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Colonization of Pregnant Women with Group B *Streptococcus* and Perinatal Outcomes in a Latin American Database

By

Elena HogenEsch

Master of Science in Clinical Research

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Colonization of Pregnant Women with Group B *Streptococcus* and Perinatal Outcomes in a Latin American Database

by

Elena HogenEsch
B.S., Emory University, 2014

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An abstract of
a thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
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2020

ABSTRACT

Background: GBS is a primary cause of life-threatening bacterial infections in neonates and is prevented by screening pregnant women for GBS before delivery and intrapartum antibiotic treatment. However, there are limited data regarding national GBS screening practices and the epidemiology of maternal GBS colonization in Latin America.

Methods: We conducted a retrospective observational study using de-identified records of pregnant women from a regional database in five Latin American countries. A total of 444,972 records collected from January 1, 2009 through December 31, 2012 met study criteria and were included. These records were analyzed as follows: a) Maternal screening rates for GBS were determined; b) Association of demographic variables (ethnicity, age, education level, and civil status) with maternal screening for GBS was determined using logistic regression; c) Maternal GBS colonization prevalence was determined by year; d) Association of demographic variables with maternal GBS colonization was determined using logistic regression; e) Relative risk and confidence intervals were calculated to compare the risk of adverse perinatal outcomes among GBS positive versus GBS negative women; f) Binomial logistic regression was performed, adjusting for covariates associated with maternal GBS colonization, to assess if GBS remained independently associated with outcomes.

Results: Maternal GBS screening was less than 15% in each country, except Uruguay which screened greater than 65% of women. The final regression model examining maternal screening rates and demographic variables included the covariates ethnicity, maternal age group, education level and civil status. In Uruguay, GBS prevalence over the study period was 18.5%. Black women, older women and women without a primary education had higher rates of GBS colonization (21.3%, 20.4% and 21.9% respectively). Among Uruguayan women screened for

GBS, maternal GBS colonization was associated with an increased relative risk of preterm birth and chorioamnionitis.

Conclusions: Our study highlights the need for national policy and investments to increase maternal GBS screening and better understand the prevalence of maternal GBS colonization in Latin America. Further research on the burden of neonatal GBS disease within Latin America is needed to inform the introduction of a maternal GBS vaccine, when available.

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INTRODUCTION

Group B *streptococcus* (GBS) infection is a major cause of infant morbidity and mortality with recent estimates of over 300,000 cases of invasive infant disease worldwide(1). Additionally, maternal colonization with GBS may result in adverse birth outcomes such as stillbirth, preterm birth, and miscarriage (2). Early onset neonatal disease (EOD) (0-6 days after birth) is attributed to vertical transmission of the bacteria from a GBS colonized mother to her infant during labor and delivery (3, 4). Intrapartum antibiotic prophylaxis (IAP), in which penicillin is administered to women with GBS colonization during labor, has prevented an estimated 3000 neonatal deaths due to EOD, globally (5). IAP implementation relies on maternal screening for GBS prior to labor, between 35-37 weeks of gestation, through rectovaginal swab and culture or PCR, to identify those with GBS colonization who would benefit from IAP (6). The reduction in EOD-attributable deaths has occurred predominantly in high-income countries, where access to routine prenatal care and reliable laboratories has made implementation of IAP feasible (7). In low and middle income countries, limited access to prenatal care and insufficient laboratory resources have limited implementation of IAP (5). Additionally, research suggests that administration of intravenous IAP during labor may not be safe in resource-poor settings with inadequate access to clean needles and safe sharps disposal methods (2, 5).

Maternal immunization against GBS is an alternative promising approach to reduce the burden of perinatal GBS globally that is currently in development (8, 9). Given previous trends in implementing maternal immunization with tetanus and influenza vaccines, there is a great potential for Latin American countries to be early adopters of an approved maternal GBS vaccine (10). However, within Latin America, little is known about the epidemiology of maternal GBS colonization and GBS-associated perinatal outcomes. Previous data from the region are mostly

from single center studies and are limited by small sample size (4, 11). In order to measure the effectiveness and cost-effectiveness of a maternal vaccine against GBS colonization and to develop future health policies regarding maternal immunization, realistic estimates of the burden of maternal colonization with GBS and neonate GBS disease are needed.

The Pan American Health Organization (PAHO) established the Center for Latin American Perinatology (CLAP) which serves as the largest, multi-country network dedicated to the health of mothers and their infants in Latin America. Perinatal Information System (SIP), developed by CLAP, is a free electronic database initiative to collect individual patient data on maternal and neonatal health from healthcare facilities in participating Latin American countries. Countries that use SIP are able to voluntarily contribute back the collected de-identified data to a SIP regional database (SIP RD). We aim to describe current maternal GBS screening practices, to identify sociodemographic characteristics associated with GBS screening, and identify factors associated with maternal GBS colonization using data collected in SIP RD from 5 countries between the years of 2009-2012. Additionally, we report on the relationship between maternal GBS colonization and adverse maternal, birth and neonatal outcomes.

This evidence is critical to understand the status of GBS screening practices in Latin American countries and to help developing a foundation for future impact trials for candidate maternal GBS vaccines and other interventions to reduce the burden of neonatal GBS.

BACKGROUND

Microbiology and Pathogenesis of GBS. GBS is a beta-hemolytic, encapsulated Gram-positive bacterium with ten known serotypes and is the most common cause of life-threatening invasive bacterial infections during the neonatal period, worldwide (12, 13).GBS is often a normal component of the vaginal microbiome (9). It was first described as a causative agent of puerperal sepsis in the United Kingdom in 1938 (14). Since then, it has been further characterized as an important perinatal pathogen with a spectrum of disease that includes chorioamnionitis, stillbirth, and invasive infant disease, namely sepsis and meningitis (3). Invasive infant disease is divided into two categories, early onset disease (EOD), occurring within 0 – 6 days of birth, and late onset disease (LOD), occurring within 7– 89 days of birth (4, 15).

