Distribution Agreement

Predictors of Treatment-Seeking Behavior Among Bolivian Caregivers of Children Under Five With Acute Diarrhea

By

Stephen Ragan, MD

Master of Public Health

Epidemiology

____

Juan Leon, PhD, MPH

Faculty Thesis Advisor

Predictors of Treatment-Seeking Behavior Among Bolivian Caregivers of

Children Under Five With Acute Diarrhea

By

Stephen Ragan, MD

BS, University of Georgia, 2000

MD, Medical College of Georgia, 2008

Faculty Thesis Advisor: Juan Leon, PhD, MPH

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2014

Abstract

Predictors of Treatment-Seeking Behavior Among Bolivian Caregivers of Children Under Five With Acute Diarrhea

By Stephen Ragan, MD

In 2010, Bolivia's under-five mortality rate (per 1,000 live births) was 54 deaths, much higher than the regional average of 18 deaths. Diarrheal illness is responsible for an estimated 9% of Bolivia's elevated <5 mortality. Because both the economic burden and heath outcomes of childhood diarrhea may be associated with the treatment-seeking behavior of caregivers, the primary goal of this study was to identify predictors of treatment-seeking behavior among Bolivian caregivers of children under five years old with an acute diarrheal illness. In order to assess whether any of the six specified risk factors (e.g., age of child; gender of child; rural vs. urban home environment; reported history of difficulty paying for treatment; reported history of withholding treatment because of fear of cost; and monthly household income) were good predictors of treatment-seeking behavior, we collected data from caregivers in six Bolivian hospitals from 2007 to 2009. The strength of the six specified risk factors as predictors of treatment-seeking behavior was assessed through three separate regression analyses. This study found that the age of the child was a strong predictor of the type of treatment (informal care vs. formal care vs. a combination of both) sought by caregivers. Children aged one year or younger were significantly less likely to receive a combination of informal and formal care than were children older than one year. In terms of when medical care was accessed, a caregiver's past behavior was found to be a strong predictor of future behavior. A history of having not sought medical care because of fear of cost was significantly associated with longer delays in caregivers taking a child with diarrhea to the hospital. Interestingly, household income was not significantly associated with the type nor the timing of medical treatments accessed by caregivers. These results suggest that both patient-specific risk factors (e.g., age) and caregiver-specific risk factors (e.g., a history of withholding treatment because of fear of cost) can serve as predictors of treatment-seeking behavior. Studies such as this deepen our understanding of the associations between risk factors and caregiver behavior and can help inform public health policy.

Predictors of Treatment-Seeking Behavior Among Bolivian Caregivers of Children Under Five With Acute Diarrhea

By

Stephen Ragan, MD

BS, University of Georgia, 2000

MD, Medical College of Georgia, 2008

Faculty Thesis Advisor: Juan Leon, PhD, MPH

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2014

Table of Contents

Tables

LITERATURE REVIEW

Global Burden of Disease

Worldwide, acute diarrheal disease represents a major cause of morbidity and mortality in children under five years old, with approximately 1.4 billion episodes annually (1). Children in low-income nations are disproportionately affected, representing approximately 85% of the 2.1 million diarrheal deaths that occur each year (1). The possible etiologies of acute diarrhea are myriad and include both infectious and noninfectious agents. Among these, rotavirus deserves particular consideration from the public health community. Rotavirus is one of the most common causes of gastroenteritis world wide, with an estimated annual global incidence exceeding 135 million (1). Data from global surveillance studies implicate rotavirus in 20% to 70% (regional median 39%) of all cases of diarrhea requiring hospitalization of a child under five years old (2).

Epidemiology of Rotavirus Gastroenteritis

Gastroenteritis is an inflammatory process affecting the stomach and intestine. Symptoms commonly include fever, vomiting, and diarrhea. Gastroenteritis caused by rotavirus is so common that nearly every child in the world will have at least one episode by age 5. Worldwide, in children under 5 years old, rotavirus causes about 24 million cases of gastroenteritis requiring outpatient treatment and 2.4 million cases requiring hospitalization each year (3). A recent study estimates that among children under 5 years old, rotavirus is responsible for approximately 527,000 deaths annually, or about 1440 deaths each day. While the incidence of rotavirus disease in industrialized countries is similar to that in developing countries, deaths caused by rotavirus disease are rare in industrialized countries (4). In contrast, resource poor countries are disproportionately affected, with more than 80% of all rotavirus deaths estimated to occur in south Asia and sub-Saharan Africa (5).

Much of the morbidity and mortality associated with rotavirus can be attributed to the fact that it is a highly contagious pathogen. Transmission occurs primarily via the fecal-oral route when uninfected susceptible individuals come into contact with infected individuals or fomites, food, or water that have been contaminated with infected feces (reviewed in 6). Rotavirus can remain infective on human hands for over 4 hours and on dry surfaces up to 10 days. Those infected can begin shedding the virus in their stool before the onset of symptoms and continue for several weeks thereafter (reviewed in 6). The estimated minimum rotavirus dose needed to cause infection (i.e., its minimum infective dose or MID) is less than $1.5*10^3$ virus particles for some healthy adults. Estimates of the MID for young children, who are more susceptible to rotavirus infection than adults, have not been experimentally determined. With a single gram of stool containing $>10^{12}$ virus particles, as little as 1 μg of stool could contain many times the minimum viral dose needed to cause infection (reviewed in 7).

