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Lisa Marie Mac Date

BARRIERS TO TIMELY COMPLETION OF ROTAVIRUS IMMUNIZATION SERIES IN EL ALTO, BOLIVIA

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BARRIERS TO TIMELY COMPLETION OF ROTAVIRUS IMMUNIZATION SERIES IN EL ALTO, BOLIVIA

By

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2011

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

BARRIERS TO TIMELY COMPLETION OF ROTAVIRUS IMMUNIZATION SERIES IN EL ALTO, BOLIVIA

By Lisa Marie Mac

Purpose: Rotavirus is a common cause of severe and fatal diarrhea in children under five, with 95% of deaths occurring in developing countries. Bolivia, a developing country in South America, introduced the rotavirus vaccine, Rotarix, in 2008. It has been demonstrated that adherence to vaccination timelines in middle and low income countries is low, thus hindering true disease protection. There is a need to assess adherence to the rotavirus immunization timeline, as 15% of deaths in Bolivian children under five are caused by diarrheal disease.

Goal: To evaluate the timing of the Rotarix vaccine series, and possible barriers/incentives to receiving the vaccine within the recommended timeframe, among infants in El Alto, Bolivia.

Methods: Caregivers with infants $\geq$ 8 months or a completed Rotarix series were recruited from the Los Andes and Corea hospitals. They completed a questionnaire inquiring about demographics, rotavirus vaccine knowledge, and beliefs regarding rotavirus vaccine safety and importance. Infant birthdate and immunization dates were collected from each infant's vaccination card. A multivariable logistic regression model was used to analyze the effect of variables on timely completion of two vaccine schedules.

Results: Approximately 61% of infants received their first dose within 8-9 weeks since birth and 66% received their second dose within 17-18 weeks since birth. Over 97% of infants were vaccinated according to the Bolivian MOH rotavirus immunization timeline, while only 51% adhered to the 2, 4-month clinician recommended timeline. Barriers could not be assessed for the MOH timeline because of its timely receipt, however knowing other vaccinated infants and believing the rotavirus vaccine was safe were statistically significant ($p<0.05$) for the clinician recommended timeline.

Conclusion: Caregivers exhibited a high level of adherence to the MOH immunization timeline, possibly due to simultaneous vaccination and immunization-only services within comprehensive care hospitals. Adherence to the clinician recommended timeline was poor, however, possibly due to personal, non-structural issues between caregivers and providers. Better communication and education regarding the specified 2, 4 month schedule is needed. If caregivers continue having difficulty complying with the clinician recommended schedule, infants will continue to be at risk, despite adherence to the MOH timeline.

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I. Diarrheal Disease

Global Burden of Diarrheal Disease

The burden of diarrheal disease is evident with approximately 1.7 billion cases occurring each year.(Reviewed in (1)) Diarrhea, as defined by The World Health Organization (WHO), is the passage of three or more loose or liquid stools per day.(1) The short term effects of diarrheal disease can often weaken a person by causing dehydration and exasperate any underlying nutritional deficiency, while long term effects could include diminished cognitive ability and possible contribution to chronic health issues.(2, 3) Consequently, diarrheal disease is the second leading cause of death among children under 5 years of age, causing the death of approximately 760,000 children every year.(Reviewed in (1)) In addition to the direct effects of diarrheal disease on the child, healthcare systems, especially in developing countries, also experience the burden of this disease through clinic visits and hospitalizations.(4, 5) A study conducted in Haiti during a cholera epidemic demonstrated this effect by documenting that more than 33% of its hospitalizations from 2010-2012 were diarrheal disease related.(6) Furthermore, Brazil has also been experienced this burden on their healthcare system, with 62.2% of all hospitalizations in children aged 1-4 years old from 2000-2010 being gastroenteritis-related.(7) It is clear that the impact of diarrheal disease is felt worldwide and further exploration of the patients who experience this disease has revealed key pathogens responsible for its devastation.

Implications of Rotavirus Infection

Diarrheal disease is recognized by the symptom of diarrhea, which results from an infection with bacterial, viral, or parasitic organisms.(1) Although a multitude of organisms can invade the host and cause diarrhea, rotavirus is one of the most commonly found etiologic agents in patients with diarrhea in developing countries.(Reviewed in (1)) In many studies fecal samples are used to identify the enteropathogens culpable for causing the patient's diarrhea. The Global Enteric Multicenter Study is a three year matched case control study conducted in four sites in Africa and three sites in Asia, which determined that rotavirus was one of four pathogens in the most attributable cases of moderate to severe diarrhea in children under 5 years old.(8) Laboratory data was also collected for children under 5 years of age in rural Kenya's district hospital and two outpatient facilities. The authors detected rotavirus in 27% of the stool specimens in the hospital and 20% in the outpatient facilities.(9) Furthermore, surveillance data from 2009-2001 in Argentina reported that rotavirus was responsible for 40% of all acute diarrheal hospitalizations for children under 5 years of age.(10) According to WHO, based on their hospital sentinel surveillance sites, 40% of global hospitalizations for diarrhea in children under 5 years old are a result of rotavirus infection. The burden of rotavirus infection extends beyond hospitalizations and clinical visits as it is estimated to cause 527,000 deaths annually, or 29% of all deaths related to diarrheal disease in children under 5 years of age.(11) Overall, rotavirus infection is a major contributor to the global morbidity and mortality of diarrheal disease. Developing countries often suffer a greater morbidity and mortality due to rotavirus even when a preventive method like a vaccine has been developed.

II. Diarrheal Disease Intervention

Rotavirus Vaccine

With recognition of the diarrheal disease burden worldwide and rotavirus as a common etiologic agent, vaccines against rotavirus infection were developed. The rotavirus vaccine history dates back to 1998 with the development of Rotashield. Although significant safety issues surrounding the risk of intussusceptions resulted in its withdraw from the market in the subsequent year, new vaccines, Rotateq and Rotarix, developed in 2006 proved safe and effective.(12) This summary of rotavirus vaccine will focus on Rotarix, as it is the monovalent vaccine currently used for rotavirus immunizations in Bolivia.

Global Rotavirus Vaccine Efficacy

Rotarix is a live, oral vaccine that follows a two dose regimen. The U.S. Food and Drug administration prescribing information states that each dose is 1mL and can be safely administered at 6 weeks of age for the first dose and prior to 24 weeks of age for the second dose, allowing at least 4 weeks in between doses.(13) However, Rotarix is typically given simultaneously with other vaccines on a set schedule of 2 and 4 months of age. Countries, other than the U.S., such as Bolivia, may have slightly expanded timelines since each respective government decides on the national vaccine schedule appropriate for the epidemiology of their country. Clinical studies for efficacy were conducted in both Europe and Latin America through two rotavirus seasons. In Europe, the efficacy of Rotarix through two rotavirus seasons against all severity of gastroenteritis was 78.9%. (Reviewed in (13)) Higher efficacy, 90.4%, was experienced against severe

gastroenteritis through two rotavirus seasons.(Reviewed in (13)) Additionally, this study showed that the efficacy in reducing hospitalizations for rotavirus gastroenteritis was 96.0%. (Reviewed in (13)) The clinical trials performed in Latin America reported lower efficacy. The efficacy of Rotarix on severe rotavirus gastroenteritis through two seasons of rotavirus was 80.5%.(Reviewed in(13)) Similarly, the efficacy for reducing hospitalizations was 83%. Although specific details on rotavirus types will not be discussed, efficacy against specific rotavirus types in Latin America was explored and found to be statistically significant.(Reviewed in (13)) Clinical trials were also conducted in the African region, albeit considerably low efficacy was found compared to the other countries. The efficacy in a cohort of Malawian children was 49.4% in the first year of life and 17.6 % in the second year of life, while the efficacy in South Africa children was 76.9%.(14, 15) These clinical trials performed by the Rotarix vaccine manufacturers demonstrate favorable efficacy against rotavirus in Europe and moderate efficacy in Latin America. In contrast, controlled clinical trials in South Africa and Malawi have demonstrated much lower vaccine efficacy for unknown reasons, despite the vaccine's ability to significantly reduce the cases of severe gastroenteritis in the child's first year of life.(15)

Global Rotavirus Vaccine Effectiveness

Since vaccine efficacy is tested in controlled clinical trials, it is important to mention the results of effectiveness studies as well. A case-control study conducted in the United States examined the effectiveness of the monovalent Rotarix vaccine in children receiving care in three hospitals in Georgia and two hospitals in Connecticut in (January

through June) 2010 and 2011.(16) Overall, the authors found the monovalent vaccine to be 91% effective against rotavirus gastroenteritis among children 8 months of age or older.(16) Another case-control study, conducted in a teaching hospital in Recife, Brazil demonstrated encouraging effectiveness results for an impoverished setting.(17) The authors found that the monovalent rotavirus vaccine was 77-85% effective against severe rotavirus diarrhea during the first year of life.(17) An additional effectiveness study conducted in Colombia from August to October 2010 used a cross sectional population survey.(18) The estimated effectiveness in preventing hospitalization for severe diarrhea was 68%.(18) Although, the case-control studies most likely offer more reliable estimates than the cross sectional study approximation, the level of Rotarix effectiveness, in addition to its efficacy, is important for understanding the its ability to prevent rotavirus infection. Furthermore, to achieve this effectiveness, infants must receive their rotavirus vaccine doses in accordance with national schedules and clinician recommendations.