EOD is believed to be acquired from vertical transmission of a GBS colonized mother to infant. The majority of EOD presents as sepsis (80-83%) with a smaller percentage presenting as pneumonia (10%) or meningitis (7%) (4). In contrast, meningitis is a much more common manifestation of LOD, comprising 43% of LOD cases globally with sepsis accounting for 53% of all LOD cases (4, 15). The mechanism of GBS transmission in LOD is not well defined although there is evidence for mother to child transmission with possible early GBS colonization of the infant gastrointestinal tract leading to subsequent invasive disease after the first week of life (15).

In addition to EOD and LOD, maternal colonization with GBS is associated with stillbirth, defined by the World Health Organization (WHO) as fetal death after 28 weeks of gestation (1, 16). Stillbirth is an important adverse birth outcome that has historically been overlooked in global and national policies due to stigma surrounding the event. Current global estimates of

GBS-attributable stillbirths range from 57,000 to 96,000 cases (16). However, data on GBS-related stillbirths are limited and the WHO has identified further study of this outcome as a priority in developing our understanding of the burden of GBS (2).

Preterm birth, defined by the WHO as live birth before 37 weeks of gestation, is a risk factor for invasive GBS disease. There is also evidence that maternal colonization with GBS may be associated with an increased risk of preterm labor, but the published data are not entirely consistent in this regard (2). A 2009 meta-analysis from the Netherlands that examined 11 cohort studies and five cross-sectional studies, did not show an association between maternal GBS colonization and preterm birth (17). However, only two studies in this review were from Asia and Africa and there were no Latin American countries included. A more recent meta-analysis by Bianchi et al. (2017) which included studies from all regions of the world, indicated that GBS colonization was associated with an increased risk of preterm birth (18).(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18)(18) Further research is needed to assess if maternal colonization with GBS contributes to preterm birth.

Burden of GBS and Known Risk Factors. Estimates of maternal colonization with GBS range from 8-35% of pregnant women worldwide (11, 19). These estimated rates differ by geographic location, with the highest prevalence reported from studies in Africa and the lowest prevalence reported in southeast Asia and the western Pacific (11, 19). There is marked variation within regions and countries as well. For example, in Brazil, prevalence estimates vary from 1% to 40% and in Mexico estimates range from 8% to 14% (19). Over half of infants born to untreated GBS-positive women become colonized and of these colonized infants, 2% develop invasive disease (4, 20).

Perinatal GBS disease is a global problem with an estimated incidence of 319,000 cases, the majority of which are EOD (205,000). Furthermore, invasive GBS disease was attributed to 90,000 infant deaths globally (1, 12). The risk of EOD disease is higher in preterm infants, infants born after prolonged rupture of amniotic membranes, and infants born to mothers with maternal fever during delivery, chorioamnionitis and a history of previous infant with invasive GBS disease (21).

In order to fully understand the epidemiology and burden of neonatal GBS disease in Latin America, maternal risk factors and neonatal outcomes need to be identified. In the United States, Black race is an independent risk factor for both EOD and LOD. However, published data from Brazil suggests that race is not a predictor of GBS disease (22).(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22)(22) Additionally, Rick et al., demonstrated unique risk factors such as advanced maternal age in association with neonatal GBS disease in Guatemala (23).(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23)(23) These findings suggest that the risk factors associated with maternal carriage of GBS and subsequent neonatal disease may vary by region and also by country.

Prevention Strategies. In 2010, the Centers for Disease Control released guidelines to reduce the prevalence of neonatal GBS disease through universal screening of pregnant women at 35-37 weeks of gestation with rectovaginal swab and culture. Maternal carriers of GBS are then treated with intrapartum antibiotic prophylaxis (IAP) to prevent transmission during delivery (24). Sixty countries have adopted GBS IAP guidelines based on maternal culture or screening of maternal risk factors (5). While implementation of IAP has successfully prevented an estimated 3000 neonatal deaths due to early onset GBS disease, it has had little impact on late onset GBS

disease, preterm birth, and stillbirth (2, 5). Furthermore, the reduction in deaths caused by EOD has predominantly occurred in high-income countries, such as the United States, where access to routine prenatal care and reliable laboratories has made implementation of IAP feasible (7). In low and middle-income countries, late or scant prenatal care, increased numbers of home births, and limited access to laboratory resources, has limited the feasibility of IAP. Additionally, research suggests that administration of intravenous IAP during labor may not be safe in resource-poor settings (2, 5). Maternal immunization is an alternative promising approach to reduce the burden of perinatal GBS globally that is currently in development (8, 9).

Latin America and the CLAP Database. Latin America is a diverse region composed primarily of low and middle-income countries that vary widely in their economic, social and demographic compositions (25). Historically, Latin American countries have been early adopters of maternal immunization against diseases such as tetanus and influenza (10). It is likely that countries within the region will be early adopters of an approved GBS vaccine as well. However, little is known about the burden of GBS disease in Latin America. To date, the majority of published data regarding perinatal GBS in Latin America have focused on one or two health centers within a single country (4, 11). In order to measure vaccine efficacy and to inform policy and practice regarding maternal immunization against GBS, we need epidemiological data about the burden of GBS disease and its associated risk factors in Latin America.

Created by the PAHO, CLAP is a large multi-country network dedicated to the health of mothers and their infants. The Perinatal Information System (SIP) developed by CLAP is an electronic system currently used by healthcare professionals in 32 Latin American and Caribbean countries to systematically record demographic and comorbidity data for pregnant women, to monitor these women through the course of their pregnancies, and to monitor both mother and

infant in the postpartum period. The addition of GBS screening at 35-37 weeks to the SIP form in 2009 was driven by the recognition that there was a paucity of data regarding the epidemiology of GBS disease in Latin America. With the addition of data from GBS screening as well as a number of related maternal and neonatal health measures and outcomes, the SIP database is an important resource for understanding the epidemiology of maternal GBS colonization and the burden of GBS disease in Latin America.

METHODS

Aims.

Our first aim was to characterize screening patterns for Group B *Streptococcus* (GBS) in the Perinatal Information System Regional Database (SIP RD) by: a) estimating GBS screening rates in SIP RD dataset and b) determining demographic characteristics associated with maternal GBS screening in SIP RD.

