is important to note that this shortened dosing schedule (0, 2, 6 months) is not the same as the schedule implemented with the nationwide Brazilian HPV vaccination program (initially, 0, 6 and 60 months; as of 2016, 0 and 6 months). Offering all doses of the vaccine within one school year can limit the potential of missing students for future dosages and as a result, increase the likelihood of vaccine completion.

Many HPV pilot programs are school-based interventions, largely due to the feasibility of limiting loss to follow up; but other programs, such as that in the United States, rely on health care providers to educate and recommend HPV vaccinations for patients. School-based programs often have higher uptake rates, as seen in Australia, Rwanda, and in the Barretos pilot, but may overlook populations who are not a part of the school system, yet are at high-risk for contracting

the HPV virus. This is an issue that is not sufficiently acknowledged in the literature and must be recognized.

HPV trends – When? Vaccination Schedule

The HPV vaccine is most effective when administered to individuals prior to HPV exposure or sexual debut; therefore it is often recommended for individuals aged 9-13 [7]. However, there is also the possibility of administering secondary catch-up vaccines for individuals who are not in this target age group, especially in the early stages of HPV vaccine coverage [7].

Currently, the Brazilian HPV vaccination program excludes females above the age of 13 from receiving the vaccine through PNI, citing it is more cost-effective to vaccinate adolescents prior to HPV exposure [15]. However, this does not take into account the ability for sexually active females to acquire new strains of HPV. While the highest incidence rates of high-risk HPV (types 16 and 18) occur within the first few years of sexual debut, there is still the potential to contract an oncogenic HPV infection later in life. Castellsague et al., conducted an analysis of literature and clinical trial data to show that sexually active females are vulnerable to new HPV infections [71]. The quadrivalent HPV vaccine has demonstrated its effectiveness and safety for females aged 24-45 and can be used as a catch-up vaccination for this age group. Of note is the consideration that the cost-benefit becomes less favorable as a female's age increases and thus, routine immunization programs should target the younger females, but should also extend coverage to 25-26 year old females when feasible [71].

To demonstrate the potential opportunity and need to introduce catch-up vaccines for older females, two cross-sectional studies were conducted from June 2006 through February 2007 in Hospital Maternidade Leonor Mendes de Barros (HMLMB), a large, public maternity

hospital in São Paulo, Brazil [72,73]. Participants included 301 females 15-24 years old who were recruited for study participation 43-60 days after the birth of their first child and provided cervical specimens to be tested for HPV DNA. After testing, HPV was found in 58.8% (95%, CI 52.7-64%) of the samples, suggesting that females who give birth to their first child at a young age are a high-risk group for HPV infection [73]. Awareness and knowledge of HPV among the participants was also assessed; 37% reported having heard of the virus, 19% knew HPV was a sexually transmitted infection and 7% knew HPV could cause cervical cancer [72]. All of the 301 participants would accept the HPV vaccine after delivery if available, including those who already had HPV, suggesting that while knowledge is low, acceptability of the vaccine is high among participants and thus further education and awareness is needed for this high-risk population [72].

Like the HPV gender debate, the age of vaccination for individuals is a dichotomy between medical need for coverage and financial resources available to sustain a comprehensive immunization program. Rama et al., clearly demonstrate the need for vaccine catch-up in Brazil in order to not only educate this high-risk population about HPV, but also provide equal access to health care and opportunity to cover all individuals who show interest in receiving the vaccine[72,73]. However, as demonstrated, the Brazilian SUS is a resource-limited system attempting to maintain universal health coverage through diminishing federal, state and municipal funding [24]. In the midst of one of the worst economic recessions in recent Brazilian history, the government is faced with the challenge of curbing spending while still ensuring the health and welfare of its citizens.

HPV Trends – Why? Provider Knowledge and Beliefs

An important component of an effective immunization program is the support of health care providers who administer and educate their patients about the vaccine. Prior to and since the licensure of the HPV vaccine, studies have been conducted around the world assessing provider knowledge and attitudes toward the vaccine. Though it is important to note that many of these studies are older and thus attitudes might have changed, they still provide insight as to the common concerns of providers and factors that influence their attitudes toward the HPV vaccine and administering the vaccine to patients.

United States Providers

Within the United States, the HPV vaccine can be a controversial issue to discuss among patients, parents and providers due to questions of vaccine safety and efficacy and the vaccine's association with a sexually transmitted infection, which implies the onset of sexual activity at a young age [58,74]. Providers with lower vaccination rates report vaccine delay for patients who they consider low-risk for sexual activity and thus vaccination can wait until the female is older [75]. The obvious challenge with this approach is predicting the patient's sexual debut; as a result, providers miss opportunities for HPV vaccination in patients who may have already become exposed to HPV despite their perceived low-risk [75]. Another concern is that the HPV vaccine will influence and encourage the onset of sexual activity, though this has been proven to be unfounded [76,77]. More troubling is that a provider's recommendation is shown to be the most important factor in HPV vaccine uptake, in addition to parental knowledge of the vaccine [75,78].

In general, when providers do make a recommendation, they are more likely to endorse the HPV vaccine for female patients as opposed to males and at older ages. For example, August through October of 2005, prior to the licensure of the quadrivalent HPV vaccine in the United

States, a cross-sectional study assessed the likelihood of vaccine endorsement among 431 randomly sampled pediatricians from the American Academy of Pediatrics [79]. If the vaccine was endorsed by national health organizations, 46% would recommend the vaccine for 10-12 year old females and 37% for males of the same age group; 77% for 13-15 year old females and 67% for males; 89% for 16-18 year old females and 82% for 16-18 year old males, largely due to the assumption of increased sexual activity after vaccination [79]. With this preference for administering the vaccine at an older age in the United States, further studies are needed to assess whether this preference is also shared within Brazil or countries who target vaccine implementation to 9-13 year olds.

Similar trends favoring females for vaccination are seen when providers are asked about recommendations for two hypothetical vaccines: a joint cervical cancer and genital wart vaccine and a cervical cancer vaccine [74,80]. Just as in the Daley study, providers showed greater intention of recommending both vaccines to the females as opposed to males and to a higher age group as opposed to a younger one [74,80].

Why providers make their recommendations has also been evaluated. Kahn's qualitative study goes further to explain that a provider's intention to recommend is largely based upon the efficacy, safety and potential health impacts of vaccination and preventing HPV-related diseases[81]. Perceived barriers among providers' recommendations include anticipated parental beliefs and the provider's reluctance to discuss sexual activity with pre-adolescent aged patients[81]. Additional barriers to recommending the HPV vaccine include cost and safety, as determined by Ishibashi et al.'s study that showed 88% of participants would provide the vaccine to all patients [82]. Of those who would not recommend the vaccine to all eligible patients, these

providers were more likely to be self-described conservatives or have other characteristics that would suggest a reluctance to immunize patients [82].