III. Adherence to Vaccine Schedules

Adherence to Rotarix Vaccine Schedule

The Rotarix two dose schedule was specifically designed to adequately protect infants from rotavirus illness during the age when they are most vulnerable and prior to initial exposure.(13, 19) There is limited information on adherence to the Rotarix schedule and it appears that the U.S. is the only country where this topic has been formally studied. The first U.S. study looked at a commercially insured population and found that only 85% of patients completed the monovalent rotavirus vaccine schedule and only 69% completed it on schedule (previously mentioned Rotarix FDA approved

schedule used).(20) The authors concluded that despite the effectiveness of the rotavirus vaccine, it is currently being underutilized. The second U.S. study identified children aged less than 1 year with an initiated rotavirus vaccine series between January and June of 2009.(21) The authors results were that 91% of the cohort completed the monovalent rotavirus vaccination and 75% of that cohort completed the vaccination according to the FDA approved administration schedule previously mentioned.(21) These results can be considered in the context of the efficacy studies estimated for high, middle, and low SES countries. It may be important to note that these adherence studies were conducted in a high SES country (U.S.) and lower adherence to rotavirus timelines may exist in middle and low SES countries.

Adherence to Pediatric Vaccine Schedules Globally

The introduction of rotavirus vaccine is still fairly recent for countries in South America. Adherence information for countries like Nicaragua, Bolivia, and Honduras, which had some of the earliest rotavirus vaccine introductions in 2006, 2008, and 2009 respectively, is still non-existent.(22) In order to gain a better perspective on possible rotavirus vaccine timeline adherence in lower SES countries, timeliness studies conducted in developing countries on other pediatric vaccines were explored. The first study analyzed vaccination cards from demographic and health surveys in 45 low and middle income countries between 1996 and 2005. The study results indicated that the median delays in the 45 countries was 2.3 weeks for BCG; 2.4 weeks for DTP1; 2.7 weeks for MCV1; and 6.2 weeks for DTP3.(23) These delays increased dramatically when looking at the 12 countries with the longest delays, which included being up to 19

weeks late for DTP3.(23) The authors also addressed rotavirus vaccination delays in their discussion, stating that it is currently scheduled with DTP, but that the adherence is not promising as most of the countries in the study had 30% of their children receiving the DTP vaccination past the WHO recommended age group for rotavirus immunization. The poor adherence to vaccination timelines are further examined in another study, which explored the timeliness of childhood vaccination in 31 low and middle income countries between 2005 and 2007 using multiple indicator cluster surveys.(24) The median delays across all countries was 2.1 weeks for BCG, 2.4 weeks for DTP1; 6.3 weeks for DTP3; 2.0 weeks for polio1, 6.6 weeks for polio3 and 4.1 weeks for MCV.(24) The authors concluded that although high vaccination coverage was seen, significant vaccination delays were present and a more accurate representation of coverage could be depicted with more surveillance of vaccination timeliness.(24) Although limited studies on rotavirus vaccine adherence exist for the United States and only general immunization timeline adherence information is available for infants in developing countries, it is clear that compliance to these pediatric vaccine timelines is suboptimal. The importance of following immunization timelines is known, however, it has been demonstrated that adherence to the vaccination timelines of pediatric vaccines in middle and low income countries is not ideal for disease prevention. In order to improve the receipt of timely immunization, a better understanding of the barriers and incentives to adhering to recommended vaccine schedules is needed.

IV. Known Barriers and Incentives to Adherence

National Pediatric Timelines

Reviewing studies that focused on the adherence to common pediatric immunizations for infants, especially in developing countries, offered beneficial insight to factors that may be associated with noncompliance of the Rotarix dosage schedule. The aforementioned studies describing timeliness of childhood vaccines in 45 and 31 middle and low income countries identified factors such as rural or urban residence, mother's education, birth order, child's age at interview, mother's age at child birth, number of children in the household, and socioeconomic status as predictors that delayed infant immunization.(23, 24) Another publication in a journal that focuses on pediatric clinics in North America, explored the topic of vaccine compliance by reviewing various articles on the topic. For studies that evaluate a target population for delay immunizations, factors such as more children in the household, women as the only adult household member, and parents under 30 years of age were found in households with delayed vaccination. (Reviewed in (25)) Although these studies may be helpful in identifying factors associated with a lack of compliance with a national immunization schedule, factors for adherence to a clinician recommendation of a 2, 4 month rotavirus vaccination schedule may be different.

Clinician Recommended Timelines

Numerous studies were identified that explored reasons why caregivers may or may not adhere to a clinician's specific 2, 4 month vaccination recommendation. The topic of simultaneous vaccination, in which a child receives more than one scheduled

vaccination at a healthcare appointment, is an important convenience, allowing caregivers to forgo multiple trips to the hospital and ensure vaccinations are received on schedule.(26, 27) Studies have also been conducted on caregivers' beliefs and feelings toward physician and vaccines. A caregiver's trust in the advice of their child's clinician is an important factor since it may motivate adherence to a specified return date for vaccination.(28) Furthermore, caregivers whom believe that a vaccine is safe may not have hesitations to vaccinate their child, which would create better adherence to clinician recommendations. This association is seen in research conducted in Uganda and the U.S. where vaccine refusal and/or delay occurred among parents who do not believe that vaccinations are safe or prevent diseases.(29-31) While these factors affecting vaccination timeliness may be the direct effect of the caregiver, other factors involving the clinician may also affect timeliness. A healthcare provider's ability to remind caregivers of the return clinic date for vaccination is crucial for adherence. Developing countries such as the Dominican Republic and Mozambique use a vaccine reminder system where the return date is written in on the top of the vaccine card.(32) Although writing the return date on the card was effective, only 27% of the cards examined in their study had this done.(32) Moreover, a clinician's misunderstanding of rotavirus immunization contraindications could be harmful to timely vaccination. Even though the recommendation is to vaccinate preterm and low birth weight babies on time, this does not always happen and this issue has been seen in countries such as the Netherlands and Chile.(33, 34) In conclusion, there are a number of factors that potentially affect general pediatric immunization compliance with timelines, but little is known about barriers specific to adhering to the Rotarix dosage timelines. This literature review will further

explore these topics within the context of Bolivia and address the lack of existing data on adherence to the Rotarix dosage schedule.

V. Bolivia

Burden of Diarrheal Disease in Bolivia

Bolivia is one of the poorest and least developed countries in South America, with 59% of the population living in conditions of poverty, according to a 2001 National Population Census.(35, 36) As a possible consequence of these poverty levels, Bolivia also has a tragic under 5 mortality rate (measured in 2008) of 54 deaths per 1,000 children which falls well below the regional average of 18.(37) Of these deaths, approximately 15% are caused by diarrheal disease.(37)

Burden of Rotavirus Infection in Bolivia

The rotavirus-specific mortality rate for Bolivia is not well documented, yet some evidence is available to make approximate assumptions. A study conducted in five sentinel hospitals in Bolivia, which participated in Bolivia's rotavirus surveillance program, analyzed inpatients and outpatients with acute diarrhea from 2005-2006 in order to determine rotavirus-specific mortality. This study population experienced a positive test for rotavirus infection in 40% of hospitalized children.(38) Using the infection percentage as a substitute for a rotavirus-specific rate, along with WHO reports of diarrheal disease mortality, Bolivia's National Rotavirus Surveillance Network data, and National Statistics Institute in Bolivia data, the authors concluded that over 47,000 outpatient visits, more than 9,000 hospitalizations, and 813 deaths are caused by rotavirus

infection each year.(38) Given these data, the impact on health due to diarrheal disease and rotavirus specific infections can be seen, ultimately contributing to the elevated under 5 mortality rate and possibly furthering the poverty already experienced.

Economic Impact of Diarrheal Disease and Rotavirus Infection in Bolivia

With compelling data representing the burden of disease, cost analyses were also performed. Two studies that examined these topics in depth describe the economic impact of diarrheal disease and rotavirus-specific infections in Bolivia. One study, which focuses on the costs of diarrheal disease incurred by Bolivian families, analyzes interviews conducted from 2007 to 2009 of caregivers of patients less than 5 years of age receiving diarrheal treatment in the sentinel hospitals mentioned previously. The authors found that 45% percent of patient families spent greater than 1% of their annual income on a single diarrheal episode and Bolivian families, overall, incurred US$2.2MM in diarrhea-related costs annually.(39) Another study focuses on the economic burden experienced by the Bolivian government and analyzes the direct medical costs of inpatients and outpatients in 5 sentinel hospitals in Bolivia between 2005 and 2006. The authors concluded that Bolivia would bear US$3MM in direct medical costs due to rotavirus illness. However, the reported benefits of vaccination with rotavirus were positive.(38) A rotavirus vaccine was hypothesized to reduce at least 60% of outpatient visits, hospitalizations, deaths, and direct medical costs caused by rotavirus-specific diarrhea.(38) Therefore, the evident burden of diarrheal disease caused by rotavirus infection in Bolivia would potentially be positively impacted by the introduction and utilization of a rotavirus vaccine.

Rotavirus Vaccination in Bolivia

In August 2008, in order to reduce the burden of rotavirus-induced gastroenteritis, the Rotarix vaccine was introduced in the standard child vaccination schedule. Bolivia was one of the first GAVI Alliance eligible countries to introduce the vaccine and due to their support, Bolivian children can now be vaccinated against rotavirus free of charge in government health centers.(40) The current schedule for the rotavirus vaccine, Rotarix, follows a two-dose regimen The first dose can be given as early as 6 weeks of age and up to 3 months of age. The second dose is then given between 4 months and 8 months of age with an interval of at least 4 weeks between each dose.(41) This schedule was altered in 2010-2011 to extend the age, from 6 months to 8 months, for which the second dose could be administered.(41) Although this is the detailed schedule set forth by the Bolivian Ministry of Health, indicating guidelines on when the vaccine is most effective and safe, it is also assumed that most clinicians administer the rotavirus vaccine according to the general 2, 4 month schedule at the same time in which polio and pentavalent are also administered.