Pathophysiology of Rotavirus Gastroenteritis

Rotavirus primarily infects the epithelial cells of the small intestine, resulting in fever, vomiting, and diarrhea (reviewed in 3). The vomiting may be severe enough to frustrate oral rehydration efforts. If this occurs in the presence of diarrhea, the resulting dehydration and electrolyte abnormalities may require hospitalization. The symptoms of rotavirus gastroenteritis are often most severe in younger children (i.e., those between 3 months and 3 years old). Neonates, however, rarely develop clinical illness (reviewed in 6).

Rotavirus Virology

Rotavirus consists of a non-enveloped triple-layered capsid surrounding a genome of double-stranded RNA. This RNA codes for 6 structural proteins (VP1, VP2, VP3, VP4, VP6, and VP7) and six non-structural proteins (NSP1 through NSP6). Of these proteins, the VP7 (G type) protein and VP4 (P type) protein are the most important in terms of classification of the different rotavirus strains (reviewed in 6). The genome of an individual rotavirus virion will code for a specific VP7 genotype (denoted G1, G2, G3, etc.) and a specific VP4 genotype (denoted P[1], P[2], P[3], etc.). In humans, G1, G2, G3, G4, and G9 are the most common VP7 genotypes, and P[8], P[4], and P[6] are the most common VP4 genotypes (reviewed in 6). A particular rotavirus strain is classified according to its VP7/VP4 genotype pair. Globally, the genotype combinations G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] comprise 70-90% of the circulating rotavirus strains. However, predominant circulating rotavirus strains vary region to region and year to year (reviewed in 6).

Rotavirus Vaccination

The evidence that the incidence of childhood rotavirus gastroenteritis is similar for both industrialized and developing countries indicates that “improvements in housing, water supply, sanitation, personal hygiene, food quality, nutrition, and maternal education are unlikely to reduce the overall incidence of rotavirus infections.” (6) As such, widespread pediatric vaccination against rotavirus remains the most effective public health intervention available (reviewed in 6).

Two rotavirus vaccines are currently in use internationally: pentavalent rotavirus vaccine (i.e., PRV or RotaTeq) and human strain rotavirus vaccine (i.e., HRV or Rotarix). Both are live oral vaccines. RotaTeq contains 5 human-bovine strains (G1P[5], G2P[5], G3P[5], G4P[5], and G6P[8]) and requires 3 doses. Rotarix contains a single attenuated human rotavirus strain (G1P[8]) and requires only 2 doses (reviewed in 6). Both vaccines have been shown to be highly efficacious in large-scale trials. The Rotavirus Efficacy and Safety Trial (REST), a phase III trial conducted primarily in Western Europe and the United States, determined that vaccination with RotaTeq was associated with substantial decreases in the incidence of infants receiving outpatient treatment for rotavirus gastroenteritis in health clinics (86% reduction) and emergency departments (94% reduction) as well as decreases in the number of infants hospitalized for rotavirus gastroenteritis (96% reduction) (reviewed in 6). In a phase III trial covering 10 Latin American countries, vaccination with Rotarix was associated with a large decrease in the incidence of severe rotavirus gastroenteritis among infants (81% reduction) as well as a decrease in rotavirus-associated hospitalizations among infants (83% reduction). Furthermore, although Rotarix incorporates only one rotavirus strain, cross protection against other strains (e.g., G3, G4, and G9) has been demonstrated (reviewed in 3, reviewed in 6). A third rotavirus vaccine, the Lanzhou lamb rotavirus vaccine (LLR), has only been approved for use in China and will not be discussed here (8).

Rotavirus Vaccine Availability

RotaTeq is currently available in 97 countries, including the European Union. More than 10 countries have included it in their national immunization programs, including the United States, Nicaragua, Belgium, and Iraq. It was included in WHO's 2008 list of vaccines for purchase by the UN (reviewed in 8).

Rotarix is currently available in over 116 countries, including the United States. Brazil, El Salvador, Mexico, Panama, South Africa, and Venezuela are among more than 20 that have included Rotarix in their national immunization programs. Like RotaTeq, it has been added to WHO's 2008 list of vaccines for purchase by the United Nations (reviewed in 8). Rotarix has been the rotavirus vaccine used in Bolivia since its introduction there in 2008 (9).

Global Costs of Rotavirus Gastroenteritis

In addition to the health burden described above, rotavirus gastroenteritis imposes a substantial economic burden on a country, especially in the absence of a comprehensive vaccination program. The economic burden of rotavirus on a country can be defined in different ways depending on the specific research goals and the available data. For example, one researcher may estimate the total costs for a specific annual birth cohort while another may define the economic burden of rotavirus as the total annual costs for all children less than 5 years of age (10).