Our second aim was to characterize the epidemiology of GBS in SIP RD by: a) estimating the prevalence of maternal GBS colonization in SIP RD and b) identifying demographic and clinical variables associated with maternal GBS colonization.

Our third aim was to determine if maternal colonization with GBS was associated with adverse pregnancy, neonatal and maternal outcomes. Hypothesis: We hypothesized that GBS colonized pregnant women have a higher incidence of adverse pregnancy, neonatal and maternal outcomes (e.g., sepsis, stillbirth, preterm birth, and chorioamnionitis) compared to uncolonized women.

Study Design.

Our study was a retrospective cohort study using de-identified records collected in SIP RD between January 1, 2009-December 31, 2017.

Study Population.

The study population comprised of all women who received care at a facility that participated in SIP RD from 2009 (the year in which data on GBS screening and status was first included in the database) to 2017 (the last full year of records preceding the beginning of this study).

We first analyzed the number of records per year and per country. Due to significant missing data from 2013-2017, stemming from delays in incorporating the country data into the SIP regional database, we restricted our analyses to 2009-2012.

Records from women who received prenatal care in a health center using SIP and reporting to SIP RD from January 1, 2009 through December 31, 2012 were included in our study.

Records were excluded if a) the pregnancy ended before 35 weeks of gestational age as maternal screening for GBS occurs between 35 and 37 weeks of pregnancy, b) if the record was missing an Estimated Due Date (EDD) or if the EDD was inconsistent with record collection (i.e. prior to 2009 or after 2012) or c) if GBS screening status was missing.

Measures.

Covariate data were collected by healthcare providers during routine prenatal visits using the Prenatal Clinical Record. There were two sets of covariates: demographic and clinical. The *demographic covariates* were defined as follows: *Year of delivery* was derived from Estimated Date of Delivery (EDD); *Maternal age* was categorized into three groups: (1) ≤20 years, (2) 21-34 years of age and (3) ≥ 35 years of age; *Ethnicity* was categorized as White, Indigenous, Black, Mixed, or Other; *Educational level* was categorized into four groups: None, Primary, Secondary, or University; *Civil Status* was defined as common law, married, single, or other.

The *clinical* covariates were defined as follows: *Premature Rupture of Membranes* (PROM) and *Urinary Tract Infection* (UTI) were dichotomized in SIP RD as "yes" or "no". UTI was assessed clinically.

Outcomes of interest were *GBS Screening, GBS Status, Chorioamnionitis, Post-Partum Infection, Preterm birth, Stillbirth, Neonatal Sepsis, Neonatal Meningitis, and Neonatal Pneumonia.* All outcomes were dichotomized "yes" or "no". *Preterm birth* was defined using the

WHO definition as gestational age at delivery less than 37 weeks (26). *Stillbirth* was defined in accordance with WHO guidelines as death during or before delivery (26). Due to the small number of neonatal outcomes, we created a composite outcome, *Neonatal Adverse Outcome* which was denoted as "yes" if a record had neonatal sepsis, meningitis or pneumonia and "no" if it did not.

Sample Size and Power.

From January 1, 2009 – December 31, 2017, a total of 712,061 total records from 12 countries were collected in SIP RD. The largest exclusion category was for records missing an estimated delivery date (128,024 records) followed by records missing data for GBS screening (53,391 records). A total of 444,972 records met our study criteria (Figure 1), providing statistical power to determine if there were differences in GBS screening by demographic characteristics and GBS status.

Analytic Plan.

Sensitivity Analysis. Our analyses were conducted excluding records that lacked data for GBS screening, under the assumption that there was no significant difference between women who had GBS screening denoted as "not done," and women who lacked data for GBS screening. In order to verify this assumption, we ran a sensitivity analysis comparing the GBS unscreened group with a combined GBS unscreened and missing data group on four sociodemographic variables (ethnicity, age, education level, and civil status).

Aim 1 Statistical Analysis. Chi square tests were used to compare four sociodemographic variables: ethnicity, age, education level, and civil status by country. Logistic regression was performed and odds ratios were calculated to examine the effects of four sociodemographic variables on the odds of maternal screening for GBS. The reference variable for each group was

as follows: ethnicity (White), age (≤ 20 years), education (primary), and civil status (Common Law).

Aim 2 Statistical Analysis. Maternal GBS prevalence was calculated by year and by group for each sociodemographic and clinical covariate. For each covariate, prevalence differences were calculated for each group with the reference category. Logistic regression was performed and odds ratios were calculated to examine the association between the four sociodemographic and two clinical covariates with the odds of maternal GBS colonization.

Given that Uruguay had significantly higher rates of screening and differed on important demographic variables (i.e. race and maternal education level) from the other four countries, we first separated our analysis into Uruguay and the other four countries (El Salvador, Honduras, Nicaragua, and Bolivia). Since Uruguay was the only country in our dataset to screen a majority of women, we restricted our analysis of maternal colonization GBS to Uruguay. Maternal GBS prevalence was calculated by year and by group for each sociodemographic and clinical covariate. For each covariate, prevalence differences were calculated for each group relative to the reference category. Logistic regression was performed and odds ratios were calculated to examine the effects of the four sociodemographic and two clinical covariates on the likelihood of maternal GBS colonization.

Aim 3 Statistical Analysis. Chi square tests (restricted to Uruguay) were performed to compare adverse maternal, birth, and neonatal outcomes by maternal GBS status. Relative risk and confidence intervals were calculated to compare the risk of each outcome among GBS positive versus GBS negative women. A log-binomial model was used adjusting for covariates associated with maternal GBS colonization, to assess if maternal GBS colonization remained independently associated with outcomes.

For all analyses, a p value <0.05 was considered significant. All statistical analyses were conducted using SPSS Version 25.0.0.14.

RESULTS

Aim 1.

Sociodemographic Comparisons by Country. The five countries that met our study criteria were Honduras, El Salvador, Nicaragua, Bolivia and Uruguay (see Figure 2). The sociodemographic characteristics of the women in the 5 countries included in the analysis are described in Figure 3. Uruguay had a larger population of white woman compared to the other four countries in the analysis. The three central American countries (El Salvador, Honduras and Nicaragua) had similar ethnic distributions. Uruguay had the largest population of university-educated women and had the smallest population of women with education level "none" (<1%). The majority of women in each country were in a common-law relationship.