Rotavirus Vaccine Coverage rates in Bolivia

According to the GAVI Alliance, over 200,000 Bolivian children received the vaccine in 2009, with coverage rates of 80% for the first dose and 64% for the second dose, exceeding their goals.(42) The WHO and The United Nations Children's Fund (UNICEF) have also reviewed data on national immunization coverage based on reports given to them from the member states and published and grey literature.(43) Based on the WHO/UNICEF estimates for coverage of the second Rotarix dose, Bolivia

had achieved 40% coverage in 2008, 65% coverage in 2009, 76% coverage in 2010, 80% coverage in 2011, and 76% coverage in 2012.(44) Although these coverage rates are not ideal, they do show a general increase each year after the vaccine was introduced.

Rotavirus Vaccine Efficacy in Bolivia

Studies on the efficacy of Rotarix vaccine in the setting of Bolivia have not been published. However, the GAVI Alliance has commissioned special studies coordinated by the Vaccine Implementation Technical Assistance Consortium (Johns Hopkins University and Centers for Disease Control) to provide evidence in support of the implementation of rotavirus vaccines in developing countries. One study aimed to explore the efficacy of rotavirus vaccine in high socioeconomic status countries (SES), middle SES countries, and low SES countries using a mathematical model based on specific data for each setting. Since studies were not performed in Bolivia, this study, which models rotavirus vaccine efficacy based on country SES status, may give an estimation and prediction for the Rotarix efficacy for Bolivia. The authors found that rotavirus vaccination was predicted to prevent 93% of cases of severe gastroenteritis in high SES countries, 86% in middle SES countries, and 51% in low SES countries.(45) They concluded that their predictions are consistent with clinical trials performed, therefore reassuring their data.(45) Since Bolivia would not be described as a high SES country, the Rotarix efficacy should be expected to fall within the range of 51-86% based on the GAVI special study. Unlike efficacy, effectiveness of rotavirus vaccine has been studied in Bolivia and will allow us to better understand the protection conferred.

Rotavirus Vaccine Effectiveness in Bolivia

A study on the effectiveness of the rotavirus vaccine was conducted specifically in Bolivia in six hospitals between March 2010 and June 2011. The authors of the case-control study found that the effectiveness against hospital admission for rotavirus was 69% with rotavirus negative controls and 77% with non-diarrhea controls and concluded that the monovalent vaccine provided high protection against rotavirus-specific hospitalization of Bolivian children.(46) These conclusions fit into the general claims made by the aforementioned study examining rotavirus vaccine efficacy according to the country SES status. The monovalent rotavirus vaccine in Bolivia demonstrates a vaccine effectiveness that falls within the efficacy of a middle and low SES country.

Adherence to Rotarix Schedule in Bolivia

The information summarized thus far describes the heavy burden of diarrheal disease globally and in Bolivia, focusing on the role that rotavirus plays in creating this devastation. The prevalence of rotavirus infection in Bolivian communities contributes to the high under 5 mortality rate, increased hospitalizations, direct healthcare costs of the state, and indirect costs borne by the families. After recognition of these effects and adequate funding, provided by the GAVI Alliance, the introduction of the monovalent rotavirus vaccine, Rotarix, took place in Bolivia. Although coverage rates seem to be increasing, the limited information on its effectiveness of 69-77% shows that further efforts could still be made to increase this measure. Common to all vaccines, an important component of the success of Rotarix in reducing rotavirus illnesses is following the recommended immunization schedule.(19) Adhering to the given rotavirus dosage

timeline enables a high vaccination coverage to be reached, ultimately reducing rotavirus disease and improving the health and economic status of Bolivia.(47) However, an underwhelming amount of information on adherence to the Rotarix vaccine schedule for infants is available in developing countries like Bolivia, where the rotavirus vaccine is crucial for reducing the burden of diarrheal disease in their infant population. A previously mentioned study, which examined the effectiveness of rotavirus vaccine in Bolivia, also collected information on when the study infants received their rotavirus vaccination. The authors found that 10% of infants were vaccinated outside of the 2, 4 month dosage schedule with the majority of infants receiving their first dose at 8 and 9 weeks of age and their second dose at 17 and 18 weeks of age.(46) The figure produced by the author demonstrates that the first dose was given was given as early as the first week since birth and as late as 32 weeks since birth. In addition to the poor availability of adherence data for Bolivia, even less is known about the specific barriers or incentives for Bolivian women to comply with correct dosage intervals of the Rotarix series.

VI. Research Goals

Based on these data gaps, there is a need to assess the adherence to the rotavirus vaccine timeline for infants in Bolivia The goal of my research is to evaluate the timing of the Rotarix vaccine series and possible barriers to receiving the first and second dose according to the Bolivian Ministry of Health immunization schedule and the 2, 4 month clinician recommended timeframe among Bolivian infants in El Alto. The aims of my study are to:

Specific Aim 1: Determine the age that children in El Alto, Bolivia receive the first and second dose of the rotavirus vaccine and length of time between the two dose series using information found in infant vaccination cards.

Specific Aim 2: Describe the knowledge, barriers, and incentives of adherence to both rotavirus dosage timelines using a questionnaire completed by mothers in El Alto with eligible children.

Specific Aim 3: Assess the relationships between these barriers/incentives informed through survey response and the outcome of receiving the rotavirus vaccine series on time.

Specific Aim 4: Based on these results, propose recommendations to the ongoing longitudinal study in El Alto, Bolivia to encourage mothers to adhere to the rotavirus dosage timeline and achieve the best vaccine effectiveness possible.

VII. Significance of the Study

The goal of this study is to evaluate the timing of the Rotarix vaccine series and possible barriers to receiving the first and second dose according to the Bolivian Ministry of Health immunization schedule and the 2, 4 month clinician recommended timeframe among Bolivian infants in El Alto. Knowing when the infants are receiving their Rotarix vaccine doses will provide information on the proportion of infants adhering to the recommend dosage guidelines. It is important to determine whether these guidelines are being met and why in order to increase incentives for completion and help mothers overcome any barriers to completing the series within the timeline. Results from this

study will lead to an initial understanding of the motivations and abilities of mothers to follow the recommended rotavirus dosage timeline. This understanding will lead to the identification of issues in complying with the rotavirus vaccine series timeline, which will be incorporated into an ongoing longitudinal rotavirus study. The longitudinal rotavirus study requires participants to have completed the rotavirus vaccine series. By identifying barriers to timely completion and incorporating this information in the longitudinal study, more mothers will be able to participate in the longitudinal study, therefore furthering their research goals. In addition, this understanding of barriers and incentives to obtaining rotavirus vaccine series at its required dosage intervals will also lead to infants achieving the best vaccine effectiveness possible, therefore improving health and preventing rotavirus diarrheal disease in Bolivian children.

INTRODUCTION

Diarrheal disease is a leading cause of child mortality and morbidity in the world. Each year, about 1.7 billion diarrheal cases occur, which consequently become fatal for approximately 760,000 children under five.(1) Among these diarrheal disease deaths in infants and young children, rotavirus is one of the most common etiologic agents. (40, 48) Rotavirus is a highly contagious virus that causes gastroenteritis or inflammation of the stomach and intestines, which leads to vomiting and diarrhea, causing a loss of bodily fluids. (49) Globally, rotavirus is estimated to cause about 453,000 deaths, 2 million hospitalizations, and 25 million clinic visits annually among children younger than 5 years of age. (11) In addition, this burden of rotavirus related mortality remains elevated among developing nations, as 95% of the deaths due to rotavirus occur in these countries. (1) Rotavirus infection, therefore, presents tremendous economic implications for both households and health care systems, potentially exacerbating poverty and contributing to existing illnesses. (38)

To address the burden of diarrheal disease caused by rotavirus, the licensure of two effective vaccines against rotavirus were issued in the United States. Rotarix is a single-strain attenuated human rotavirus vaccine, while RotaTeq is a pentavalent bovine-human reassortant vaccine. (50) Although both vaccines are prequalified by WHO, Rotarix has greater importance for developing countries, as it only requires two doses, compared to the three recommended by RotaTeq, and is also heat stable. Specifically, Rotarix prevents rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9).(Reviewed in (51)) The dosage timeline is approved for use in infants 6 weeks to 24 weeks of age in the U.S. The first dose can be administered to infants beginning at six

weeks of age and the second dose is given after an interval of four weeks, and prior to 24 weeks of age.(Reviewed in (51)) This timeline varies for other countries, however. Efficacy studies for the vaccine were conducted in six European countries followed by eleven Latin American countries, and Finland. These studies were large phase III randomized, double-blind, placebo-controlled clinical trials, which determined that the efficacy against severe rotavirus gastroenteritis through two rotavirus seasons was 90.4% in European countries and 80.5% in the Latin American countries and Finland. (Reviewed in (51)) Clinical trials were also conducted in the African region, demonstrating considerably lower efficacy. The efficacy in a cohort of Malawian children was 49.4% in the first year of life and 17.6 % in the second year of life, while the efficacy in the first year of life for South African children was 76.9%. (14, 15) In addition, the effectiveness of Rotarix was examined in studies in Brazil and Bangladesh. In Brazil, the effectiveness of the vaccine against G2P[4] diarrhea was 77%, while in the cluster randomized trial in Bangladesh, the vaccine effectiveness was estimated at 39%. (17, 52) It is clear that the protection against rotavirus has varying efficacy and effectiveness rates, but lower percentages can be consistently found in developing countries.