While it is important to acknowledge the attitudes and beliefs of providers in offering recommendations for the HPV vaccine, in the United States, where vaccines are administered in physician offices, the procedures of individual offices must also be considered. Between December 2006 and May 2007, Huey conducted a study assessing accessibility of the HPV vaccine among primary care providers in Appalachian Pennsylvania, an area with cervical cancer incidence rates higher than the national average [83]. Of the practices who agreed to participate in the study, a majority (44/55) offered the vaccine to their patients, including females aged 9 to 26 (40/44), and a majority (46/49) actively recommended the vaccine to patients [83]. Consequent vaccine coverage within this area was not reported as outcome in this study.

Global Providers

Similar trends of female preference in HPV vaccine recommendations are seen worldwide. For example, a study examining knowledge, attitudes and beliefs about the HPV vaccine among Canadian obstetricians, family physicians and pediatricians showed 95% preference for the vaccine to be administered to females before their sexual debut [84]. As follows, 80% believed the optimal age for vaccination is below the age of 14, presumably to circumvent the effects of the patient's sexual debut, and 88% intended to recommend the HPV vaccine if it was publically funded and at no cost to the patients [84].

A greater emphasis is placed on provider knowledge of HPV in global studies. In a pilot of 311 Italian pediatricians, a lack of HPV knowledge and prevention was prominent across all types of providers (primary care pediatricians, hospital pediatricians and residents in pediatrics), though most would recommend the HPV vaccine [85]. Bednarczyk et al., conducted a similar

cross-sectional study in Georgia and found while 68.9% of physicians correctly identified that HPV is spread through sexual contact, other knowledge regarding the virus, such as where the infection can occur and how many strains of HPV exist, varied [86]. Despite potential gaps in knowledge, 47.8% of physicians both offered and recommended the HPV vaccine [86]. Most notably, 93.5% indicated a desire for additional education on cervical cancer and 93.9% indicated the same interest in HPV; with this supplementary training, 84% would recommend the HPV vaccine more often [86]. Both the Italian and Georgian study highlight the need for further education among these providers, which is a theme also found within Brazil.

Prior to the 2014 Brazilian HPV immunization campaign, a non-randomized cross-sectional study was conducted among health professionals from the Southeast region of Brazil to assess knowledge of HPV [87]. Overall, knowledge of HPV was high: 98.7% correctly indicated that HPV is sexually transmitted; 82.3% reported the asymptomatic nature of the virus; and 88.6% determined the pap smear is a screening method to identify potential changes in the cervix[87]. Despite high levels of knowledge comprehension, 38% of participants did not know the status of current vaccines used to prevent specific HPV variants and 44.3% did not indicate knowing that not all HPV variants are cancerous [87]. While provider knowledge of the HPV vaccine has most likely changed in Brazil since the PNI HPV implementation, the study results do emphasize a lack of communication relating the connection of HPV to cervical cancer prevention.

As shown, attitudes and knowledge toward the HPV vaccine vary among providers and are influenced by an array of factors. However, a common theme across all countries, is the need for further education among the providers to encourage knowledge increase about the virus and dispel any concerns regarding the vaccine's safety, efficacy and acceptability.

Right to Health

Decades of political and social movements have led to what Brazilians know today as their constitutional right to health. While still under military dictatorship, the mid 1970s in Brazil was a time of reform with citizens seeking to restore democracy in the country [25]. The Brazilian Health Reform Movement, which supported the belief that health was a social and political issue that should not be managed through large bureaucracies without public participation, was also becoming a part of public discourse [25]. This unprecedented social movement came after years of a predominately private health care system that catered to those who could afford the private health insurance and fee-for-service payments [25]. Shortly thereafter, the country began its transition into a democratic nation and the Federal Constitution of the Brazilian Republic was enacted, which not only explicitly included health as a fundamental right for all citizens, but also the duty of the State to create policies to provide "universal and equal access" to health services through SUS [22]. With this foundation, SUS was created to serve as an integrated, decentralized public health system that promoted coordination at the federal, state and municipal level and guaranteed universal health coverage and access for all Brazilians [25].

Brazil's recognition of health as a human right extends beyond the country's own legislation; the country has signed and ratified several international human rights treaties, including the International Covenant on Economic, Social and Cultural Rights (ICESCR), which was adopted by the United Nations General Assembly in 1966 and enacted in 1976 [88]. Brazil ratified the ICESCR in 1992. The ICESCR seeks to protect individuals' economic, social and cultural rights, which most notably include the right to non-discrimination, gender equality, and the right to health [88]. Article 12.1 of the ICESCR defines health as "the right of everyone to the enjoyment of the highest standard of physical and mental health" [88]. It is important to note, the

right to health does not guarantee a right to be healthy per se, but instead considers the right to health as the *availability* and *accessibility* of services and *acceptability* of all individuals to receive *quality* services [89].

According to the ICESCR, States are obligated to use the maximum resources available for enforcement so that citizens may achieve the greatest realization of their rights; however, as outlined in General Comment 14, certain 'core obligations' are required to be upheld regardless of the States' resources, including but not limited to: primary health care, availability of essential drugs, and a national public health strategy that addresses the health concerns of the entire population [89]. The State, in turn, has an obligation to provide health care services and other initiatives that can influence an individual's socioeconomic status, such as clean water and sanitation, access to information, safe housing, and vaccines [89].

As such with international treaties, there is no legal enforcement agency in place to hold States accountable to the rights outlined in the ICESCR. The ICESCR does have the Committee on Economic, Social and Cultural Rights (CESCR), which serves as an enforcement mechanism used to monitor the implementation of the ICESCR through reports which are submitted every 5 years by each Member State [90]. The CESCR also receives communication from individual citizens who can report their State for human rights violations [90]. The CESCR then publishes observations, recommendations and areas of concern for each Member State, which can then influence policy creation [90]. However, reports to determine adherence and achievements of fulfilling the right to health may not be accurate and instead, the role of treaty signatory may have more political than social justice motivations [31]. Nevertheless, how the constitutional right to health and the ICESCR are implemented, or not, and enforced, or not, both globally and in Brazil are discussed next.