In addition, the national economic burden of rotavirus can be investigated from different perspectives, for example, the societal perspective or the state perspective (which, depending on the country, may be synonymous with the healthcare system perspective). When estimating economic burden, different perspectives are defined by the specific cost data that should be included in the analysis. For instance, rotavirus-associated healthcare costs borne by the government would contribute to a country's economic burden of rotavirus from the state perspective, but the healthcare costs borne by the caregivers of children with rotavirus gastroenteritis would not be included in the state perspective (10).

The different types of costs that contribute to the economic burden of disease include: direct medical costs (e.g., medication, personnel, hospital bills, etc.) borne by providers, patients and caregivers; non-medical direct costs (e.g. travel costs) borne by patients/caregivers; and indirect costs (e.g., the cost of time lost from paid/productive work) borne by patients/caregivers and/or society (10).

The economic burden of rotavirus gastroenteritis from the perspective of the healthcare system comprises the total cost of treatment provided by formal healthcare facilities (e.g., hospitals and outpatient clinics). These include the costs of medication, diagnostic tests, and the time of healthcare professionals as well as less-obvious costs, such as laundry, electricity, and equipment maintenance. While these are all direct medical costs, one must remember that only direct medical costs to formal medical facilities/institutions contribute to the economic burden from the healthcare perspective. Other direct medical costs (i.e., those associated with informal healthcare providers such as traditional healers or fees paid by caregivers for treatment at a formal facility) would not be included (10). The economic burden of rotavirus from the healthcare system perspective has been investigated in several countries and regions. In one study of several Latin American and Caribbean countries, the estimated economic burden of rotavirus disease incurred from birth to 5 years of age (by all children born in 2003) was

$7,061,108 in Argentina, $25,332,499 in Brazil, $4,641,283 in Chile, and $696,601 in the Dominican Republic. In this study, higher direct medical costs were seen in higher income countries (11).

From the societal perspective, the economic burden of rotavirus gastroenteritis includes all costs borne by the families and caregivers of children with rotavirus gastroenteritis. To achieve a complete picture of the economic burden associated with rotavirus, one must investigate the societal perspective. In this study, the societal perspective includes all costs borne by caregivers of children <5 years old who are receiving treatment for rotavirus disease. These cost include "out-of-pocket" costs and indirect costs. Out-of-pocket costs include both direct medical and direct non-medical costs. Direct medical costs to caregivers (also known as household out-of-pocket costs) represent the portion of direct medical costs borne by a household and can come from many sources. These may include fees paid prior to hospital admission (e.g., from visits to a clinic or emergency department) and after discharge (e.g., from outpatient follow-up). Also, direct medical costs to caregivers may also include those associated with treatment in the informal sector (i.e., treatment that is not accessed through a hospital admission or a visit to an outpatient facility). The informal healthcare encompasses a broad spectrum of resources and may include treatment received from village healers, family members, or pharmacists. Direct nonmedical costs primarily encompass expenses from transportation (e.g., fuel, taxi fare, etc.) and overnight lodging during hospitalization (e.g., room and board) (10-13).

Indirect costs (i.e., productivity losses) are defined as "the value of the time lost by…caregivers from other productive activities [such as paid work]" during the acute episode of diarrhea (10). Because the value of lost productivity depends on the multiple factors specific to an individual caregiver such as age and occupation, estimating indirect costs can be complicated. Also, estimates of productivity losses rely on data reported by caregivers who may be inclined to over report such costs. As such, researchers may decide to report estimates of societal burden with and without estimated productivity losses (10).

In the previously mentioned study of Latin American and Caribbean countries, the estimated economic burden of rotavirus from the societal perspective was $8,137,641 in Argentina, $33,537,642 in Brazil, $5,402,388 in Chile, and $1,032,454 in the Dominican Republic (11). Because the societal cost includes the direct medical costs of formal treatment included in the state perspective plus any direct medical costs of informal treatment, direct non-medical costs, and indirect costs, the economic burden of rotavirus from the societal perspective can be substantially greater than that from the state perspective. The proportion of the societal burden that is borne by the household depends on multiple factors such as the availability of government subsidized medical coverage or the type of hospital (public vs. private) providing care (12, 14).

There is commonly an inverse relationship between a country's rotavirus health burden and economic burden. In general, wealthier populations suffer decreased morbidity and mortality compared to less-wealthy populations while potentially incurring much greater costs for each episode of rotavirus-associated diarrhea (13, 15, 16). However, for caregivers in developing countries, the out-of-pocket and indirect costs associated with treating a single episode of gastroenteritis may require a large percentage of their household income. For families in Kyrgyzstan, the mean total cost of treating a single episode of rotavirus gastroenteritis requiring hospitalization (including all associated outpatient costs) was about 30% of the average monthly income (17). In Uzbekistan, the inpatient costs alone represent approximately 37% of a family's monthly income (18). In a study conducted in India, for each diarrheal episode requiring hospitalization, median cost to caregivers was estimated to be 2.2% or 5.8% of household annual income, depending on the type of hospital (12).