GBS Screening Rates per Year. GBS screening rates for each country are presented in Table 1. Uruguay was the only country in our analysis to screen a majority of women and the screening rates in Uruguay increased from 62.8% in 2009 to 67.3% in 2012. No other country in our analysis screened more than 10% of women per year.

GBS Screening Rates and Sociodemographic Characteristics. In both the crude and adjusted analysis, across all countries, non-white women had decreased odds of screening compared to white women and older women had increased odds of screening compared to younger women.

Logistic Regression Excluding Uruguay. Adjusted analysis for El Salvador, Honduras, Nicaragua and Bolivia, indicated that none-educated women were less likely to be screened (see Table 2). The differences in screening between university and primary educated women were not statistically significant. For civil status: married women and women with "other" relationship status were more likely to be screened

Logistic Regression, Uruguay. Among Uruguayan women, Ethnicity, maternal age, education level attained, and civil status were all significantly associated with GBS screening by Chi-Square test at $p<0.05$. All non-white ethnicities had decreased odds of screening in comparison to white women. Older women had increased odds of screening compared to younger women. Women with higher levels of education (secondary and university) had increased odds of screening compared to women with a primary education, while women with education level "none" had decreased odds of screening. For civil status, "married" was associated with increased odds of screening compared to common-law, whereas single and other were associated with decreased odds of screening compared to common-law.

Aim 2.

Maternal GBS Colonization Prevalence. Among Uruguayan women prevalence rates for GBS increased from 17.5% in 2009 to 19.3% in 2012 (Figure 4). Further, GBS prevalence varied with among demographic and clinical characteristics with 21.3% of screened black women having GBS positive status compared to 18.6% of screened white women (Table 3). GBS prevalence also increased with increasing maternal age. For education, women with no education and women with a university education had the highest prevalence of GBS colonization. GBS prevalence did not vary widely between women with and without PROM. However, GBS colonization was much greater among women with a UTI compared to those without (Prevalence difference 4.4%, 95% CI 3.48-5.32).

Logistic Regression of Maternal GBS Colonization by Risk Factor. In the adjusted model, controlling for ethnicity, maternal age, education level, civil status, PROM and UTI the following covariates were significantly associated with maternal GBS colonization ($p<0.05$): Black ethnicity, maternal age group, education level, and presence of UTI. In the multivariate model adjusting for

all other covariates, Black ethnicity, lack of education and UTI had the greatest Odds of GBS positivity (see Table 3). Increasing maternal age was also associated with increased odds of GBS positivity.

Aim 3.

Perinatal Outcomes and Maternal GBS Colonization in Uruguay. From January 1, 2009 – December 31, 2012, there were a total of 142,612 pregnancies reported to SIP RD from Uruguayan healthcare facilities and of those pregnancies, 86,438 were screened for GBS.

Adverse Maternal Outcomes. Of the 86,438 pregnancies included in our study, 94 (0.1%) were complicated by chorioamnionitis and 106 were complicated by postpartum infection (0.2%). GBS positive status conferred a two-fold increased risk of chorioamnionitis (RR 2.02; 95% CI (1.31-3.13), $p<0.001$). Presence of postpartum infection was not associated with GBS status (Table 4).

In a multivariate log-binomial model controlling for the risk factors associated with GBS (ethnicity, maternal age, education level, and presence of UTI) in SIP RD, GBS remained independently associated with chorioamnionitis (adjusted RR 2.11; 95% CI 1.36-3.29).

Adverse Birth Outcomes. 2,323 preterm births (2.7%) occurred in the study population. Maternal GBS colonization conferred a 13% increased risk of preterm birth (RR 1.13; 95% (1.03-1.25, $p< 0.05$). Maternal colonization with GBS conferred a 23% increased risk of stillbirth, however the association between maternal GBS status and stillbirth was not significant by Chi-square analysis ($p=0.375$).

In a multivariate log-binomial model controlling for the risk factors associated with GBS (ethnicity, maternal age, education level, and presence of UTI) in SIP RD, GBS remained independently associated with preterm birth (adjusted RR 1.13; 95% CI 1.01-1.25).

Adverse Neonatal Outcomes. There were 13 cases of neonatal sepsis (0.02%), 1 case of meningitis (0.00%) and 12 of pneumonia (0.01%). One infant had both neonatal sepsis and meningitis for a total of 25 unique cases of adverse neonatal outcomes. Maternal GBS positive status was not associated with increased risk of adverse neonatal outcome (see table 2).

Sensitivity Analysis. There were no significant differences between the GBS unscreened group and the combined GBS unscreened and missing data group on any of the sociodemographic variables ((ethnicity, age, education level, and civil status).

DISCUSSION

We found that with the exception of Uruguay, no other Latin American country that contributes to SIP RD and contributed 30,000 over the 2009-2012 time period, screened more than 10% of pregnant women for GBS. This is consistent with previously published reports of GBS screening policies, as to our knowledge, Uruguay is the only country in our analysis with a national GBS screening policy (5). Compared to the other countries included in the analysis, which are middle and lower middle-income countries, Uruguay is a high-income country and has a well-supported national health system (27). Additionally, Uruguay has a predominantly white population as represented in the SIP data where 99.4% of Uruguayan women were white (28). The low rates of screening region-wide suggest increased risk to maternal and fetal health associated with untreated GBS.

Our analyses indicate that there are region-wide disparities of screening based on ethnicity, education and maternal age. These trends were present in Uruguay as well, with university educated, older, and white women more likely to be screened than women with a primary or secondary education, younger and non-white women. Studies in other developed countries, such as the US, also show similar disparities in GBS screening (29). As described under results, we found that despite low representation among the women screened for GBS, Black women and women with education level "none" had higher than average rates of GBS colonization. These patterns suggest that the true regional GBS burden is higher than indicated in the current sample. Our findings highlight that even in countries with national GBS screening policies and high rates of GBS screening, concerted efforts are needed to address socioeconomic barriers that contribute to disparities in screening.