In terms of the HPV vaccines, current literature highlights who should receive the vaccine, where the vaccination should take place, when the vaccine should be administered and provider's knowledge and attitudes toward HPV and the HPV vaccine, but does not address the issue of whether eligibility requirements limit an individuals' ability to access and evoke their right to health. Though limited, the discussion of access to essential medicines, such as antiretroviral therapy (ARTs), as a human right has been cited in literature [91-93].

The Brazilian management of the HIV/AIDS epidemic throughout the past three decades is an example of how access to ARTs, or access to treatment and essential medicines, in addition to access to health care, can be considered a human rights issue [91]. To uphold the constitutional right to health, Brazil managed the HIV/AIDS crisis by simply treating every HIV-positive individual equally. Every Brazilian citizen was then and continues to be constitutionally guaranteed a right to health care and access to ARTs free of charge through SUS [22]. Individuals who are HIV-positive are no exception, though often they were in other countries [91]. Gruskin conceptualizes this concept of access as an issue of human rights by suggesting that laws and policies, health systems, social and economic contexts all influence the services and programs provided which, in turn, effect an individual's rights [92].

Though not considered an essential medicine by the WHO, the HPV vaccine is included as a recommended vaccine for both adults and children on the WHO Model Lists of Essential Medicines [94]. It can then be suggested that the HPV vaccine should hold the same significance as a medicine on this list. As such, Hogerzeil provides an analysis of court cases in low- and middle-income countries where individuals claim access to essential medicines could be enforceable with reference to a right to health [93]. Of 71 cases from 12 countries, 59 cases, largely from Central and Latin America, were determined to be enforceable through the courts and

usually found to be successful when constitutional rights to health and human rights treaties were upheld within the specific country [93]. Of importance is Hogerzeil's conclusion that while individuals can use litigation to ensure their governments are upholding their constitutional and international treaty obligations, it is more beneficial for lawmakers to incorporate human rights standards within their legislation during the policy development phase [93].

While the HPV vaccine is not explicitly addressed in literature as a public service that can promote or infringe upon an individual's right to health, other medicines, such as ARTs, have proven to do so. What is important to note is how these other medicines are managed through proper legislation both in Brazil and in the world and how similar policies can be adapted to facilitate similar access equality.

Literature Gaps

The HPV vaccine has only recently become commonplace within country immunization programs and still is evolving, for what began as a quadrivalent and bivalent vaccine is now a 9-valent vaccine, protecting against nine variants of the HPV virus. As such, literature about the HPV vaccine and program implementation on a global scale is in abundance and ever-changing in terms of cost-effectiveness analyses, understanding acceptability within different cultures and populations, and patient and provider knowledge.

Currently, cost-effectiveness assessments of male and female vaccinations have been analyzed and show that male vaccination efforts are negligible if female vaccination coverage is high and as such, a focus should be placed on increasing uptake rates of the HPV vaccine among females [44-47]. In general, social acceptability of vaccinating males is high among parents, patients and providers [61].

Though vaccine program implementation should take place in settings most appropriate for the population, literature shows that school-based approaches are usually successful and result in high levels of vaccine coverage [65,66,68-70]. However, there is the potential for populations to be missed in a school-based program, which leads to the discussion of catch-up programs. Catch-up vaccines have been shown to be effective in preventing disease within older populations who have continual risk of HPV infection, especially when the HPV vaccine is first beginning implementation [71-73]. But in the case of Brazil, where rates of vaccine uptake and coverage are declining, is it irresponsible to limit vaccine access through eligibility requirements? This will be considered through understanding providers' attitudes toward Brazil's HPV program.

Provider knowledge regarding HPV and the HPV vaccine has also been assessed through literature and highlights variances between countries regarding both attitudes and understanding of the virus [58,74-76,78-87]. Universally, however, it is a fair assessment to conclude that the studies all show a need for additional education about HPV for both providers and patients to assuage potential unfounded concerns or discomfort when conversations about sexual activity may arise. This research will provide an additional perspective by assessing whether HPV knowledge influences a provider's attitudes toward implementing the vaccine.

Most importantly, what is lacking from the discussion is an understanding of how the HPV vaccine and its implementation influences an individual's human rights and more specifically, his or her right to health. In Brazil, females above the age of 13 and all males are not eligible to receive the HPV vaccine at no cost; if they want to be vaccinated, they must pay for these services. However, these excluded populations are still at risk for developing HPV and potentially cervical cancer.

This study seeks to fill these gaps in literature and understand how a health care provider's understanding of the Brazilian right to health and the eligibility requirements for the HPV vaccine influence their attitudes toward the vaccine. With a human rights approach, we will begin a discussion of how policies influence an individual's right to health and how this constitutional right ought to be incorporated into future policies.

Chapter III: Methodology

From May to August 2015, we conducted a cross-sectional study using a paper-based, self-administered survey in eight public health clinics located in the city of Mauá, a suburb of São Paulo, Brazil. Healthcare providers were recruited to better understand the extent to which human rights considerations influence the sexual and reproductive health care provided to males and females over the age of 13 in the state of São Paulo, Brazil, specifically in terms of access to the quadrivalent human papillomavirus (HPV) vaccine. The study was reviewed by the Emory University Institutional Review Board and the Mauá municipal Institutional Review Board and was found to be exempt research, as the project did not meet the definition of research with human subjects and instead was classified as public health practice.

Population

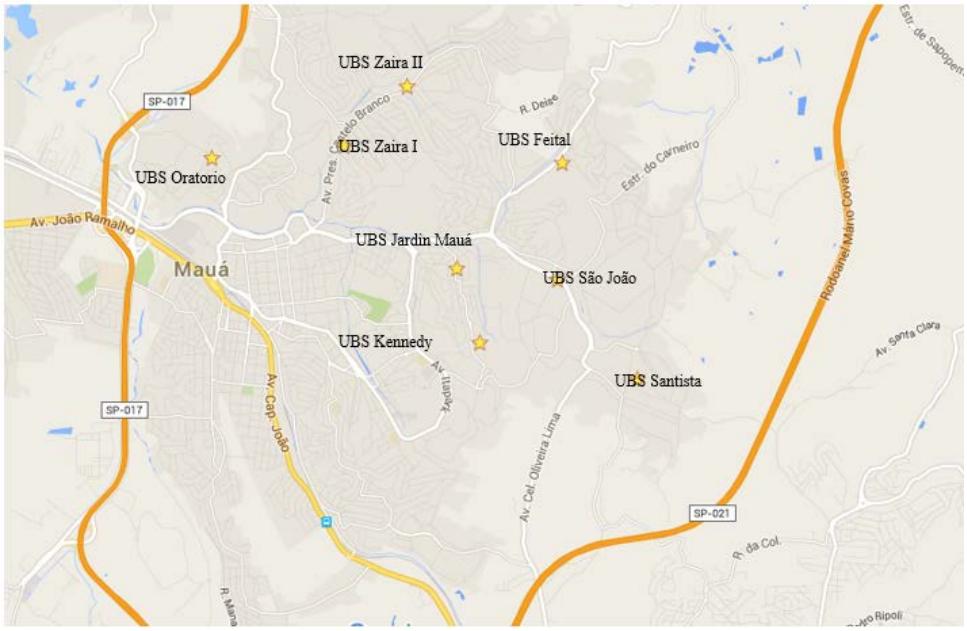
The city of Mauá is an industry-based, low income community [26]. Nearly 70% of the city's population depends on the Sistema Único de Saúde (Unified Health System or SUS), which is also used by residents of neighboring communities, creating a high demand for health services that are not accounted for in the municipal city budget [26]. There are a total of 23 health clinics and 1 hospital, among other health facilities, in the city [26]. Mauá was chosen as the population of interest for this study, as it represents a low income, high-risk demographic within São Paulo, Brazil.