Cost Effectiveness of Rotavirus Vaccination

The effectiveness of vaccination can be measured in disability-adjusted life years (DALYs) averted, with one DALY representing the loss of one year of healthy life (19). The net cost of vaccination is equal to the total cost of the vaccine delivery minus the total treatment cost saved through vaccination (10). Cost effectiveness analyses (CEAs) can be performed by calculating the incremental cost effectiveness ratio (ICER). The ICER compares the net cost of an intervention to the DALYs averted by said intervention (10, 19). The lower the ICER, the more cost effective the intervention is. Interventions are considered "cost effective" if each DALY averted costs between one and three times GDP per capita and "very cost effective" if each DALY averted costs less than GDP per capita (19). If the net costs are negative (i.e., the costs of vaccination are less than the costs of treatment in the absence of vaccination), then one could not calculate the ICER and vaccination would be considered "cost saving" compared to no vaccination (10). Another common metric used in CEAs is the vaccine break-even price. This is the price at which the costs of vaccination are equal to the costs of treatment without vaccination (i.e., net costs equal zero) (20). In contrast to the ICER, a higher break-even price indicates greater vaccination cost effectiveness.

Like the economic burden of rotavirus gastroenteritis, the cost effectiveness of rotavirus vaccination can be investigated from different perspectives (e.g., state/healthcare system vs. societal). From the healthcare system perspective, net costs would equal the costs of vaccination minus the direct medical costs that would be borne by the state in the absence of vaccination. In contrast, net costs from the societal perspective would equal the costs of vaccination minus the "out-of-pocket" and indirect costs that would be borne by caregivers of children <5 years old in the absence of vaccination (20).

Multiple studies report that, from the healthcare system perspective, introduction of rotavirus vaccination through a national vaccination program would be very cost effective in developing countries (20). A CEA study of low- and middle-income countries from 2009 reported that implementing rotavirus vaccination would be very cost effective for all income groups studied over a range of vaccine prices. The researchers found that this was particularly true for low-income countries because their higher rotavirus-associated mortality (13). These results were supported in a more recent study of 72 resource-poor countries eligible for financial assistance from the Global Alliance for Vaccines and Immunizations (GAVI). Under all vaccine-pricing scenarios, rotavirus vaccination would be either cost effective or very cost effective (from the state perspective) regardless of whether all countries were analyzed together or grouped into regions (21).

Because the economic burden of rotavirus gastroenteritis from the societal perspective is potentially much greater than that from the state perspective, the cost effectiveness of universal vaccination are also potentially greater from the societal perspective (16, 20). In a 2008 study, the break-even price in Brazil (2004 Brazilian reais) would be R$9.98/dose from the societal perspective and R$4.24/dose from the healthcare perspective (22). In Kyrgyzstan, the healthcare system break-even price (2008 US$) was $0.65/dose, and the societal break-even price was $1.14/dose (17). In Vietnam, assuming a vaccine price of US$5.00/dose (2004 US dollars), the ICER was $540 (per DALY averted) from the societal perspective and $550 from the healthcare system perspective. With a per-capita GDP of $580, universal rotavirus vaccination was found to be very cost effective from both perspectives, yet more cost effective from the societal perspective (23). Regardless of the perspective, the cost effectiveness of universal rotavirus vaccination is largely dependent on factors specific to a given country. Such factors may include vaccine price relative to per capita GDP, the relative cost of treatment, and the severity and disease burden (including the mortality rate) of rotavirus gastroenteritis (reviewed in 6, 20, reviewed in 24). As such, the results of vaccination CEAs in one country may not be applicable to another country.

Factors Associated With Seeking Professional Medical Treatment for Childhood Diarrhea

In addition to performing cost effectiveness analysis, investigators may develop a more thorough understanding of the economic burden of disease by researching the behavior of patients and caregivers. Unfortunately, the available literature lacks an abundance of consistent data regarding factors associated with healthcare-seeking behavior in caregivers of children with acute diarrheal illness. Although certain common trends can be identified for developing countries, the results of published studies can seem variable and inconsistent. In general, greater family wealth was associated with seeking formal medical care (25-28). Associations between care-seeking behavior and other factors were less consistent. For instance, in a study comparing 3 African countries, Rheingans et al. reported that greater cost was associated with male sex in Gambia and Mali (but not in Kenya) and with increased severity of illness in Kenya and Mali (25). In contrast, Burton et al. reported that males in Kenya were more likely than females to receive hospital-based medical care for diarrhea, but they found no evidence of such an association with increased severity of illness (26). While Page et al. found no sex-based differences in care-seeking behavior in Niger, they did find statistically significant associations with age (3-23 months) and an increased number of children in the household (≥3) (29).

Factors that influence treatment-seeking behavior may also be described as barriers to healthcare. In rural areas of developing countries, there may be decreased access to adequate formal medical care compared to urban areas (30, 31). Other barriers may include travel costs/distance (25, 28, 32) or a belief by caregivers that a child's acute diarrhea does not require medical treatment (25, 28).