Our findings that Black and low-income women have less access to GBS screening itself, also suggest that these demographic groups may have limited access to implementation of IAP, especially in low-income and middle-income Latin American countries. Studies from both high-income and low-income countries, such as the US, the UK and South Africa, have demonstrated that a maternal GBS vaccine could be a cost-effective solution for reducing the GBS burden and the associated risks to maternal and fetal health, as it would eliminate the need for screening and IAP implementation during pregnancy (30-32).

We can only draw conclusions about the prevalence of maternal GBS colonization and associated perinatal outcomes from Uruguay, due to the limited data from other countries in our analysis. In our study, GBS colonization affected 18.5% of Uruguayan pregnancies, with women who were university-educated, married, and older than 35 years, over-represented among the GBS positive population. Adverse outcomes associated with maternal GBS colonization were chorioamnionitis and preterm birth.

Our data support maternal GBS colonization as a risk factor for chorioamnionitis, an adverse outcome that has implications not only for the mother, but also for the neonate. Maternal infections, such as chorioamnionitis, have been shown to contribute to preterm birth, neonatal sepsis and other adverse neonatal outcomes (33). Interestingly, despite the association between maternal GBS colonization and chorioamnionitis, we did not detect an association between maternal GBS and post-partum infection. This may be due in part to timely and appropriate dosing of antibiotics to women with intrapartum infection and fever during delivery.

Known risk factors for chorioamnionitis include prolonged membrane rupture, prolonged labor, multiple digital examinations, and use of internal uterine pressure monitors (34). Unfortunately, this information was not available in our dataset. It is possible that women with

GBS were more likely to experience these risk factors. Future studies examining the impact of these established risk factors for chorioamnionitis on the relationship between maternal GBS colonization and chorioamnionitis are needed.

In our study, maternal GBS colonization was associated with increased risk of preterm birth. This association held in our multivariate analysis adjusting for risk factors associated with maternal GBS colonization. Risk factors for preterm birth such as Black ethnicity and advanced maternal age (age ≥ 35 years) have been shown to be associated with maternal GBS colonization, making the relationship between maternal GBS colonization and preterm birth difficult to interpret in studies that did not control for confounding (23, 35). Our findings demonstrate that within our study population, maternal GBS colonization is an independent risk factor for preterm birth. Our findings are consistent with a recent meta-analysis of global data of an increased risk of preterm birth among GBS colonized pregnant women (18). There is a biological plausibility for such an association as demonstrated studies in mouse models demonstrating the ability of GBS to produce extracellular membrane vesicles containing virulence factors and proteases that may breakdown the placental membrane, resulting in preterm birth (36).

Despite the fact that our maternal GBS screening data was limited to 35 to 37 weeks, our study findings show that maternal GBS colonization is a risk factor for preterm birth in our population. Given our findings, it is possible that maternal GBS colonization also contributes to preterm birth before 35 weeks in our population. In order to better elucidate the impact of maternal GBS colonization on preterm birth, prospective cohort studies are needed in which women are screened for GBS at earlier and routine intervals of pregnancy. This data is essential to the assessment of the cost-effectiveness of an approved maternal GBS vaccine. Such a vaccine

would likely be administered in the second or third trimester and has the potential to reduce the burden of GBS-associated preterm birth before 35 weeks.

Maternal GBS colonization was associated with a 23% increased risk of stillbirth, however, that association was not significant. It is possible that given the small number of stillbirths in our population (n=110) and the limitation of our analysis to pregnancies that survived to 35 weeks, our study was underpowered to detect a significant association between the outcome and maternal GBS colonization. Two previously published reviews have estimated that GBS is responsible for 1% to 12% of global stillbirths (18, 37). However, neither review included data from Latin American countries. Examining stillbirths has been historically difficult due to varying case definitions and persistent stigma surrounding stillbirth that has limited reporting (38). Similar to preterm birth, prospective studies in which women are screened for GBS at early and routine intervals in pregnancy are needed to better characterize the potential impact of maternal GBS colonization on stillbirth.

Despite our large sample size (N=86,438), the comparatively low incidence of adverse neonatal outcomes limits our ability to draw conclusions about the relationship between maternal GBS status and adverse neonatal outcomes. Additionally, our database lacked information regarding the pathogen identified in the neonatal outcomes of sepsis, meningitis and pneumonia which further limited our ability to draw meaningful conclusions about the relationship between maternal GBS status and neonatal outcomes.

Our study was limited by missing data with 10.2% (53,391) of records from the 5 countries included in this analysis missing data for GBS screening. In our study, inconsistent data reporting to SIP RD over the study period from certain countries such as Argentina, Honduras, and Bolivia restricted our analysis and limits the generalizability of these results to

other Latin American countries. Additionally, due to limited resources, only a limited number of records were incorporated into SIP RD following 2012 and it is possible that more recent data will reflect a change in maternal GBS screening practices. Given these limitations, prospective studies that include a wider representation of countries in Latin America are needed to better understand national and regional trends in maternal GBS screening.

In addition to prospective studies, national and regional investments in health data systems are needed to further our understanding of the gaps in routine antenatal care in Latin America. Similar to our findings, previous research has documented socioeconomic disparities in maternal access to health care including preventative care resulting in disparities in adverse maternal and neonatal outcomes (39, 40). The WHO 2016 World Health Statistics has identified a lack of data for health indicators as an important challenge to reducing maternal and child mortality (41). Further, the WHO advocates for significant investments to improve country health information systems and increase the availability of disaggregated statistics for health indicators (42).

In Latin America, a region with high rates of prenatal care and hospital births, there is great potential to utilize health information systems and technology to capture epidemiologic data related to maternal immunization and prenatal practices (43). In 2016, a new version of SIP, SIP-PLUS was made available to participating countries and facilities. SIP-PLUS has been updated to include information on vaccines currently recommended before, during and after pregnancy. Many countries in Latin America have expressed to PAHO their interest in contributing data from SIP-PLUS to the SIP RD. SIP-PLUS represents a promising new platform to evaluate the effectiveness of an approved GBS vaccine as well as the success of targeted policies to improve maternal GBS screening rates.