Participant Recruitment

We recruited within eight health clinics in Mauá: Jardin Mauá, Kennedy, Santista, São João, Oratorio, Feital, Zaira I, and Zaira II (Figure 1). Selection was based upon convenience sampling and willingness to participate. Administrators at each clinic were contacted directly by

a community partner, who approached each clinic and discussed the opportunity and feasibility for participation in the study.

Figure 1: Map of 8 Participating UBSs in Mauá: Jardin Mauá, Kennedy, Santista, São João, Oratorio, Feital, Zaira I, and Zaira II



Source: Google Maps

Participant recruitment was then facilitated by administrators within each clinic who identified potential participants. Inclusion criteria required participants to meet the following: 1) must be a citizen of Brazil and 2) must be a practicing provider with clinical knowledge and direct contact with male and female patients of reproductive age. Participants were excluded if they did not meet these criteria; a total of 17 respondents were excluded for these reasons. Participants included physicians, nurse assistants, nurses and community health agents. All providers who were interested in participating and met the eligibility requirements were included. Participation was voluntary.

Instrument

The survey instrument was based upon previous studies analyzing healthcare providers' knowledge, attitudes and practices regarding HPV vaccine implementation [57,74,79,80,82]. It was further adapted to reflect the 2014 Brazilian HPV immunization program and eligibility requirements. The survey design incorporated quantitative and qualitative questions to assess the knowledge and attitudes of Brazilian providers regarding the program. Specific questions addressed the Brazilian constitutional right to health and assessed the opinions of providers as to whether the immunization program's eligibility requirements infringed upon this right. The survey was originally written in English. It was then translated into Portuguese and then back translated by a native Portuguese speaker to ensure consistency.

The survey was first pilot tested among 7 providers from Jardin Mauá, a health clinic in Mauá. Participants were asked to record comments where there was confusion within the questions or directions if applicable. This feedback was collected and compiled. Updates were then incorporated into the instrument. Revisions included rewording or formatting of questions to provide more clarity. After revisions, we commenced study recruitment. The revised, self-administered, paper-based surveys were provided to all participants and surveys took approximately 30-45 minutes to complete.

Procedures

The study was presented to participants as a study with the goal of understanding more about the Brazilian HPV immunization program. Participants were told that participation was voluntary and answers should be knowledge and opinion based. All interested participants received informed consent information verbally, in both English and Portuguese. The lead study investigator spoke a sentence in English, which was then translated into Portuguese by study

staff. Informed consent with study procedures was provided in English and Portuguese in tandem to ensure comprehension. If participants provided oral consent, they were enrolled in the study. This process of introducing the study and providing informed consent was done either individually or in a group.

A written version of the informed consent information was included on the survey instrument and provided to all participants who provided prior oral consent. Participants could retain this version for their personal records. Both oral and written consent was incorporated to ensure all participants were fully informed about the study and participation was entirely voluntary. This was also done to avoid potential employer bias, as participants were initially informed of the study through their administrative supervisors.

All participants were assigned a study identification number, which corresponded with their initials, to be maintained only by study staff. This was implemented to prevent missing data due to lost surveys and ensure participant confidentiality. Participants had the ability to complete the survey immediately or complete it at another time.

Participants were instructed during the introduction to the study that their answers were opinion or knowledge based and they should answer to the best of their ability. If a participant did not know the answer, then they were asked to leave the question blank.

All community health workers were introduced to the study, then received study information and training on study procedures simultaneously at a weekly staff meeting. Those who then provided oral informed consent, received the survey to then be completed immediately. In this situation, study staff were available for questions if needed for clarification purposes only. Study staff were trained and explicitly instructed not to guide participant answers. Surveys were then collected upon completion by study staff. Surveys that were not completed during the

community health worker meeting were collected by the coordinating administrator at each clinic and kept in a locked cabinet until retrieved by study staff on the assigned date, usually one week after drop-off and initial consent.

Data Entry and Management

Signed consent forms were immediately collected after written informed consent was provided and were stored in a secure file folder. All completed surveys were collected from participants or administrators and stored in a second secure file folder to ensure confidentiality for participants. Both file folders were maintained by the lead study investigator to ensure data security.

All data were manually entered during the study period and recorded in a password protected excel document with study identification numbers and survey responses. Questions with "select all" answers were separated into individual response options with yes/no responses. If a participant did not select an option, the response was recorded as "no." Duplicate data entry and verification was conducted to prevent potential data entry discrepancies. Initial data entry was conducted during the study period, May – August 2015 and the second data entry was conducted in January 2016; both were completed by the lead study investigator.

Data Analysis

Frequency analysis was conducted across the three main subject areas: knowledge, attitudes and access. Comparisons focused on variance in responses based on occupation. The main outcome of analysis considered whether or not providers believe the population exclusions and eligibility requirements of the HPV vaccination program limit an individual's right to health. Comprehensive knowledge regarding the HPV vaccine and opinions regarding eligibility were analyzed in comparison to the main outcome of interest related to the right to health. Additional

analysis comparing how providers discuss the HPV vaccine and whether or not patients and parents have sufficient knowledge of the HPV vaccine is also addressed.

Data analysis was conducted using SAS 9.4 software. Missing data was excluded from analysis, which is reflected in variations of sample population (N) in outcome results. Duplicate or illegible responses were also coded as incorrect and excluded from analysis. Three qualitative questions were excluded and will be considered for future analysis.