Bolivia

This study is based on data gathered at hospitals located exclusively in the Plurinational State of Bolivia. Bolivia is a landlocked South American republic. It borders Brazil to the north and east, Paraguay and Argentina to the south, and Chile and Peru to the west. It has a population of approximately 10.3 million people with 67% living in an urban area (33). Boliva covers total area of almost 1.1 million sq. kilometers, making it almost three times the size of Montana. Of its three official languages, ~61% speak Spanish, ~21% speak Quechua, and ~15% speak Aymara (33).

Despite experiencing sustained growth during 2010-2012, Bolivia remains one of the poorest Latin American countries. The unemployment rate in 2012 was 7.5% and, according to a 2009 estimate, approximately 51% of the population lives on less than $2/day. The per capita GDP (PPP) is US$5,000 (2012 dollars), putting Bolivia at 156th place worldwide (33). The World Bank classifies Bolivia's economy as lower middle income. Along with all low-income and middle-income economies, Bolivia would also be classified as a developing economy (34).

Bolivia's economy can be divided into three major income sources: agriculture, industry, and services (33, 35, 36). Agriculture, which includes both forestry and fishing, accounted for about 13% of Bolivia's 2010 GDP. Industry, which includes mining, manufacturing, construction, and energy production, represented about 37% of GDP. The remaining 50% of the 2010 GDP was composed of service industries. These service industries include such widely varying fields as tourism and banking (33, 35-37).

Bolivia is also ranked low in many measures of population health and national development. The Human Development Index (HDI), a comprehensive indicator of a population's well-being, is calculated from various measures of population health, education, and income. It can be used to track a population's developmental progress over time as well as compare different populations (38). In 2011, Bolivia's HDI was 0.663. This score fell below the global HDI of 0.682 and ranked Bolivia in 108th place out of a 187 total countries assessed. Bolivia's HDI was also well below 0.731, the HDI calculated for the entire region of Latin America and the Caribbean (38). The implications of this lagging HDI are echoed in several more specific indicators of Bolivia's health and development. In 2009, Bolivia's life expectancy at birth was 68 years, well below the regional average of 76 years. In 2010, its maternal mortality rate (per 100,000 live births) of 190 deaths was substantially above the regional average of 63, and the under-five mortality rate (per 1,000 live births) was 54 deaths compared to a regional average of 18. (39). At first glance, Bolivia's current situation appears bleak. However, examination of the statistics from previous years shows that, while the under-five mortality rate is still high, Bolivia has made substantial and consistent improvements for the past two decades. In 1990, the under-five mortality rate was well over 100 deaths per 1000 live births. Although the 2010 rate is not acceptable, it nonetheless represents a major improvement (39).

Bolivia's severe poverty and poorly developed infrastructure also contribute to decreased access to education and family planning services for its citizens. These factors, in turn, contribute to the elevated fertility rates consistently seen in Bolivia. In 2012, the total fertility rate was 2.93 children/woman (33). Like the aforementioned reduction in the under-five mortality rate, this represents a relatively large decrease from the total fertility rate of 4.9 of 1990 (36).

Regarding modern utilities, Bolivia still lags behind the Latin American and Caribbean region as a whole. In 2009, Bolivia provided 77.5% of the population with access to electricity compared to the region's 93.4%. In 2010, 88% of Bolivians had access to an improved water source (such as in-home plumbing or a public tap) compared to 94% overall (36). However, Bolivia has had less success providing improved sanitation facilities (i.e., a system that prevents all human and animal contact with human waste). In 2010, only 27% of Bolivians had such access compared to 79% through the region (36). According to 2001 census data, the mean number of people per household in Bolivia did not differ much between urban homes (4.3 people) and the general population (4.2 people) (36). Unfortunately, data regarding the percentage of urban households living in overcrowded conditions (i.e., 2 or more people per room) were not available. However, in this census, 40% of all homes in Bolivia were identified as overcrowded (36).

Rotavirus Disease and Vaccination in Bolivia

In 2008, Bolivia initiated a nationwide immunization program using Rotarix, the 2-dose rotavirus vaccine (9). This program was made possible with financial support from GAVI (40). Coverage rates for rotavirus vaccination in Bolivia have been regularly documented since 2008. Although only about 40% of Bolivian children completed the rotavirus vaccination regimen in 2008, coverage increased dramatically in subsequent years: 65% in 2009; 76% in 2010; 80% in 2011; and 76% in 2012 (41).

Although rotavirus vaccination coverage rates have remained stable in the last few years, surveillance studies suggest that rotavirus still accounts for a substantial percentage of Bolivia's pediatric hospitalizations for diarrhea. In 2011, there were over 1,900 hospital admissions of children <5 years old for diarrheal illness in Bolivia. Of those admissions where patients were eligible to participate in a rotavirus surveillance study, epidemiological data and stool specimens were collected for 1,456 cases. Approximately 34% (n=495) of these 1,456 cases of pediatric diarrheal illness requiring hospitalization tested positive for rotavirus (42). When one considers that diarrheal illness is responsible for an estimated 9% of Bolivia's elevated <5 mortality, one can better appreciate the threat posed by rotavirus (39).