Although efficacy and effectiveness of the rotavirus vaccine are indications of its performance, coverage rates and adherence to the vaccine are also important factors of a child's protection from disease. Limited studies on rotavirus vaccine adherence in the United States exist, but only general pediatric immunization timeline adherence information is available for infants in developing countries. Two U.S. cohort studies have indicated only a moderate compliance of 69% and 75% of insured infants with the approved rotavirus timeline, while infants in developing countries displayed poor

compliance for other pediatric immunizations. (20, 21) Median delays in 45 middle and low income countries were 2.3 weeks for BCG; 2.4 weeks for DTP1; 2.7 weeks for MCV1; and 6.2 weeks for DTP3. (23) Infants in developing countries with the worst timeliness for immunization received the DPT3 vaccine more than 19 weeks late. (23) Ultimately, this lack of compliance with vaccine timelines results in delayed vaccinations for children who are otherwise eligible, suggesting that they are left unprotected from disease for a longer period of time than necessary. In developing countries with increased disease prevalence and more opportunity for exposure, following these timelines is crucial to prevent infection and to reduce the diarrheal disease burden.

Bolivia, one of the poorest and least developed countries in South America, has an under-five mortality rate estimated to be 54 deaths per 1,000 children in 2010. (35, 36) Of these childhood deaths, approximately 15% are caused by diarrheal disease, and result in over 47,000 outpatient visits, more than 9,000 hospitalizations, and 813 deaths each year. (37, 38) In order to reduce the burden of rotavirus-induced gastroenteritis, the Rotarix vaccine was introduced in the Bolivian pediatric vaccination schedule in 2008. The Bolivian schedule for Rotarix follows a two dose regimen. The first dose can be given as early as 6 weeks, and up to 3 months, of age. The second dose is then given between 4 months and 8 months of age with an interval of at least 4 weeks between each dose. Although this is the detailed schedule set forth by the Bolivian Ministry of Health (MOH), it is assumed that most clinicians recommend rotavirus vaccine administration according to the general 2, 4 month schedule, which coordinates with previously established vaccines and achieves protection at an earlier age.

An important component of the success of Rotarix (and all vaccines) in reducing rotavirus illnesses is following the recommended immunization schedule. (19) The Rotarix two-dose schedule was specifically designed to adequately protect infants from rotavirus illness prior to initial exposure and during the age when they are most vulnerable. (13, 19) Despite the limited studies on rotavirus vaccine adherence in the United States and general immunization adherence in developing countries (previously discussed), it is clear that compliance to these pediatric vaccine timelines is suboptimal. While the importance of following immunization timelines is understood, adherence to the Rotarix schedule is not known in developing countries like Bolivia, where this vaccine is newly introduced and crucial for reducing the burden of diarrheal disease.

In addition to the poor availability of immunization adherence information from Bolivia, even less is known about the specific barriers or incentives for Bolivian caregivers to comply with the MOH and clinician recommended Rotarix timelines. Studies that focused on the adherence rates of common pediatric immunizations for infants, especially in developing countries, offered beneficial insight to factors that may be associated with noncompliance of rotavirus dosage timelines. Two studies, describing timeliness of childhood vaccines in 45 and 31 middle and low income countries, identified factors such as rural or urban residence, mother’s education, birth order, child's age at interview, mother’s age at child birth, number of children in the household, and socioeconomic status, as predictors that delayed infant immunization. (23, 24) Additionally, factors contributing to noncompliance of the clinician recommended 2, 4 month vaccination schedule were identified. Variables such as trust in a clinician, belief in the safety of a vaccine, appointment reminders, and knowing correct contraindications

were recognized as potential determinants to timely immunization.(28, 29, 32, 34) It is clear there are a variety of factors that can affect general pediatric immunization compliance, but little is known about barriers specific to adhering to the Rotarix dosage timeline, especially in a developing country such as Bolivia. Therefore, it is important to explore these specific challenges that may be faced by the caregivers of Bolivian infants.

Thus, the goal of this study was to evaluate the timing of the Rotarix vaccine series and possible barriers to receiving the vaccine according to the Bolivian MOH immunization schedule and the 2, 4 month clinician recommended timeframe among Bolivian infants in El Alto. The specific aims of the study were to determine the age that children in El Alto, Bolivia receive the first and second dose of the rotavirus vaccine, and assess the relationships between barriers/incentives and the outcome of receiving the rotavirus vaccine series on time. By identifying the issues associated with untimely rotavirus immunization, efforts can be made to help caregivers overcome these barriers and increase timeliness. An increase in timeliness will result in infants achieving better protection from rotavirus illness and a continued decrease in the burden of diarrheal disease in Bolivia.

MATERIALS AND METHODS

I. Study Area

This study was conducted in El Alto, the largest city in the department of La Paz, Bolivia. Two hospitals, Los Andes and Corea, located in El Alto were used as study sites for collecting participant information. Both sites are hospitals equipped with pediatric, immunization, and specialty services. The routine vaccination program in Bolivia recommends six vaccines: Bacillus Calmette-Guerin (BCG); Pentavalent for diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenza type b; DPT for Diphtheria, tetanus, and whooping cough; Oral polio vaccine; Rotavirus vaccine; and Seasonal influenza. This study focused on the timely vaccination of the rotavirus immunization (Rotarix) in which the first dose is given between the second and third month of age and the second dose is given between the fourth and eighth month of age. (See appendix I)

II. Sample size calculation

The sample size required was calculated based on the prevalence of factors possibly associated with the outcome of adherence to Rotarix vaccination timeline. A total target population sample size of 190 was determined based on the following assumptions: an alpha level of 0.05, a study power of 80%, a conservative prevalence of 50% adherence, and ability to detect at least a 20% difference between the possible exposures and outcome (timeliness).(53) The sample size was further adjusted for a total target population of 70 based on the following assumptions: an alpha level of 0.05, a study power of 80%, a conservative prevalence of 50% adherence, and ability to detect at least a 32% difference between the possible exposures and outcome (timeliness).

III. Study Population

This study included children who were at least eight months old who had or had not completed the Rotarix vaccination, in addition to infants of any age with a completed Rotarix series. This age span was chosen to allow for detection of any infants who did not receive the rotavirus vaccination as beyond 8 months is the age a child becomes ineligible to receive the rotavirus immunization according to the Bolivian immunization schedule. Including children younger than 8 months who had already received two doses of the rotavirus vaccine was done to better understand the timing of the doses received by the infant. Children who did not have a vaccination card were excluded from the study to avoid any recall bias of vaccination dates. There were 135 caregivers approached initially, of which 112 were willing to participate. Of the caregivers willing to participate, 34 infants were younger than 8 months and did not have a completed rotavirus vaccination, 6 did not have a vaccination card, and 1 child was vaccinated prior to the rotavirus vaccine's introduction in the schedule. Applying these exclusion criteria led to a total of 71 children which could be included in the analysis.

IV. Recruitment

Caregivers and their infants who fit the aforementioned eligibility criteria were recruited from two hospitals in El Alto, Bolivia. The two hospitals included Los Andes and Corea, which already had vaccine coverage data from previous pilot studies. These hospitals were also associated with existing longitudinal Rotarix vaccine research, studying the relationship between a child’s nutritional status and rotavirus vaccine

efficacy. Healthcare workers, who were participating in the clinical care of a child, assisted in identifying eligible infants. Caregivers were also approached in the waiting areas to determine further eligible infants.

V. Enrollment and consent

Eligible caregivers were identified as having an infant greater than eight months of age or a child with the completed Rotarix immunization series. Once an eligible caregiver was identified, consent was required before any additional action or enrollment. Caregivers had the study explained to them and they were asked to repeat back their understanding of the study to ensure they correctly interpreted the research goals and requirements of participants. After ensuring the caregiver had a clear understanding of the study and she had verbally consented, which was indicated on the survey, he/she received a paper copy of the study information for her records. This procedure introduced an increased level of confidentiality among participants as no signatures or identifying information was recorded.

VI. Study Instrument

A cross-sectional survey using an adaptation of the Systems Model of Clinical Preventive Care was designed and developed in collaboration with partners from the Instituto de Biología Molecular y Biotecnología (IBMB) de la Universidad Mayor de San Andrés and the Bolivian Rotavirus Surveillance Program (RVSP).(54) This model focuses on the physician, the patient, and the factors that which influence them. These individual variables are categorized into overarching groups which include: predisposing

factors such as demographic factors which may have influence on a patient's decision to seek preventive care; enabling factors such as skills or resources which enable a person to perform the preventive activity; patient reinforcing factors such as benefits or support received for engaging in the preventive activity; organizational factors in the healthcare delivery system such as access to care, cost of care, and coordination with community services; preventive activity factors such as the efficacy, efficiency and cost-effectiveness of the preventive activity as well as any discomfort the activity may cause; and situational factors which involve cues to engage in the preventive activity such as symptoms which may trigger a reason to seek care or reminders by the physician to seek preventive care. This survey concentrated mostly on the factors which affect the infant and caregiver. Predisposing factors included mother's age at delivery, infant's gender, education level, marital status, monthly income, infant's birth order, and prenatal care received. Enabling factors included knowledge of the rotavirus vaccine timeline. Reinforcing factors included knowing other infants who had also received the vaccine and the belief that the vaccine prevents disease or diarrhea. Organizational factors were not used. Preventive activity factors included the belief that the vaccine was safe, belief that the vaccine improved an infant's health status, and the belief that the infant had received the vaccine on time. Situational factors included vaccine reminders given by a clinician. The survey also included an open ended follow-up question regarding why the infant may not have received his or her vaccine on time, if the caregiver believed that the vaccine was given before or after a clinician's recommendations. Before study initiation, protocols and study instruments were reviewed and approved by the Emory IRB (#00056127). The survey was piloted in advance and questions were revised or clarified accordingly. Surveys took

no more than fifteen minutes of a participant's time. Caregivers participating in the study were required to give informed oral consent and were provided with complete study information. Their participation to provide infant health history posed minimal risk. To preserve confidentiality, personal identifiers were not collected.