Limitations

This study includes limitations in terms of both study design and methodology. Clinics were recruited based upon convenience sampling, which limits the scope and generalizability of the study. The instrument was translated and back translated for clarity, but the design and nature of the questions were based upon surveys developed for healthcare providers in upper and middle-income countries with post graduate and specialized education. Participants in our study included all healthcare providers (physicians, nurse assistants, nurses and community health agents), though the majority of participants were community health agents who participate in vocational training but do not have other education requirements [95]. After the study began, we discovered that the community health agents were the healthcare providers who had the most contact with patients and often were the main resource for information for the community. Therefore, it was imperative that the community health agents were included as study participants. As a result, however, the survey instrument reading comprehension level may have been too high for our target audience. In addition, the community health agents were able to complete their surveys in a large room together. Participants were asked not to discuss questions or answers, but this could not be ensured. Finally, if unable to complete the survey immediately, participants had the option to complete the survey at another time. This flexibility introduced the

possibility that participants could research the questions that they could not answer independently.

With these potential limitations, the study may be limited in scope. However, we believe the outcomes that emerged from the data are still valuable and warrant further health policy consideration.

Chapter IV: Results

A total of 171 surveys were completed; 17 were excluded from analysis for a total sample of 154 providers. The participants were primarily female (135 [88%]) and ages ranged from 19 to 69 years old with a mean age of 38 (median: 37, interquartile range (IQR) 30-43) (Table 1). Almost half of the participants were community health agents (76 [49%]); other careers included nursing assistants (36 [23%]), nurses (22 [14%]), and physicians (20 [13%]). One medical resident was coded as a physician for the purposes of analysis. Participants were asked to select all of self-reported areas of expertise, which included family and community medicine (46 [30%]), general practice (9 [6%]), pediatrics (6 [4%]), and obstetrics/gynecology (5 [3%]). Fifty eight participants did not declare an area of expertise; 30 other participants listed expertise outside of these common fields, which included: cardiology, homeopathy, and vaccines. The majority (124 [81%]) of participants had less than 15 years of experience since completing their medical training; 48 individuals (31%) had under 5 years, 76 individuals (49%) had 5-15 years, 11 (7%) had 16-25 years of experience and 6 (4%) had more than 25 years of experience.

Table 1: Demographics of health care providers surveyed about HPV and the HPV vaccine in 8 UBSs of Mauá, Brazil, 2015, n=154

	Mean	**SD**
Age	38	9.9
Missing	0	
	N	**%**
Gender		
Male	19	12.3
Female	135	87.7
Missing	0	
Career		
Physician	20	13.0
Nursing Assistant	36	23.4
Nurse	22	14.3
Community Health Agent	76	49.4
Missing	0	
Area of Expertise		
Pediatrics	6	3.9
Obstetrics/Gynecology	5	3.3
General Practice	9	5.8
Oncology	1	0.7
Family and Community Medicine	46	29.9
Other	30	19.5
Does Not Apply	58	37.7
Missing	12	
Years of Experience		
Under 5 years	48	31.2
5-15 years	76	49.4
16-25 years	11	7.1
More than 25 years	6	3.9
Missing	13	8.4

Provider HPV Knowledge

Medical knowledge of the human papillomavirus (HPV) was assessed through a series of five questions that describe common characteristics of the virus. Correct knowledge was

relatively high among all Mauá health providers (Table 2). A majority (74% or higher) answered correctly to questions that relate to the incidence rates of the virus and population who are at risk for acquiring the virus. However, two key questions of interest that associate cervical cancer with HPV and highlight the peak age of HPV incidence showed gaps in knowledge, signified by either incorrect responses, the response of "I don't know" or missing responses.

Table 2: Clinical Knowledge Assessment of HPV among all participating health care providers in 8 UBSs of Mauá, Brazil, 2015

	Correct n (%)	**Incorrect n (%)**	**Don't Know n (%)**	**Missing n**
HPV is an uncommon sexually transmitted infection. *n=149*	111 (74.5)	33 (22.2)	5 (3.4)	5
Almost all cervical cancers are caused by HPV infection. *n=147*	77 (52.4)	42 (28.6)	28 (19.1)	7
The incidence of HPV in females is highest among those in their 30s. *n=146*	62 (42.5)	66 (45.2)	18 (12.3)	8
Most HPV infections are asymptomatic. *n=149*	115 (77.2)	25 (16.8)	9 (6.0)	5
Who is able to acquire HPV? *n=151*	130 (86.1)	18 (11.9)	3 (2.0)	3

Levels of knowledge varied by profession, with higher levels of knowledge among physicians and nurses and lower levels of knowledge among nursing assistants and community agents (Table 3). Correct knowledge of HPV was assessed through a comprehensive knowledge score of 0-5, which demonstrates the cumulative correctly answered knowledge questions. Knowledge was defined as low if a participant scored between 0 and 1, medium if a participant scored between 2 and 3, and high if a participant scored between 4 and 5. A total of 14 of 154 participants (9.1%) exhibited low knowledge levels; 72 participants (46.7%) had medium knowledge levels; and 68 participants (44.1%) had high knowledge levels. Of the 20 physicians, 9 (45%) correctly answered all knowledge questions (average score: 4.3). A majority of nurses

(11 [50%]), answered 4 knowledge questions correctly (average score: 3.6), while nursing assistants and community health workers answered correctly to an average of 3-4 questions (24 [67%], average score: 3.1 and 47 [62%], average score: 2.9, respectively).

Table 3: Correct Clinical Knowledge Assessment and Comprehensive Knowledge Scores of HPV stratified by health care profession in 8 UBSs of Mauá, Brazil, 2015