CONCLUSIONS

Our study demonstrated sociodemographic disparities in GBS screening rates among Latin American countries. These results highlight the importance of the existence of a national policy for GBS screening in order to increase rates of maternal GBS screening. Investments by Latin American countries are needed in order to increase GBS screening rates and develop a more complete understanding of the prevalence of maternal GBS colonization in the region that can inform the development and introduction of an approved maternal GBS vaccine. In Uruguayan pregnant women screened for GBS between 35 and 37 weeks of gestation, GBS was associated with an increased risk of chorioamnionitis and preterm birth. While maternal screening and IAP has been shown to successfully reduce EOD GBS disease in infants, it does not prevent preterm birth. Maternal immunization is a promising alternative approach that could reduce the burden of GBS-associated preterm births.

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TABLES

Table 1. Annual GBS screening rates in pregnant women in 5 countries in SIP RD: 2009-2012

	2009	2010	2011	2012
Country	N (% Screened)	N (% Screened)	N (% Screened)	N (% Screened)
El Salvador	42,008 (0.9)	44,245 (0.5)	35,256 (1.3)	55 (1.8)
Honduras	2,881 (3.8)	23,572 (2.7)	37,555 (2.4)	35,417 (1.9)
Nicaragua	8,227 (1.2)	15,281 (0.5)	21,720 (0.9)	22,216 (0.8)
Bolivia	4,520 (3.7)	7,415 (1.9)	10,074 (2.1)	2,914 (10.0)
Uruguay	30,430 (62.8)	34,986 (65.0)	35,694 (67.4)	30,506 (67.3)

Table 2. Association of demographic characteristics with GBS screening in pregnant women in SIP RD: 2009-2012

Logistic regression, *excluding* Uruguay (N=313,356)						
Covariate	Missing data n (%)	% GBS Screened	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Ethnicity	3,060 (1.0)					
White		4.10	ref	ref	ref	ref
Indigenous		1.20	0.29	(0.20-0.43)	0.3	(0.20-0.44)
Mixed		1.40	0.33	(0.25-0.43)	0.33	(0.25-0.44)
Black		2.20	0.52	(0.28-0.97)	0.47	(0.24-0.90)
Other		3.70	0.91	(0.69-1.21)	0.93	(0.69-1.24)
Maternal Age	550 (0.2)					
≤ 20 y.o.		1.40	ref	ref		
21-34 y.o.		1.60	1.11	(1.04-1.19)	1.09	(1.02-1.17)
≥ 35 y.o.		1.70	1.21	(1.08-1.35)	1.18	(1.05-1.33)
Education Level	5,595 (1.8)					
Primary		1.50	ref	ref		
None		1.20	0.79	(0.69-0.92)	0.79	(0.68-0.92)
Secondary		1.50	1.01	(0.95-1.08)	0.95	(0.89-1.01)
University		1.70	1.14	(1.03-1.27)	0.97	(0.87-1.08)
Civil Status	5,287 (1.7)					
Common Law		1.40	ref	ref		
Married		1.70	1.22	(1.13-1.31)	1.14	(1.06-1.24)
Single		1.60	1.12	(1.02-1.24)	1.05	(0.95-1.16)
Other		2.60	1.85	(1.09-3.15)	1.80	(1.06-3.07)
Logistic regression, Uruguay (N=444,972)						
Covariate	Missing data n (%)	% GBS Screened	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Ethnicity	1,167 (0.9)					
White		67.2	ref	ref	ref	ref
Indigenous		50.9	0.51	(0.42-0.61)	0.57	(0.48-0.70)
Mixed		35.6	0.27	(0.25-0.29)	0.37	(0.35-0.39)
Black		38.6	0.31	(0.28-0.34)	0.41	(0.36-0.45)
Other		57.6	0.66	(0.49-0.90)	0.79	(0.56-1.10)
Maternal Age	230 (0.2)					
≤ 20 y.o.		55.1	ref	ref	ref	ref
21-34 y.o.		68.4	1.76	(1.72-1.81)	1.32	(1.28-1.36)
≥ 35 y.o.		69.9	1.89	(1.82-1.97)	1.25	(1.20-1.31)
Education Level	1,617 (1.2)					

Primary		46.3	ref	ref	ref	ref
None		48.9	1.11	(0.89-1.39)	1.08	(0.85-1.37)
Secondary		66.9	2.34	(2.28-2.41)	2.2	(2.13-2.26)
University		85.9	7.06	(6.76-7.38)	5.3	(5.05-5.56)
Civil Status	3,113 (2.4)					
Common Law		64	ref	ref	ref	ref
Married		75.7	1.75	(1.70-1.80)	1.28	(1.24-1.32)
Single		55.3	0.7	(0.68-0.72)	0.81	(0.78-0.83)
Other		54.6	0.67	(0.60-0.76)	0.67	(0.59-0.75)

Table 3. Association of sociodemographic and clinical characteristics with GBS positive status among Uruguayan pregnant women in SIP RD (N=86,438)