VII. Data collection

The survey was administered to eligible, consenting caregivers in the two hospitals prior to or post clinical visits for the infant. In order to improve accuracy and response rates, along with being sensitive to any illiteracy, each participant was read the survey questions and answers were recorded by the interviewer. This also enabled any participant questions about the survey to be resolved. The questionnaire was composed of both open and close-ended questions regarding the overarching factors mentioned in the study instrument section above. During the same encounter with the questionnaire, information on the timing of the rotavirus vaccine was retrieved from vaccination card that the caregiver had for the infant. Date of birth, dates of the first and second dose of the Rotarix vaccine administration, and other vaccines received during the same immunization appointment were collected from these cards and recorded.

VIII. Data management

Completed surveys were stored in a locked file cabinet accessible only to members of the research team and were password-protected in electronic form. Preliminary analyses were conducted in Bolivia in order to share findings with the Hospitals and the rotavirus longitudinal study, *Effect of Nutrition, Immunity, and*

Vaccines on Pediatric Enteric Infections. Before statistical analysis was started, double data entry was performed. Data was entered into an electronic database by two separate researchers. Then, the data was analyzed with SAS 9.3 for any discrepancies and these differences in data entry were manually cross checked with the physical surveys.

IX. Statistical analysis

Timeliness with Bolivian Ministry of Health Rotavirus Immunization Schedule

A multivariable logistic regression model was applied in order to analyze exposures that could be predictive of timely completion of the Bolivian MOH rotavirus vaccination schedule. The outcome variable was divided into two categories: timely completion and untimely completion. If the first rotavirus vaccine was given between the second and third month of age and the second dose was given between the fourth and eighth month of age, then the vaccinations were considered timely completion. This timeliness definition was used because it follows the eligibility age limits for receiving rotavirus vaccine set forth by the Bolivian MOH. The infants who received vaccinations outside of this range were considered untimely completion. No outcomes were considered missing as all the infants considered eligible for the study had a vaccination card. Further exploration with this outcome and modeling detected quasi-complete separation of data points due to zero cells found with all variables. This model was consequently deemed highly unreliable.

Timeliness with Clinician Recommended 2, 4-month Immunization Schedule

A second multivariable logistic regression model was applied to analyze the exposures that could predict a caregiver's adherence to a clinician's recommendation of the 2, 4 month rotavirus vaccine timeline. The outcome was categorized as timely or untimely. If the first vaccination was given within 7 days prior or post the child's second month of birth, then the first dose was considered timely. The second dose was considered timely if it was given within 7 days prior or post the child's fourth month of birth. If either of the two individual rotavirus immunizations were considered untimely, then the outcome was assigned to the category untimely. This timeliness definition was used because it followed the recommendations of age limits imposed by clinicians, while allowing for a 7 day margin for emergency issues experienced by the caregivers. No missing outcome variables were present as all infants included in the study had a vaccination card.

Description of models used

The effects of the independent predictors on the timeliness of a clinician's recommended 2, 4 month rotavirus immunization timeline were analyzed in two separate multivariable logistic regression models. The first model was hierarchically designed with the overarching group of predisposing factors leading to the timeliness outcome with the intervening categories of enabling factors, reinforcing factors, cues to action, and preventive activity factors. The second model, however, treats all the groups as independent risk factors for the timeliness outcome. Therefore, all the variables from these groups are included in the second model.

Independent variables contained in the adaptation of the Systems Model of Clinical Preventive Care

Independent variables considered for the multivariable analysis include the predisposing factors of mother's age at delivery (continuous), gender of the child, caregiver's education (completed high school -did not complete high school), marital status (married-unmarried), monthly income (>500 Boliviano- $\leq$ 500 Boliviano), Birth order (first born or other), Prenatal care (yes-no). Enabling factors included knowledge of the vaccine timeline (yes-no). This variable was assigned to the yes category if the caregivers answered that the first rotavirus vaccine was given at 2 months and the second rotavirus vaccine was given at 4 months. Reinforcing factors included the belief that the vaccine prevented diarrhea and/or disease and whether they knew other infants who had received the rotavirus vaccine. The preventive activity factors included the belief that the vaccine was safe, belief that the vaccine improved the infant's health, and their belief that the infant received the vaccine on time. In order to gauge the caregiver's beliefs without using a leading question, participants were prompted to check which beliefs they had instead of independent yes/no questions for each belief. Situational factors included whether the caregiver had received a clinical reminder to get their infant vaccinated. No organizational factors were included. Some variables collected were excluded. The predisposing factor, zone of residence, was excluded as it had not been properly recorded throughout the survey since the zones listed on the vaccination cards were illegible or not present. The child's birthplace and vaccination location were excluded because they consistently took place in a hospital and furthered details pertaining to a specific hospital were not obtained. An enabling factor variable such as other vaccines received in the

same appointment as the rotavirus vaccine, was excluded because all infants had received both pentavalent and polio consistently with the rotavirus immunization.

Model 1: Predisposing factors associated with failure of adhering to the clinician recommended of Rotarix 2, 4 month dosage schedule

For model 1, only the aforementioned predisposing factors were considered. First, a collinearity analysis was performed to screen out potential variables that are strongly related to other variables in the model. Screening for collinearity issues eliminated maternal age and prenatal care as these variable had a conditional index (CI) greater than 8, which was +4 larger than the other CIs, and a VDP of 0.5 or higher. The preliminary model included infant gender, mother's educational status, marital status, monthly income, and birth order. Backwards elimination with an alpha critical of 80% (0.20) was used to further screen out variables. The variables present in previous literature were kept in the model to give a final model, which included infant's gender (previous literature), mother's education, and birth order (previous literature). Lastly, the Hosmer Lemeshow (HL) statistic was used to determine if there was enough evidence to indicate that the model had lack of fit.

Model 2: Predisposing, enabling, reinforcing, preventive activity, and situational factors associated with failure of adhering to the clinician recommendation of Rotarix 2, 4 month dosage schedule

For model 2, all aforementioned factors were considered. First, a collinearity analysis was performed to screen out potential variables strongly related to one another.

Screening for collinearity issues eliminated maternal age, prenatal care, belief that the vaccine prevents disease or diarrhea, and belief that the child received their doses on time, as these variable had a conditional index (CI) greater than 8, which was +4 larger than the other CIs, and a VDP of 0.5 or greater.(55) The preliminary model included infant gender, mother's education, marital status, income, birth order, knowledge of vaccine timeline, knowing other infants who received the vaccine, belief that the rotavirus vaccine is safe, belief that the vaccine improved the infant's health, and vaccine reminders. A Quasi-complete separation message was indicated and it appeared to only be present for the variable, knowledge of vaccine timeline. Instead of discarding this model, since all the other variables were unaffected, or omitting this variable, since this would provide no information on its effect, a modification of the score function of logistic regression using the Firth procedure was used.(54) Backwards elimination with an alpha critical of 80% (0.20) was used to further remove variables. The variables present in previous literature (infant gender and birth order) were eliminated through backwards elimination and were not re-added due to the small sample size and the potential unreliability of the model upon addition of more variable. The final model included marital status, knowledge of the vaccine timeline, knowledge of other infants receiving the vaccine, belief that the rotavirus vaccine is safe, and belief that the vaccine improved the infant's health. Lastly, the Hosmer Lemeshow (HL) statistic was used to determine if there was enough evidence to indicate that the model had lack of fit. (SAS 9.3 was used for statistical analysis)

RESULTS

It was important to collect information on the characteristics of the study population to identify factors possibly associated with timely vaccination. To describe the characteristics of caregivers and infants, a questionnaire containing demographic related questions was completed by study participants. Participants were recruited from two hospitals, with a substantial portion of caregivers and infants (79.9%) from Los Andes Hospital (table 1). Within the hospitals, some caregivers (69%) were recruited from the clinical room where vaccinations were offered, while the remaining caregivers (31%) were recruited from the waiting room (table 1). The caregivers resided in a number of zones within El Alto, with the largest percentage of respondents (21%) from Alto Lima (table 1). Female infants were slightly more represented than male infants, and the majority of surveyed caregivers reported being the mother of the infant (94%) (table 1). The education and marital status of caregivers were also obtained. More caregivers had not completed high school than those who had completed high school or higher education (table 1). Similarly, more caregivers were not married compared to caregivers who were married (table 1). Alternatively, the monthly income status of respondents was more evenly divided, as slightly more than half of caregivers received less than 500 Bolivianos per month, while nearly half of caregivers received 500 Bolivianos or more per month (table 1). These demographics demonstrated the variation in characteristics of the study population, despite the fact that all caregivers resided in El Alto. Furthermore, it was important to recognize the potential significance of the mother's role in the vaccination status of infants.