	Physician n/N (%)	**Nursing Assistant n/N (%)**	**Nurse n/N (%)**	**Community Health Agent n/N (%)**	**Total n/N (%)**
HPV is an uncommon sexually transmitted infection.	17/20 (85.0)	25/35 (71.4)	16/21 (76.2)	53/73 (35.6)	111/149 (74.5)
Almost all cervical cancers are caused by HPV infection.	19/20 (95.0)	20/35 (57.1)	16/21 (76.2)	22/71 (31.0)	77/147 (52.4)
The incidence of HPV in females is highest among those in their 30s.	9/20 (45.0)	12/33 (36.4)	8/21 (38.1)	33/72 (45.8)	62/146 (42.5)
Most HPV infections are asymptomatic.	20/20 (100.0)	29/35 (82.9)	18/20 (90.0)	48/74 (64.9)	115/149 (77.2)
Who is able to acquire HPV?	20/20 (100.0)	24/35 (68.6)	21/21 (100.0)	65/75 (86.7)	130/151 (86.1)
Comprehensive Knowledge Score (0-6)					
	n=20 n (%)	**n=36 n (%)**	**n=22 n (%)**	**n=76 n (%)**	**n=154 n (%)**
0 Correct	0 (0.0)	2 (5.6)	1 (4.6)	0 (0.0)	3 (2.0)
1 Correct	0 (0.0)	3 (8.3)	0 (0.0)	8 (10.5)	11 (7.1)
2 Correct	1 (5.0)	4 (11.1)	1 (4.6)	17 (22.4)	23 (14.9)
3 Correct	2 (10.0)	12 (33.3)	6 (27.3)	29 (38.2)	49 (31.8)
4 Correct	8 (40.0)	12 (33.3)	11 (50.0)	18 (23.7)	49 (31.8)
5 Correct	9 (45.0)	3 (8.3)	3 (13.6)	4 (5.3)	19 (12.3)

Attitudes toward Eligibility

Providers' attitudes toward the HPV vaccine and eligibility requirements were measured through a series of questions that focus on the vaccination of females over the age of 13 and all males (Table 4). A large majority of participants reported it is medically effective to vaccinate females over the age of 13 (115/150 [77%]), females over the age of 13 should be vaccinated for HPV (126/150 [84%]), and they would vaccinate a female over the age of 13 (123/150 [82%]).

Similar responses were reported for male vaccinations; 103/149 (69%) believed it is medically effective to vaccinate males, 119/148 (80%) reported males should be vaccinated, and 108/148 (73%) would vaccinate a male.

Because the HPV vaccination program was in place for a little more than a year at the point of data collection, providers were asked if they have changed the way they discuss the HPV vaccine since the PNI program implementation in March 2014. A majority of providers (88/145 [61%]) reported a change in their practice. Of those who reported a change, 84% (74/88) included a qualitative response that details how discussions about the vaccine with patients and/or parents have changed and will be examined in future analysis.

Table 4: Attitudes toward the HPV vaccination of high-risk populations among participating health care providers in 8 UBSs of Mauá, Brazil, 2015

	Yes n (%)	**No n (%)**	**Don't Know n (%)**	**Missing n**
Female Vaccination over 13 years old				
Do you think it is medically effective to vaccinate females over the age of 13? n=150	115 (76.7)	20 (13.3)	15 (10.0)	4
Do you think females over the age of 13 should be vaccinated for HPV? n=150	126 (84.0)	13 (8.7)	11 (7.3)	4
Would you vaccinate a female over the age of 13 for HPV? n=150	123 (82.0)	13 (8.7)	14 (9.3)	4
Male Vaccination				
Do you think it is medically effective to vaccinate males? n=149	103 (69.1)	16 (10.7)	30 (20.1)	5
Do you think males should be vaccinated for HPV? n=148	119 (80.4)	11 (7.4)	18 (12.2)	6
Would you vaccinate a male for HPV? n=148	108 (73.0)	20 (13.5)	20 (13.5)	6
Brazilian HPV Vaccine Program				
Attitudes Changed since PNI Implementation n=145	88 (60.7)	48 (33.1)	9 (6.2)	9

Support of the HPV vaccine for females over the age of 13 and males varied by profession (Table 5). Physicians and nurses were almost entirely in support of vaccinating females (17/19 [90%], 20/21 [95%], respectively), while nursing assistants and community health agents were more varied in their responses, though still largely in support (26/35 [74%], 63/75 [84%], respectively). These opinions were also reflected in attitudes toward vaccinating males; physicians and nurses supported male vaccination (18/19 [95%], 20/21 [95%], respectively), while nursing assistants and community health agents varied, though still reported very high support (25/34 [74%], 56/74 [76%], respectively). Despite the overall support of vaccinating females over the age of 13 and males, when the provider was asked to report whether they would administer the vaccine to these target groups, support decreased slightly with the exception of community health workers. This group of providers reported support for vaccinating females over the age of 13 (63/73 [84%]) and showed a slight increase in support of administering the vaccine to this group (67/75 [89%]).

Table 5: Attitudes toward the HPV vaccination of high-risk populations stratified by health care profession in 8 UBSs of Mauá, Brazil, 2015

	Physician n/N (%)	**Nursing Assistant n/N (%)**	**Nurse n/N (%)**	**Community Health Agent n/N (%)**	**Total n/N (%)**
Female Vaccination over 13 years old					
Medically Effective to Receive	17/19 (89.5)	25/35 (71.4)	19/21 (90.5)	54/75 (72.0)	115/150 (74.7)
Should Receive	17/19 (89.5)	26/35 (74.3)	20/21 (95.2)	63/75 (84.0)	126/150 (84.0)
Would Administer	17/19 (89.5)	21/35 (60.0)	18/21 (85.7)	67/75 (89.3)	123/150 (82.0)
Male Vaccination					
Medically Effective to Receive	14/19 (73.7)	22/35 (62.9)	18/21 (85.7)	49/74 (66.2)	103/149 (69.1)
Should Receive	18/19 (94.7)	25/34 (73.5)	20/21 (95.2)	56/74 (75.7)	119/148 (80.4)
Would Administer	17/19 (89.5)	18/34 (52.9)	18/22 (81.8)	55/73 (75.3)	108/148 (73.0)

Right to Health

Attitudes toward a right to health were evaluated through providers' opinions regarding patient access and knowledge (Table 6). Most striking is the near consensus (148 [97%]) that Brazilians have a right to health. Interestingly, the majority of participants reported that Brazilians do not have equal access to health (120 [80%]) and parents and guardians do not have sufficient knowledge about the HPV vaccine (142 [95%] and 144 [95%]). What follows is the belief that the population exclusions of the HPV vaccination program limit an individual's right to health (108 [72%]).

Table 6: Attitudes toward the constitutional 'right to health' and perceived access to the HPV vaccine among participating health care providers in 8 UBSs of Mauá, Brazil, 2015

	Yes n (%)	**No n (%)**	**Don't Know n (%)**	**Missing n**
Do you believe Brazilians have a right to health? n=152	148 (97.4)	4 (2.6)	0 (0)	2
Do you believe all Brazilian citizens have equal access to health? n=150	29 (19.3)	120 (80.0)	1 (0.7)	4
Do you believe the population exclusions of the HPV vaccination program limit an individual's right to health? n=149	108 (72.5)	34 (22.8)	7 (4.7)	5
Do you believe parents or guardians have sufficient knowledge about the HPV vaccine? n=150	6 (4.0)	142 (94.7)	2 (1.3)	4
Do you believe patients, both male and female, have sufficient knowledge about the HPV vaccine? n=152	6 (4.0)	144 (94.7)	2 (1.3)	2

Of providers who reported the population exclusions limit an individual's right to health, a near consensus believed females over the age of 13 and males should receive the HPV vaccine (97 [90%] and 95 [88%]) (Table 7). There is a slight decrease in support of administering the vaccine as opposed to allowing eligibility, especially for male vaccination; while 95 participants (88%) reported that males should receive the vaccine, only 86 (80%) would administer the vaccine. However, again, levels of support remain very high despite this variation.