Covariate	Missing data n (%)	% GBS Positive	Prevalence Difference	(95% CI)	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Ethnicity	680 (0.8)							
White		18.6%	ref	ref	ref	ref	ref	ref
Indigenous		17.3%	1.3%	(-3.65 to 6.24)	0.92	(0.65 to 1.29)	0.98	(0.67 to 1.44)
Mixed		16.8%	1.8%	(-0.04 to 3.64)	0.89	(0.78 to 1.01)	0.95	(0.82 to 1.10)
Black		21.3%	-2.7%	(-6.16 to 0.76)	1.19	(0.96 to 1.46)	1.31	(1.04 to 1.65)
Other		12.6%	6.0%	(-2.86 to -1.54)	0.64	(0.35 to 1.16)	0.75	(0.39 to 1.41)
Maternal Age	152 (0.2)							
≤ 20 y.o.		16.5%	ref	ref	ref	ref	ref	ref
21-34 y.o.		18.7%	-2.2%	(-2.86 to -1.54)	1.17	(1.12 to 1.22)	1.11	(1.05 to 1.17)
≥ 35 y.o.		20.4%	-3.9%	(-5.00 to -3.20)	1.30	(1.23 to 1.38)	1.19	(1.11 to 1.28)
Education Level	991 (1.1)							
Primary		16.3%	ref	ref	ref	ref	ref	ref
None		21.9%	-5.6%	(-12.23 to 1.03)	1.44	(0.97 to 2.12)	1.62	(1.06 to 2.47)
Secondary		18.4%	-2.1%	(-2.82 to -1.39)	1.15	(1.10 to 1.22)	1.11	(1.04 to 1.17)
University		20.5%	-4.2%	(-5.05 to -3.35)	1.32	(1.25 to 1.40)	1.17	(1.09 to 1.25)
Civil Status	1,807 (2.1)							
Common Law		18.2%	ref	ref	ref	ref	ref	ref
Married		20.0%	-1.8%	(-2.39 to -1.21)	1.13	(1.08 to 1.17)	1.06	(1.02 to 1.11)
Single		16.1%	2.1%	(1.16 to 3.04)	0.86	(0.82 to 0.91)	0.89	(0.84 to 0.94)
Other		16.9%	1.3%	(-1.67 to 4.27)	0.91	(0.74 to 1.12)	0.85	(0.68 to 1.07)
PROM	10,448 (12.1)							
No		18.0%	ref	ref	ref	ref	ref	ref
Yes		19.2%	-1.2%	(-2.05 to -0.31)	1.08	(1.02 to 1.14)	1.05	(0.99 to 1.12)
UTI	10,141 (11.7)							
No		17.7%	ref	ref	ref	ref	ref	ref
Yes		22.1%	-4.4%	(-5.32 to -3.48)	1.32	(1.25 to 1.40)	1.33	(1.26 to 1.41)

Table 4. Relative risk (RR) of adverse pregnancy outcomes by maternal GBS status

	Chorioamnionitis*		
	Yes	No	Total
GBS Positive	29	13616	13645
GBS Negative	65	61728	61793
			RR 2.020; 95% CI (1.305-3.129)
	Post Partum Infection		
	Yes	No	Total
GBS Positive	15	12283	12298
GBS Negative	91	56404	56495
			RR 0.757; 95% CI (0.439-1.307)
	Preterm birth*		
	Yes	No	Total
GBS Positive	476	15543	16019
GBS Negative	1847	68572	70419
			RR 1.133; 95% (1.026-1.251)
	Stillbirth		
	Yes	No	Total
GBS Positive	24	15956	15980
GBS Negative	86	70149	70235
			RR 1.227; 95% CI (0.780-1.928)
	Adverse Neonatal Outcome		
	Yes	No	Total
GBS Positive	5	16014	16019
GBS Negative	20	70399	70419
			RR 1.099; 95% CI (0.413-2.928)
			*p<0.05

FIGURES

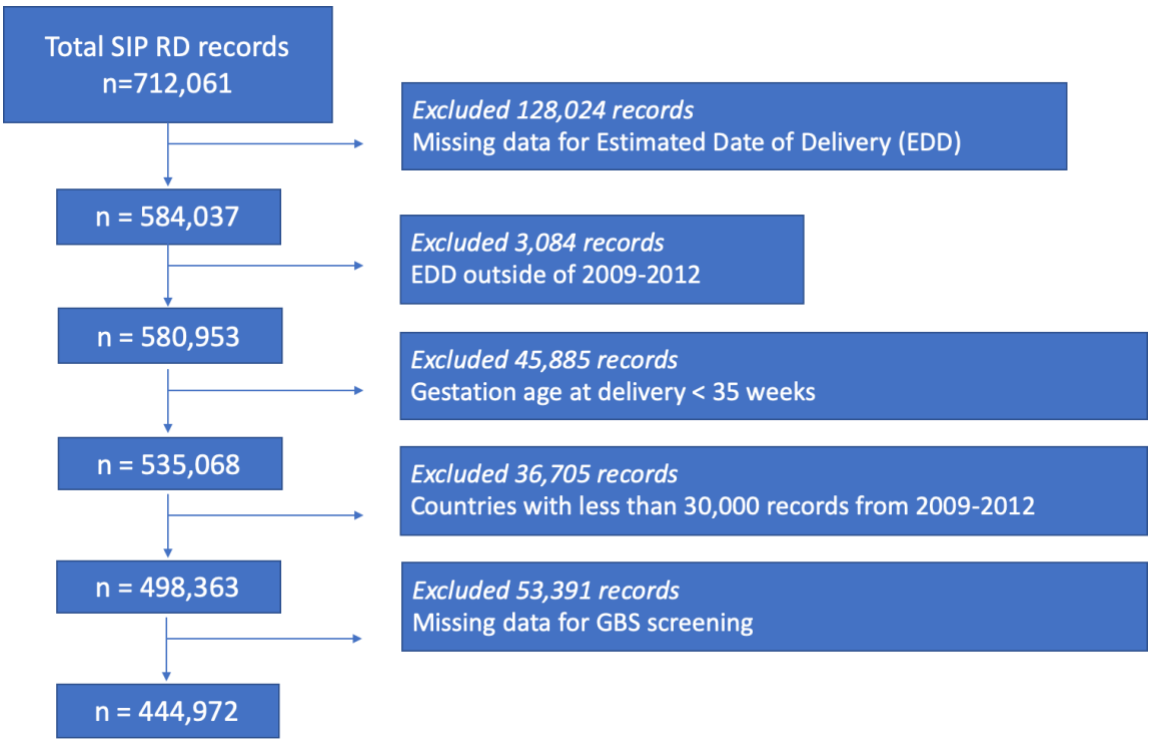

Figure 1. Flow-diagram of study selection criteria identifying eligible records from SIP RD

Figure 2. Map demonstrating SIP RD countries that met study criteria.

*Countries in grey did not participate in SIP RD.