According to the immunization schedule set by the Bolivian Ministry of Health (MOH), the first rotavirus vaccine dose should be given between the second and third month of age and the second rotavirus vaccine dose should be given between the fourth and eighth month of age. In order to quantify when the study infants received their rotavirus vaccinations, the date of birth for each infant, and the date that they received each dose, were collected from infant vaccination cards. The highest percentage (61.9%) of infants immunized with the first rotavirus vaccine dose were within their eighth to ninth week since birth, while the highest percentage (66.2%) of infants immunized with the second rotavirus vaccine dose were within their seventeenth to eighteenth week since birth (Figure 1). Additionally, all study infants received both rotavirus immunizations at least four weeks apart, with the highest percentage (46.5%) of infants having had nine weeks between each dose (Figure 2). Infants who had delayed immunization resulted in various outliers for the first or second rotavirus vaccination. Two infants in particular did not begin the series until week 20 and 56 of age, with the latter infant finishing the series at week 69, resulting in an extreme outlier. Therefore, the majority of the study infants (97. 2%) received the rotavirus vaccine in accordance with the Bolivian MOH rotavirus immunization schedule and experienced adequate time between doses. Due to this exceptional adherence to the Bolivian MOH schedule, factors associated with timely adherence could not be addressed. Supplementary information regarding the rotavirus timeline can be found in appendix I.

In order to analyze the effects of predisposing factors of caregivers and infants on adherence to clinician recommended 2, 4 month rotavirus immunization timeline, a hierarchically formulated model was designed. This model examined predisposing factors

as potential predictors, which included some of previously discussed demographic information. The final model contained gender, education, and birth order. None of these measured variables were statistically significant ($p<0.05$) and therefore, no conclusive results can be interpreted. In conclusion, it is indeterminable if gender, education, or birth order affect adherence to the clinician recommendations of Rotarix 2, 4 month dosage schedule for this study population.

To analyze the effects of all factors of caregivers and infants on adherence to clinician recommendation of the 2, 4 month rotavirus immunization timeline, a non-hierarchically formulated model, which treats all factors as independent predictors for the outcome, was designed. This model used predisposing factors, enabling factors, reinforcing factors, cues to action, and preventive activity factors collected from the participant questionnaire. The final model included *married, timeline knowledge*, *knowing others*, *safety*, and *health improvement*. Although all of the variables had a strong effect on adherence to clinician recommendations, the variables, *knowing others* and *safety*, were statistically significant ($p<0.05$). Infants of caregivers who knew other infants that had received the rotavirus vaccine were more likely to have failed to adhere to the clinician recommendations, while infants of caregivers who believed that the rotavirus vaccination was safe were less likely to have failed to adhere to the clinician recommendations. In conclusion, adherence to the clinician recommendations of Rotarix 2, 4 month dosage schedule in Los Andes and Corea Hospitals in El Alto, Bolivia was more likely in infants with caregivers who believed the rotavirus immunization to be safe and less likely in infants whose caregivers knew other rotavirus vaccinated infants.

DISCUSSION

The present study evaluated the timing of the Rotarix vaccine series and possible barriers to receiving the first and second dose, according to the Bolivian Ministry of Health (MOH) immunization schedule and the 2, 4 month clinician recommended timeframe among Bolivian infants in El Alto. The findings indicated that the majority of the study infants received their rotavirus vaccine according to the Bolivian schedule. However, only approximately half of the study infants followed the clinician's recommendations for rotavirus vaccination at two and four months. Infants of caregivers who knew other infants that had received the rotavirus vaccine were more likely to have failed to adhere to the clinician recommendations, while infants of caregivers who believed that the rotavirus vaccination was safe were less likely to have failed to adhere to the clinician recommendations.

Using vaccination cards, we have shown that the majority of infants (97.2%) at two hospitals in El Alto received their rotavirus immunization according to the Bolivian MOH dosage schedule. Similar ages of rotavirus immunization have also been reported for Bolivia.(46) Although studies have found untimely adherence for other vaccines in various developing countries, timely adherence to the rotavirus vaccine was seen for these two hospitals according to the schedule put forth by the Bolivian MOH.(23, 24) Simultaneous vaccination and exclusive immunization clinics integrated within the hospitals may have contributed to the elevated adherence demonstrated by these infants. The Bolivian immunization schedule recommends that polio, pentavalent, and rotavirus vaccines are given at the same age, and therefore, simultaneous vaccination is offered. This is an important convenience to caregivers, allowing them to forgo multiple trips to

the hospital and ensure vaccinations are received on schedule. (26, 27) Simultaneous vaccination is also necessary for achieving high vaccination coverage rates, which may have helped study infants achieve rotavirus vaccination coverage. (26, 44) All study infants had, in fact, received pentavalent and polio vaccines in concordance with their first and second dose of rotavirus vaccine, achieving 100% coverage, confirmed by the vaccination card. Furthermore, exclusive vaccination clinics, operated by nurses and requiring no appointment, were available alongside other clinical services. Caregivers were able to attend their own clinical appointments and have their infant vaccinated on the same day. Likewise, clinicians caring for infants in other specialties could indicate an immunization was needed based on the vaccination card and hand the card to the vaccination clinic so the infant could be vaccinated on the same day. This type of immunization service is favored as a way to decrease unnecessary barriers to receiving vaccinations in a timely manner.(56) Additionally, caregivers' positive perception toward vaccination may have also have played a role in timely adherence to Rotarix. All surveyed caregivers believed that it was important for their infant to receive the rotavirus vaccination. Many caregivers also believed that the rotavirus immunization was safe and improved their infant's health. Confidence in a vaccine's safety and an understanding of its importance in preventing serious disease, despite its possible side effects, has been shown to positively affect timeliness in both the U.S. and Uganda. (29, 30)

Focusing on the clinician recommendation of rotavirus immunization at two and four months, approximately half of caregivers adhered to this dosage timeline. A combination of a clinician's ability to communicate the 2, 4 month immunization schedule and a caregiver's respect and trust in clinician advice, may have influenced

infants' adherence. In the vaccination clinic, healthcare providers would write the date to return for the subsequent rotavirus vaccination, and it would be up to the caregiver to bring the child back on time. Inquiries to both caregivers and clinicians verified that these penciled dates, at the top of the vaccine card, were used to indicate when to return to the hospital for additional vaccinations. This is not uncommon is other developing countries, such as the Dominican Republic and Mozambique, where this vaccine card reminder system is used to facilitate the completion of a vaccine dosage schedule. (32) Once the reminder is placed on the card, a prompt return visit requires the caregiver to follow and trust the clinician's advised return date. Since most caregivers (studied in the U.S.) trust their child's clinician more than a government official or friend, this caregiver trust may have been motivation to adhere to the specified return date. (28) However, it is important to note that the other 50% of caregivers and infants did not adhere to this return date. This may be due to a lack of communication about the 2, 4 month timeline from the clinician. In previous studies conducted in the Dominican Republic and Mozambique, writing the return date on the card was effective, yet only 27% of the cards examined in their study had done this. (32) In some versions of the vaccine card, as new cards are created when new vaccines are introduced, the 2, 4 month schedule is written in Spanish above the rotavirus immunization boxes, indicating the first dose is to be received at the age of 2 months and the second dose is to be received at the age of 4 months. This may seem self-explanatory, but may be confusing to a caregiver who has a low literacy level, low education level, or when this indication is not explained. The exact literacy of our study population is unknown since all participants were read all questions and answers, but educational status was surveyed. More participants had low education levels (did not

complete high school), which may have affected their ability to comprehend the timeline indications on the card without further explanation. A previous analysis on the epidemiology of the unimmunized child also stated that a lack of understanding of the need for a return visit, or when to return, was a major determinant of child non-immunization. (44) While observing in the clinic, I did not see any of the clinicians explain vaccine schedules or show caregivers how to use the card, independent of writing the return date. In addition to caregivers' misunderstanding of rotavirus timelines, a clinician's misunderstanding of rotavirus immunization contraindications could be equally harmful to timely vaccination. Caregivers offered potential reasons for why their child may not have received the rotavirus vaccination according to the 2, 4 month schedule. Caregivers stated that vaccination had been delayed due to prematurity or low birth weight. In one instance, twins had been vaccinated at different dates and the mother indicated that this was because one of the babies was premature. I also witnessed another infant who was recommended to a pediatrician for low birth weight, even though the mother had come specifically for vaccinations. Even though the recommendation is to vaccinate preterm and low birth weight babies on time, this does not always happen. This phenomenon has also been demonstrated in other countries, such as the Netherlands and Chile. (33, 34) The false contraindications are also recognized by the World Health Organization (WHO) as barriers to vaccination. It is clear that both caregiver and clinician play important roles in ensuring the timeliness of rotavirus vaccination.