Gaps in Knowledge and Need

Multiple studies have shown associations between environmental/demographic characteristics and differing health outcomes of pediatric diarrheal disease. For instance, certain living environments (such as crowded housing or a rural setting) have been associated with either acquiring rotavirus gastroenteritis (43) or experiencing a worse outcome (30, 31). As described above, both the economic burden and heath outcomes of childhood diarrhea may be associated with the treatment-seeking behavior of caregivers. As such, investigating potential predictors of caregiver treatment-seeking behavior may enrich our understanding of the ultimate economic and health outcomes of diarrheal disease as well as inform the decisions of policy-makers and healthcare providers. Currently, little information is available regarding caregiver treatment-seeking behavior in Bolivia.

Goals and Aims

The goal of this study is to identify variables associated with families seeking treatment of a diarrheal illness in a child. The first aim of this study is to identify predictors of pre-hospital treatment-seeking behavior among caregivers of children under 5 years old with an acute diarrheal disease using binary logistic regression. The second aim is to further investigate specified risk factors as predictors of pre-hospital treatment-seeking behavior using polytomous logistic regression. The third aim is to assess predictors of longer delays in caregivers accessing hospital-based care for pediatric diarrheal disease using ordinal logistic regression.

Significance

National public health interventions are complicated and costly endeavors for any country. This is particularly true for countries that face increased public health challenges with limited resources. The decision to implement an intervention, no matter how promising or necessary it may seem, should be based on the best evidence available. Identifying strong predictors of treatment-seeking behavior would allow public health policy-makers and healthcare providers to make better informed decisions regarding current programs and may lead to the identification of new intervention targets in the future. This thesis is designed to help Bolivia meet both of those goals by providing information currently unavailable in the published literature. Furthermore, the results of this thesis may also benefit countries with similar public health challenges as Bolivia.

METHODS

Participants

The study population consisted of caretakers of children <5 years old suffering from a diarrheal illness who presented at a study hospital in Bolivia for treatment. Six hospitals located in four Bolivian cities participated in this study: Hospital Del Niño and Hospital Materno-Infantil, both located in La Paz; Hospital Germán Urquidi and Centro Pediatria Albino R. Patiño, both located in Cochabamba; Hospital Boliviano Holandes in El Alto; and Hospital Mario Ortiz Suarez in Santa Cruz. Individuals were eligible to participate if they were at least 18 years old, currently caring for a child <5 years old receiving treatment (either inpatient or outpatient) for acute diarrhea, and gave consent.

Caregivers were recruited from 2007 to 2009, resulting in a sample population of 1,107 participants. The sample size was determined according to guidelines published by the World Health Organization and based on a desired precision of 10% and a coefficient of variation of 0.5 for diarrheal treatment cost per patient at each hospital (10). The data from many of these participants in the sample population were not included in subsequent analyses. All data from the following sample subgroups were excluded from analysis because of their small sample sizes (n<10): all inpatients from Hospital Germán Urquidi and all outpatients from Hospital Del Niño and Hospital Maternal-Infantile. Participants were also excluded on an individual basis, for example, because of incomplete or invalid data.

Rotavirus vaccination became available in Bolivia in the latter half of 2008. Because of this, some of the data collected toward the end of the study were associated with children who had been vaccinated against rotavirus. All data associated with children with a known history of rotavirus vaccination (n = 56) were also excluded from analysis. Children with an unknown rotavirus vaccination status were considered to be unvaccinated and included in the analysis group. Henceforth, the term “unvaccinated” will be used for those with a reported negative rotavirus vaccination history as well as those missing data for their rotavirus vaccine status. The final sample used for analysis included 495 participants.

The program G*Power (version 3.1.7) was used to ensure that the number of subjects included in each regression analysis was sufficient to ensure adequate power (≥0.80). The Demidenko procedure with variance correction was used for each power calculation. We assumed an effect size of 2.0 (i.e., odds ratio = 2.0) and $R^2 = 0.1$ (44). The minimum sample size need for our analyses was determined to be 91 subjects. All regression analyses preformed in this study included data from substantially larger samples than the minimum requirement.

Data Collection and Management

Trained research personnel collected data reported by caregivers through interviews structured around an extensive questionnaire based on the aforementioned WHO guidelines (10). Handwritten data were compiled into an electronic database. To ensure accuracy during this process, all data were double-entered using Epi Info version 3.4.3. When these double-entered data were compared, discrepancies were recorded and corrections were based on hard copies of the original questionnaires. Finally, 5% of the entered data were randomly sampled and found to perfectly match the data recorded on these original questionnaires.

Analysis

All data cleaning and almost all statistical analyses were performed with SAS version 9.3 (Cary, NC). Most data were initially investigated with descriptive statistics. Throughout this study, a p-value < 0.05 was considered statistically significant.