Table 7: Attitudes and implementation of the constitutional 'right to health' in terms of access to the HPV vaccine among health care providers in Mauá, Brazil who report vaccine eligibility requirements limit an individual's right to health, 2015

	Yes n (%)	**No n (%)**	**Don't Know n (%)**	**Missing n**
Female Vaccination over 13 years old				
Should Receive	97 (89.9)	7 (6.5)	4 (3.7)	0
Would Administer	93 (86.1)	7 (6.5)	8 (7.4)	0
Male Vaccination				
Should Receive	95 (88.0)	2 (1.9)	11 (10.2)	0
Would Administer	86 (80.4)	9 (8.4)	12 (11.2)	1

Overall, there are high levels of knowledge regarding the HPV vaccine among all providers in Mauá, with a few gaps in understanding the connection between the HPV virus, reproductive health and cervical cancer. Support for vaccinating females over the age of 13 and males was high, as well; though this support slightly wanes when providers are asked if they would administer the vaccine to these populations, which could be a reflection of current policy compliance. Finally, there are clear trends in providers' opinions regarding the right to health and health accessibility for all individuals, also reflected is a lack of knowledge regarding the HPV vaccine among both guardians and patients. These results highlight the need for greater accessibility and further education, which will be addressed further in our discussion.

Chapter V: Discussion

This is the first study to consider the Brazilian PNI HPV strategy and implementation from a provider's perspective, through a human rights lens, since the program's implementation in 2014. While the results are specific to the city of Mauá, they offer insights as to what factors influence the sexual and reproductive health care of all males and females over the age of 13, specifically in terms of the human papillomavirus (HPV) vaccine, and may be reflective of larger trends throughout the state of São Paulo and the entire country of Brazil.

We found medium to high levels of clinical knowledge regarding the HPV vaccine, with higher knowledge among physicians than among community health care workers. Low levels of knowledge were reported within questions assessing the connection between cancer and the virus and the population at-risk of acquiring the virus. This reiterates a common theme of knowledge gaps found among providers, which has been shown in previous studies [85,86]. Yet despite the variation in knowledge, a provider's knowledge level does not influence their attitudes toward implementing the vaccine. This is a significant finding in our research, as it suggests motivating factors for universal implementation include: an understanding of the right to health, perceived inequities of access, and an attempt of health advocacy within populations who are excluded. Additional research should be conducted to determine the exact correlation between a provider's attitudes toward the right to health, specifically their role and responsibility in ensuring this right is achieved and maintained, and how this may influence medical practices.

Overall, there is resounding support for vaccinating at-risk populations, such as males and females over the age of 13, which has also been discussed in current literature [74,79,80]. What is of importance, however, is that the PNI policy excludes these populations; despite their ineligibility, providers still support vaccination. A majority of all providers believe vaccinating

males and females over the age of 13 is not only medically effective, but these groups *should* receive the vaccination and these providers *would* vaccinate these groups. Though there is marginally less support for vaccinating males than females over the age of 13. Most notably, providers believe the eligibility requirements that explicitly exclude certain populations do, in fact, restrict an individuals' right to health. However, the issue of justifying the additional costs of vaccinating these groups was not asked of providers and should be a focus of future research, especially if resource allocation to vaccinate these additional populations detracts from other health priorities.

Among our participating providers in Mauá, there is an overwhelming understanding of the right to health for all Brazilians. In practice, however, providers believe that not all individuals have equal access or knowledge of the health services guaranteed to them by the constitution, as seen in prior studies in Brazil assessing patient knowledge of the HPV vaccine [30]. Many providers believe the eligibility requirements infringe upon an individual's rights and as a result, of these providers, a near consensus support providing the vaccine to ineligible populations, suggesting that a provider's interpretation of the constitutional right to health does influence their understanding of the PNI strategy.

Limitations of this research stem largely from the methodology used in study design, as discussed in Chapter III, and data collection. First, the lead study investigator did not speak fluent Portuguese and therefore, it cannot be guaranteed that all information relayed to the participants was unbiased in terms of study objectives. In addition, the community partner used to facilitate clinic recruitment is a prominent member of the medical community within Mauá and may have influenced a clinic's decision to participate. Administrators at each clinic were also often in supervisory positions and as a result, their authority may have influenced an

individual provider's decision to participate. Finally, the study was introduced as a research collaboration between universities in the United States and Brazil, which may lend itself to social desirability bias from participants.

Despite these limitations, this study is among the first to consider the relationship between sexual and reproductive health policies, specifically HPV vaccine eligibility requirements, and the right to health. The results of the study are clear and simple: overwhelmingly, providers reject the population exclusions and support HPV vaccination for both males and females over the age of 13. What this research means for Brazil's PNI strategy, however, is far more complicated.

Policy Recommendations

Not only does Brazil embody an innate right to health in its constitution that serves as the foundation under which its Sistema Único de Saúde (Unified Health System or SUS) was established, but as a signatory on the International Covenant on Economics, Social and Cultural Rights (ICESCR), the country must also uphold this right within the international arena. General Comment 14 of the ICESCR specifies the State must ensure health care systems are *available* and *accessible* to the entire population, specifically in terms of non-discrimination, physical accessibility, affordability, and information accessibility[89]. Health facilities must have cultural *acceptability* and provide high *quality* services [89]. The State also has an obligation to *respect, protect* and *fulfill* this right to health for its citizens, specifically in terms of the "prevention, treatment and control of diseases" [89]. Brazil must *respect* the individual and not interfere with their pursuit of health, protect this right and *prevent* the infringement of this right from outside parties, and actively promote legislation that *fulfills* this obligation of health [89]. It can be argued that through the PNI HPV vaccine exclusion policies, Brazil is not meeting these obligations.