Further analysis revealed that knowing other infants who received the rotavirus vaccine and believing that the rotavirus vaccine is safe were statistically significant predictors of failure to follow clinician's recommendations for being vaccinated at two

and four months. Since caregivers who knew other rotavirus vaccinated infants were more likely to fail to adhere to the 2, 4 month recommendation, it is possible that interaction with that infant's caregiver may have had influence. These caregivers could have then passed along incorrect knowledge on the rotavirus vaccine timeline, seen the same clinician for vaccination, or discussed adverse reactions and negative personal opinions, allowing for failure to occur. Previous literature does suggest that friends are a source of advice for their infant's health and can influence a caregiver to delay or refuse vaccination. (28) However, these caregivers knew other infants that had received their rotavirus vaccination and further research may be needed to understand why that would have a harmful effect on adherence. In contrast to the harmful effect of knowing other vaccinated infants, caregivers were less likely to fail to adhere to clinician recommendations if they believed the rotavirus vaccine to be safe. Believing that the rotavirus vaccine is safe may have enabled caregivers to feel comfortable vaccinating their infants and possibly removed hesitations toward vaccination, allowing for better adherence to clinician recommendations. Many caregivers indicated in the questionnaire that they believed the rotavirus vaccination was safe, expressing strong and doubtless verbal answers. This association was also mirrored in previous research conducted in Uganda and the U.S., where vaccine refusal and/or delay is seen among parents who do not believe that vaccinations are safe or prevent diseases. (29-31)

Due to the restricted sample size, it was difficult to analyze barriers or incentives associated with timely vaccination according to the rotavirus dosage schedule set by the Bolivian MOH. Since the majority of infants displayed adherence to this schedule, most variables were quasi-separated when logistic regression was carried out. Caregivers with

infants older than 8 months were not commonly seen in the hospital. When a caregiver and an accompanying infant older than 8 months were present, the vaccination card was often not available, as the mother was there for services not related to the infant. Therefore, extreme delays in rotavirus vaccination, which may have been seen in infants who were near or surpassed the Bolivian rotavirus vaccination age limit, may be underestimated. Each infant included in the study had a birth date and rotavirus administration date verified by their vaccination card. This eliminated any issues that could have occurred for caregivers trying to recall specific immunization dates. The questionnaire used was short and conducted in an interview style which made it conducive to engaging caregivers in this healthcare setting. By reading each question and answer to the participants, any literacy issues were eliminated and all surveys could be accounted for.

There are numerous public health implications of timely and untimely rotavirus vaccine adherence for children under five, globally. Vaccine timelines are uniquely constructed for each vaccine, and adapted again for each particular country, in order to ensure the best possible protection against disease. Due to many infant deaths being caused by diarrheal disease and a portion of those due to rotavirus, receiving the rotavirus vaccine prior to exposure and during their most susceptible age is of utmost importance. These results indicate that the caregivers who are present in these hospitals are showing a high level of adherence to the suggested Bolivian MOH rotavirus vaccination guideline. Therefore, there should be less of an impact of rotavirus experienced by this community and herd immunity would allow benefits to those without vaccinations as well. Having high adherence levels to the rotavirus vaccination timeline should also coincide for other

vaccines received simultaneously, and offer guidance for how caregivers could adopt better practices for non-simultaneous vaccines. However, non-compliance with the clinician recommended 2, 4 month schedule could result in eligible infants having longer periods at risk for rotavirus infection. Without intermittent training or refresher courses for clinicians, issues preventing timely adherence, such as false contraindications and a lack of patient education, may perpetuate missed opportunities to vaccinate on time. If caregivers continue having difficulty complying with the clinician recommended schedule, infants will continue to be at risk, despite having excellent adherence to the MOH timeline.

In conclusion, this study has shown that the caregivers attending the hospitals of Corea and Los Andes in Bolivia have a high level of adherence to the Bolivian MOH rotavirus immunization timeline. This may have to do with the logistical benefits of offering simultaneous vaccination and an immunization only, walk-in clinic located among other hospital services, such as pediatric and women's consultation. A caregiver's belief in the importance and safety of the rotavirus vaccine may be an additional contribution affecting timeliness. The contrasting and uneven adherence to the clinician recommended 2, 4 month vaccine timeline may represent more non-structural, individual issues between caregivers and providers. Perhaps better communication and education of the specified 2, 4 month schedule is needed, as well as a review course for those clinicians not vaccinating infants due to false contraindications. Lastly, since a caregiver's knowledge of another rotavirus vaccinated infant proved to be harmful to adherence to the clinician recommendation, further research or knowledge about this situation may be beneficial to increasing adherence. Additionally, reinforcing the safety and protection

offered by the rotavirus immunization may help to increase adherence to the clinician recommendations. Barriers and incentives for adherence to the clinician recommendation for 2, 4 month vaccination were demonstrated on both a logistical and individual level. These findings, combined with further research conducted in other Bolivian hospitals may help to increase adherence to the rotavirus vaccination schedule across the infant population of Bolivia as a whole.

PUBLIC HEALTH IMPLICATIONS

- Caregivers who are present in these hospitals are showing a high level of adherence to the suggested Bolivian Ministry of Health (MOH) rotavirus vaccination guideline. Therefore, the impact of rotavirus should be lessened and herd immunity should allow benefits to those without vaccinations as well.
- High adherence levels to the rotavirus vaccination timeline should also coincide for other vaccines received simultaneously (pentavalent and polio in Bolivia)
- Without intermittent training or refresher courses for clinicians, issues preventing timely adherence, such as false contraindications and a lack of patient education, may perpetuate missed opportunities to vaccinate infants on time.
- If caregivers continue having difficulty complying with the clinician recommended schedule, infants will continue to be at risk for rotavirus infection, despite having excellent adherence to the MOH timeline.

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Table 1. Characteristics of Infants and Caregivers.

Variable	Category	Total (%)
Hospital Site n=71	Los Andes	56 (79.9)
	Corea	15 (21.1)
Place of Recruitment n=71	Vaccination clinic	49 (69.0)
	Waiting room	22 (31.0)
Zone n=62	Alto Lima	13 (21.0)
	Los Andes	8 (12.9)
	Nuevos Horizontes	7 (11.3)
	Other[1]	34 (54.8)
Gender n=68	Female	37 (59.7)
Caregiver n=71	Mother	67 (94.4)
	Other[2]	4 (05.6)
Education n=70	<High School	42 (60.0)
	≥High School	28 (40.0)
Marital Status n=71	Married	25 (35.2)
	Not Married[3]	46 (64.8)
Monthly Income[4] n=62	<500	33 (53.2)
	≥501	29 (46.8)

[1]Other zones include three or fewer caregivers in each

[2] Represents an aunt, father, or grandmother that responded to the survey

[3] Includes caregivers who are living with a partner or divorced respondents

[4] Currency is Boliviano

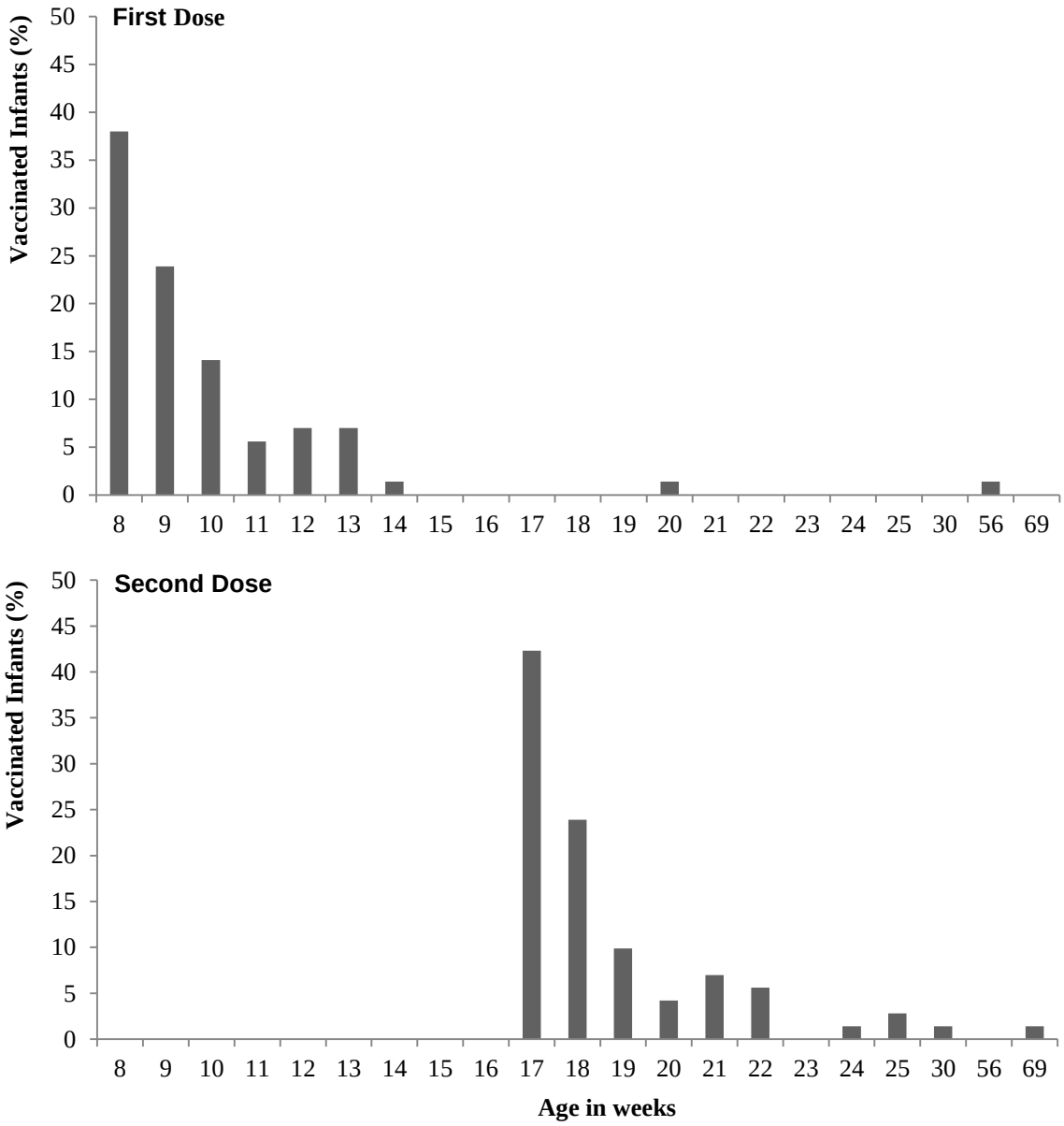


Figure 1. Age of Infant at First and Second Rotarix Vaccine Administration. Bars represent the percentage of infants who received their first or second Rotarix® vaccination at the age (in weeks) specified. The sample size is 71.