Binary logistic regression, polytomous logistic regression, and ordinal logistic regression were used to assess certain variables as potential predictors of treatment-seeking behavior among caregivers. Potential predictors were initially identified based on a literature review and biologic plausibility. During regression analysis, if SAS encounters an observation with a missing value for one of its model variables, it will often exclude the data from every variable associated with that observation. For this reason, variables were excluded if they had a large number of missing values. This was defined as ≥165 missing values (or approximately 1/3 of the 495 observations in the analysis population). The predictor variables selected for the full model were the same for all three regression models: age of child, gender, rural vs. urban home environment, reported history of difficulty paying for treatment, reported history of withholding treatment because of fear of cost, and monthly household income. Four of these risk factors were collected as dichotomous: sex of child (male vs. female); home environment (urban vs. rural); reported history of difficulty paying for treatment (yes vs. no); and reported history of withholding treatment because of fear of cost (yes vs. no). The other two variables, age of child and monthly household income, were collected as continuous.

Both were converted into ordinal variables for analysis. Age, measured in months, was categorized as follows: 0-6 months, 7-12 months, and >12 months (referent). Monthly family income, measured in Bolivianos, was categorized by quartiles (with the most affluent quartile as the referent).

For the binary logistic regression model, the outcome was a dichotomous variable indicating whether caregivers sought any treatment for the child's diarrheal illness in any setting prior to presenting at the study hospital. For this outcome, caregivers who did not seek pre-hospital treatment were in referent group. For the polytomous logistic regression model, the outcome was a polytomous variable similar to the dichotomous outcome described above. Like the dichotomous outcome, caregivers who did not seek pre-hospital treatment were in referent group. The other categories were for caregivers who sought pre-hospital treatment in the informal sector vs. the formal sector vs. both. The outcome for the ordinal logistic model related the number of days a child had diarrhea prior to presentation at the study hospital. It was defined by the following categories: 0-1 day, 2 days, 3 days, 4-5 days, ≥6 days. While data from the entire analysis population (n=495) was eligible to be included in the two previous regression models, data from any caregiver who sought pre-hospital care in the formal medical sector was automatically excluded from ordinal regression analysis. By restricting the analysis thusly, ordinal regression was used to identify risk factors associated with longer vs. shorter delays in seeking treatment in a hospital. For eligible participants, presentation at a study hospital was the earliest point at which formal medical treatment and, more specifically, hospital-based care, was accessed for the most recent bout of diarrheal illness.

Initially, full regression models, which included all six risk factors, were fitted for binary, polytomous, and ordinal regression. Each full model was then reduced by removing individual nonsignificant risk factors through backwards elimination (45). If backwards elimination produced a model with only one risk factor and that risk factor was nonsignificant, then no reduced model was presented. Because we were building predictive models instead of causal models, it was not necessary to assess confounding and interaction (45). For all regression analyses, measures of association were expressed in estimated odds ratios with 95% confidence intervals.

RESULTS

Characteristics of the Analysis Sample

In order to assess whether any of the six specified risk factors (e.g., age of child; gender of child; rural vs. urban home environment; reported history of difficulty paying for treatment; reported history of withholding treatment because of fear of cost; and monthly household income) were good predictors of treatment-seeking behavior, we collected data from caregivers of children under five with an acute diarrheal illness in six Bolivian hospitals from 2007 to 2009.

We selected a sample of 495 subjects for analysis (Table 1). The median age was 11 months, and about 75% of all children were younger than 18 months. Ages ranged from 0 – 59 months with a right skewed distribution. Males (n= 273) outnumbered females (n=221), but they did not represent a substantially greater percentage of the participants (55% vs. 45%). The different home environments were not equally represented. Over four times as many children lived in urban environment as lived in a rural environment. Over 70% of caregivers reported having had difficulty paying for medical treatment, but only one out of every five caregivers reported having withheld medical treatment because of fear of cost. The median household monthly income was 1300 Bolivianos.

Predictors of Treatment-Seeking Behavior

The strength of the six specified risk factors as predictors of treatment-seeking behavior was assessed through three regression analyses. Every initial regression model (i.e., full model) included the same six predictor variables, but each analysis assessed their association with different outcomes. Non-significant risk factors were removed from the full models one at a time to build reduced models.

To assess the association between the predictors and whether caregivers sought medical care in any medical setting (i.e., the informal sector, the formal sector, or both) prior to presenting at a study hospital, we first assessed the risk factors' ability to predict a binary outcome (i.e., medical treatment sought prior to presenting at a study hospital vs. medical treatment not sought prior to presenting at a study hospital). Caregivers who did not seek pre-hospital treatment were the referent group. In the full model, no individual risk factor was significantly associated with caregivers seeking treatment of acute diarrhea in a child under five prior to presentation at a study hospital (Table 2). Backwards elimination failed to produce a reduced model identifying any risk factors as significant predictors of the outcome (data not shown). With no significant results, our binary logistic analysis failed to identify any of the risk factors as strong predictors of caregivers seeking any medical care for acute pediatric diarrhea prior to presenting at a study hospital.