Admittedly, in the midst of an economic recession that has forced Rio de Janeiro to declare a state of emergency, close public hospitals, and cut services and a political scandal that has plagued President Dilma Rousseff with the possibility of impeachment proceedings, it is unrealistic, at this point, to suggest that Brazil's PNI strategy ought to invest more into its program and extend vaccine eligibility [96,97]. SUS is already plagued with inadequate funding and adding to this burden would be irresponsible. However, it is important for Brazil to consider its policies and State obligations; while it may be justifiable to intentionally limit populations from accessing services due to costs and limited capacity, the State has a responsibility through *progressive realization* to consider how these policies can be changed in the future with additional resources and must proactively take steps toward this goal, as there is a clear distinction between a State who is *unable* to comply with its health obligations and one who is *unwilling* to do so [89,98,99]. To address this issue, the following policy changes are suggested.

Finances

Though Brazil has established a Productive Development Partnership (PDP) between the Brazilian Ministry of Health, Butantan Institute in São Paulo and Merck, Sharp & Dohme Corp., to produce the HPV vaccine domestically and lower costs, a large initial investment in the vaccine was first required [17]. This purchase is often too high for low- and middle-income countries and as a result, access to reproductive health care medicines and technologies is often limited. This is largely the result of the pharmaceutical industry's lack of investments in new products to promote competition and consequently lower the price of drugs and the marketing of essential drugs at prices too high to purchase [100]. It is unethical for a Ministry of Health to be forced to make decisions on the health of its population based on the cost of medicine, which is exactly what many countries, including Brazil, have had to do with the costly purchase of the

HPV vaccine. Instead, there must be an initiative by pharmaceutical companies to enable HPV vaccines to be widely available at affordable public sector pricing to ensure universal access [100]. Providing equal access is an integral aspect of safeguarding the right to health and is gravely lacking, according to our results.

With this PDP investment, however, it is anticipated that costs of implementing the PNI HPV strategy will lower, as the vaccine will be produced domestically by 2019. This legal process of technology transfer has been a focus of investment within Brazil over the past few decades with the goal of increasing accessibility and affordability of vaccines for the entire population [101]. The domestic manufacturing of the influenza vaccine is an example of how long term costs can be lowered through a technology transfer, which not only enabled Brazil to produce the influenza vaccine within their own production plant, but can also facilitate preparedness for potential public health outbreaks, like the avian influenza in 2003, and decrease the potential negative health impacts of this type of crisis [102]. Brazil also produces and purchases non-patented and patented antiretroviral therapies (ARTs), respectively; while ART regimens are very different than the HPV vaccine, due to the nature of the virus and potential for drug resistance that can influence the demand and thus the costs of ARTs, the prices for domestic and imported medications have varied. Domestically produced drugs are found to be more expensive than the global generic version, which could be the result of the domestic laboratories manufacturing at a marginal cost and an increase in market demand as a result of changing World Health Organization (WHO) ART guidelines, while patented drugs are negotiated at prices lower than those reported in other low- and middle-income countries [103,104]. How the costs of manufacturing the HPV vaccine in 2019 will differ from the purchasing costs from 2014 and

whether this cost change does or should influence the vaccine eligibility policies are areas for future research.

Knowledge

Once the vaccine is accessible, a concerted effort must take place to increase knowledge within the population about HPV and the possible negative health outcomes related to the virus. Currently, the PNI strategy promotes the message of vaccination directly to females aged 11-13 with the slogan: “Cada menina é de um jeito, mas todas precisam de proteção. Para se proteger do HPV, não perca a vacinaçao” (Each girl has her own way, but all need protection. To protect yourself from HPV, don’t miss the vaccination.). While this targeted, culturally tailored message emphasizes females’ need for protection and encourages them to receive the vaccine, it ignores a large population who also can acquire the virus and culturally, are viewed as disease transmitters: males [29]. With this perspective, it would follow that males should be the target population to receive the HPV vaccine.

But clearly, the PNI HPV strategy cannot merely focus on a male only intervention; instead, the PNI campaign should educate the entire population, males, females, and health care providers, about HPV in gender neutral campaign messages that focus on the association of HPV with cervical, anal, penile and oropharyngeal cancers, and genital warts. For example, in Austria, the Ministry of Health rebranded their HPV vaccine strategy and degenderized the vaccine to focus on “saving lives” and “fighting cancer,” which successfully evoked a public need for vaccination, as opposed to a female only need for vaccination [105]. While it cannot be concluded that an increase in knowledge directly relates to an increase in vaccine uptake, just as a lack of knowledge does not equate to low vaccine uptake, educational campaigns are a necessary but not sufficient factor in vaccination programs. Nevertheless, a gender neutral message that focuses on

cancer prevention, as opposed to protection from a sexually transmitted infection, that targets males, females, and health care providers alike can better communicate the purpose and need for vaccination, which is a knowledge gap found in our study results.

Access

As a middle-income country with a strong universal health care system, Brazil is in the unique position to serve as a model for other countries to implement similar systems and health policies. The initiatives adopted in Brazil early in the HIV/AIDS epidemic that ensured access to ARTs through SUS is an example of a health policy that not only embodied the essence of the right to health, but was also recognized as an exemplary model of how the HIV/AIDS crisis could, and should, be successfully managed [91]. It is for this reason that the legislation the Brazilian Ministry of Health creates for the PNI HPV strategy must embody clear promotion of health rights and equal access, as these policies have larger, global public health impacts.

Currently, vaccine uptake rates are declining in the city of Mauá, the state of São Paulo, and the entire country of Brazil [27]. Though not ideal, low coverage rates can still reduce the prevalence of HPV within populations due to herd immunity and over time, can potentially reduce the rates of HPV associated cancers [37-39]. However, this study argues that vulnerable populations will be missed in the current PNI strategy and additional policies must be in place to enable an individual to make his or her own decision to seek health services, such as the HPV vaccine, through increased education and access, as detailed in General Comment 22 of the ICESCR [106]. Policies that limit this accessibility infringe upon an individual's right to health and decision making power. Therefore, a final policy suggestion is to recommend vaccination and provide access to all males and females over the age of 13 to receive the HPV vaccine through SUS. Through the PDP, costs of the vaccine may be lowered and a larger educational campaign

addressing all possible health outcomes related to HPV will reinforce the need for vaccination among both genders and all ages. Vaccinating this secondary population does not replace the primary, target population of females 9-13; but increasing access, both financially and in terms of knowledge, will enable individuals to make their own health decisions unhindered by restrictive policies, which is an integral aspect of the right to health. These recommendations are based directly on our study results that highlight the current contrast between the PNI HPV strategy that limits access and Brazil's inherent constitutional right to health.

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