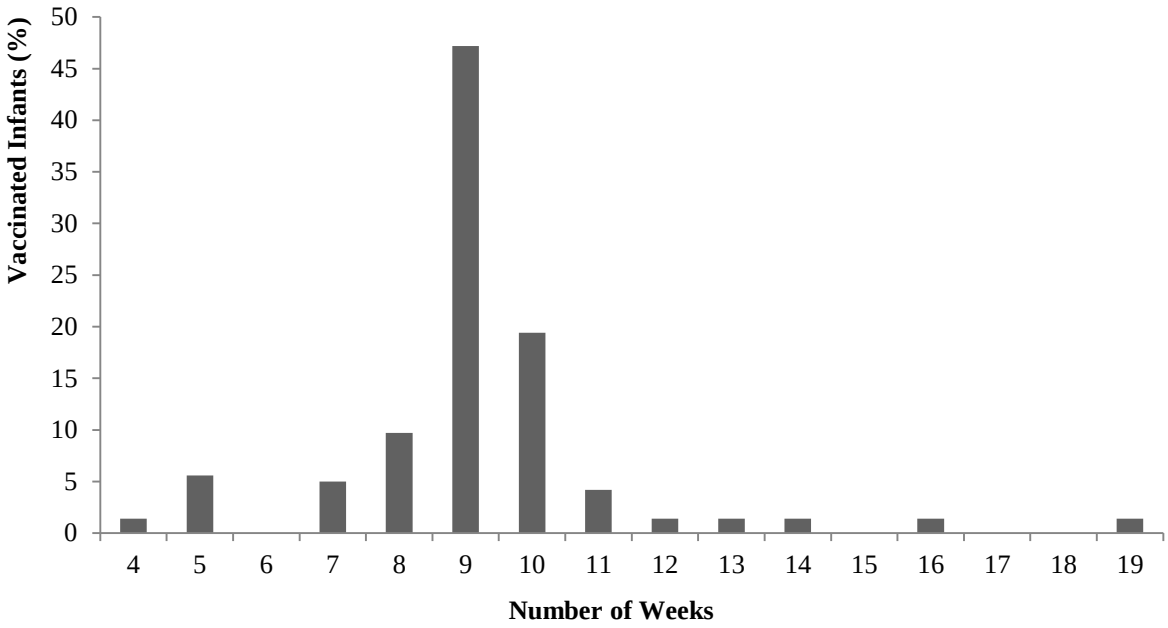


Figure 2. Length of Time in Weeks Between First and Second Rotarix Vaccinations. Bars represent the percentage of infants for each specified amount of time that elapsed between receiving the first and second Rotarix® vaccinations. The sample size is 71.

Table 2. Predisposing factors associated with failure of adhering to the clinician recommendation of Rotarix 2, 4 month dosage schedule in Los Andes and Corea Hospitals in El Alto, Bolivia in 2013 N=66

Variable	Category	OR[1]	95%CI[2]	p-value[3]
Gender	Male	1.21	0.45-3.24	0.71
Education	<High School			
	≥High School	0.65	0.23-1.86	0.42
Birth Order	First Born			
	Other[4]	1.02	0.38-2.78	0.96

[1]Odds ratio from multivariable logistic regression.

[2]95% confidence interval

[3]P-value from Wald test

[4]Includes infants up to fifth born

Table 3. Predisposing, enabling, reinforcing, preventive activity, and situational factors associated with failure of adhering to the clinician recommendation of Rotarix 2, 4 month dosage schedule in Los Andes and Corea Hospital in El Alto, Bolivia in 2013 N=52

Variable	Category	OR[1]	95%CI[2]	p-value[3]
Married[4]	No			
	Yes	4.33	0.87-21.60	0.07
Timeline knowledge	No			
	Yes	0.05	0.00-2.33	0.13
Knowing others	No			
	Yes	4.60	1.04-20.36	0.04*
Safety[5]	No			
	Yes	0.05	0.01-0.50	0.01*
Health improvement[6]	No			
	Yes	0.34	0.08-1.50	0.15

[1]Odds ratio from multivariable logistic regression.

[2]95% confidence interval

[3]P-value from Wald test

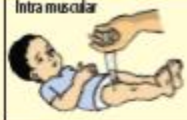
[4]Not married also includes caregivers who are living with a partner or divorced

[5]The belief that the vaccine is safe for the child

[6]The belief that the vaccine improves the child's health

* Significant at p-value <0.05

APPENDIX I

VACUNA	ENFERMEDAD QUE PREVIENE	EDAD DE APLICACIÓN	VÍA	DOSIS Y CANTIDAD
BCG	Formas graves de Tuberculosis 	Dosis unica Recién Nacido	Intra dermica 	1 Dosis 0,1 ml
Pentavalente	Difteria, Tétanos, Coqueluche, Hepatitis B, neumonías y meningitis por Hib 	1ra dosis 2 meses 2da dosis 4 meses 3ra dosis 6 meses	Intra muscular 	3 Dosis 0,5 ml
DPT	Difteria, Tétanos, Coqueluche 	1er Refuerzo 18 a 23 meses 2do refuerzo 48 a 59 meses	Intra muscular 	1 Dosis 0,5 ml 1 Dosis 0,5 ml
Antipolio	Poliomielitis 	1ra dosis 2 meses 2da dosis 4 meses 3ra dosis 6 meses 1er Refuerzo 18 a 23 meses 2do Refuerzo 48 a 59 meses	Oral 	5 Dosis 2 Gotas
Antirotavirus	Diarreas severas por rotavirus 	1ra dosis 2 meses (hasta los 3 meses) 2da dosis 4 meses (hasta los 8 meses)	Oral 	2 Dosis 1,5 ml
Influenza Estacional Pediátrica	Influenza estacional 	Niños de 6 a 11 meses: 1ra dosis al contacto 2da dosis al mes de la 1ra Niños de 12 a 23 meses: 1 sola dosis	Intra muscular 	2 Dosis 0,25 ml 1 Dosis 0,25 ml cada año
SRP	Sarampión, Rubéola, Parotiditis 	Dosis Unica de 12 a 23 meses	Subcutanea 	1 Dosis 0,5 ml
Antiamarílica	Fiebre Amarilla 	Dosis Unica de 12 a 23 meses	Subcutanea 	1 Dosis 0,5 ml
dT adulto	Difteria, Tétanos neonatal y tétanos del adulto (desde los 10 a 49 años, Hombres y Mujeres) 	1ra dosis al contacto 2da dosis al mes 3ra dosis a los 6 meses 4ta dosis al año 5ta dosis al año y un refuerzo cada 10 años	Intra muscular 	5 Dosis 0,5 ml
Influenza Estacional adulto	Influenza estacional 	Mayores a 65 años	Intra muscular 	1 dosis 0,5 ml cada año

¡La Vacunación es Gratuita en todos los Establecimientos de Salud, los 365 dias del año!

APPENDIX II

EMORY UNIVERSITY

Institutional Review Board

TO: Juan Leon
Principal Investigator
Global Health

DATE: November 7, 2013

RE: **Continuing Review Expedited Approval**
CR1_IRB00056127

IRB00056127
Effect of Nutrition, Immunity, and Vaccines on Pediatric Enteric Infections

Thank you for submitting a renewal application for this protocol. The Emory IRB reviewed it by the expedited process on 11/6/2013, per 45 CFR 46.110, the Federal Register expeditable categories F2(a), F2(b), F3, F4, F7, and/or 21 CFR 56.110. This reapproval is effective from **11/21/2013** through **11/20/2014** . Thereafter, continuation of human subjects research activities requires the submission of another renewal application, which must be reviewed and approved by the IRB prior to the expiration date noted above.

The following documents were included in this review:

- Consent Aymara, version date 10/15/2012
- Consent English, version date 10/15/2012
- Consent Spanish, version date 10/15/2012
- Primary Aim Aymara Consent, version date 10/15/2012
- Primary Aim English Consent, version date 10/15/2012
- Primary Aim Spanish Consent, version date 10/15/2012
- Secondary Aim English Consent, version date 7/18/2013
- Secondary Aim Spanish Consent, version date 7/18/2013

Any reportable events (e.g., unanticipated problems involving risk to subjects or others, noncompliance, breaches of confidentiality, HIPAA violations, protocol deviations) must be reported to the IRB according to our Policies & Procedures

at www.irb.emory.edu, immediately, promptly, or periodically. Be sure to check the reporting guidance and contact us if you have questions. Terms and conditions of sponsors, if any, also apply to reporting.

Before implementing any change to this protocol (including but not limited to sample size, informed consent, study design), you must submit an amendment request and secure IRB approval.

In future correspondence about this matter, please refer to the IRB file ID, name of the Principal Investigator, and study title. Thank you.

Sincerely,

Martha C. Patterson, CIP
Research Protocol Analyst
This letter has been digitally signed

CC:	Fabiszewski		Anna	Global Health
	Rebolledo Esteinou		Paulina	RTP
	Suchdev	Parminder	GEN PED EGLESTON	