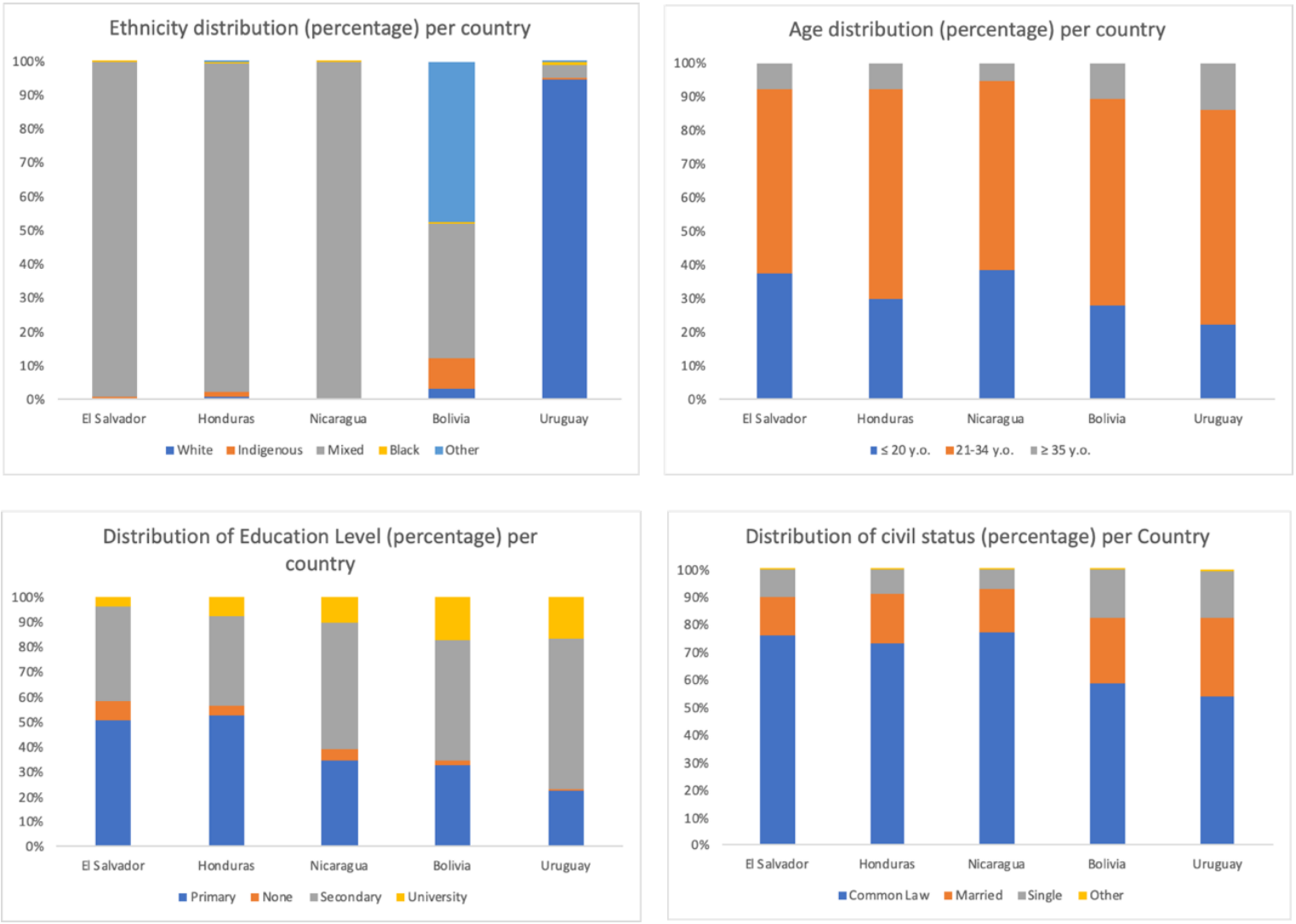

Figure 3. Distribution of four sociodemographic variables by country.

*Chi-square tests showed a significant association between each sociodemographic variable and country ($p<0.05$)

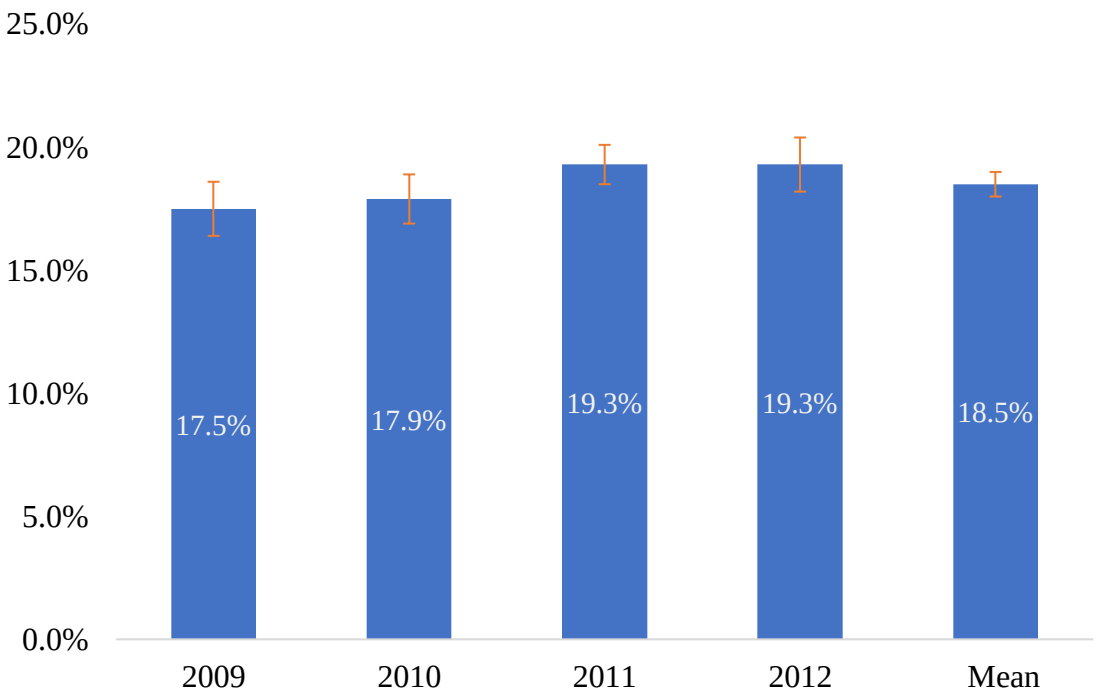

Figure 4. GBS colonization per year among Uruguayan pregnant women in SIP RD