Next, we expanded our investigation of the potential usefulness of these risk factors as predictors of pre-hospital treatment-seeking behavior. Instead of a binary outcome, pre-hospital treatment-seeking was categorized according to the type of medical care sought (i.e., informal care vs. formal care vs. a combination of both). By using several, more-narrowly-defined outcome categories, polytomous logistic regression may expose relationships that are hidden with binary logistic regression. Using different outcome groupings allows us to develop a more nuanced understanding of these associations. Again, caregivers who did not seek pre-hospital treatment were the outcome referent group. In the full model (Table 3), no risk factor was significantly associated with all three of the non-referent outcome categories. However, each of the following risk factors were significantly associated with one of those categories: a child age that fell in either half of the first year of life; a history of difficulty paying for treatment; and a household income that did not fall in the most affluent quartile. In the reduced model (Table 3), only the age of the child (both infant categories) and a reported difficulty paying for treatment remained significant predictors of care-seeking behavior. As in the full model, both of these risk factors were significantly associated with caregivers accessing combined informal and formal treatment. Specifically, compared to those caring for children older than one year, caregivers of infants aged ≤6 months were significantly less likely to seek a combination of formal and informal pre-hospital care (OR= 0.59). Similarly, caregivers of infants aged 7-12 months were significantly less likely than caregivers of children over one year to seek a combination of formal and informal pre-hospital care (OR=0.77). Caregivers who reported difficulty paying for treatment were significantly more likely to seek combined formal and informal pre-hospital care (OR=3.20) than those who denied such difficulty. By categorizing the outcome as polytomous (Table 3) as opposed to binary (Table 2), we were able to identify multiple predictors of a particular kind of pre-hospital treatment-seeking behavior among caregivers.

Finally, we used ordinal logistic regression to identify potential predictors of caregivers delaying hospital-based treatment for an acutely ill child under five. The positive outcome for the ordinal regression analysis was a longer delay (compared to a shorter delay) in caregivers seeking hospital care. In the full and reduced models (Table

4), only one risk factor was significantly associated with greater delays in caregivers seeking hospital treatment. In both models, children with acute diarrhea were three times as likely to have a longer delay in receiving hospital-based treatment if their caregivers had previously withheld medical treatment because of fear of cost (Table 4). In order to satisfy the proportional odds assumption, a non-significant risk factor (gender) was retained in the reduced ordinal regression model. In conclusion, we were able to demonstrate that a reported history of withholding treatment because of fear of cost was a significant predictor of longer delays in caregivers seeking hospital-based treatment for acute pediatric diarrhea.

DISCUSSION

The primary goal of this study was to identify predictors of treatment-seeking behavior among caregivers of children under five years old with an acute diarrheal illness. We found that infants were significantly less likely than older children to receive a combination of informal and formal pre-hospital treatment for acute diarrhea than they were to receive no medical treatment. Also, our analysis showed that caregivers who reported a history of withholding treatment because of fear of cost were significantly more likely to delay seeking hospital-based care than caregivers without a history of withholding treatment because of fear of cost.

In our analysis, caregivers were more likely to seek a *combination* of informal and formal pre-hospital care for children older than one year than they were for children younger than one year (when the regression model controlled for caregivers having had difficulty affording medical treatment in the past). This was true for infants ≤ 6 months as well as for infants aged 7-12 months (Table 3). In contrast, there was no statistical difference between older children and either infant age group regarding whether caregivers sought *exclusively* informal care or exclusively formal care prior to presenting to a hospital for diarrhea treatment. When interpreting these results, we must consider the possibility that seeking combined care, in contrast to accessing either informal or formal treatment, is a proxy for a relatively greater number of pre-hospital medical encounters. If combined care is indeed a proxy for a relatively greater number of medical encounters, the fact that younger children are more susceptible to rotavirus infection than older children may partially explain our finding that infants were less likely to receive combined informal/formal pre-hospital treatment. In developing countries, rotavirus causes moderate-to-severe diarrhea much more frequently in infants (an estimated 7.0 episodes per 100 child-years) than in children aged 1-2 years old (approximately 3.5 episodes per 100 child-years) or children aged 3-5 years old (about 1 episode per 100 child-years) (46). As a result, caregivers of infants may have been less inclined than caregivers of children older than one year to pursue multiple treatment options before ultimately seeking care at a hospital. Strong support for this interpretation is not available in the published literature. Other studies investigating age as a determinant of caregiver treatment-seeking behavior report inconsistent results. One reason for this is the use of different cut points for age. For example, in a study conducted in India, Sreeramareddy et al. reported that caregivers were less likely to access formal diarrhea treatment for infants compared to children aged 1-2 years. However, they found no significant associations in either direction for children aged 3-5 years (47). In our analysis, we grouped all participants with children older than twelve months. Such differences in variable definitions limit the extent to which our results can be compared to those of other researchers.

The second main finding of this study was that among participants who did not pursue formal medical treatment prior to presenting at a study hospital, a history of withholding medical treatment because of cost was a strong predictor of longer delays in accessing any hospital-based care. A basic interpretation is that caregivers who have delayed treatment in the past continued to do so. This is consistent with the findings of other researchers (48, 49). While this association may appear to be a powerful and intuitive predictor of caregiver behavior, it does little to indicate the mechanisms by which it operates. More specifically, without more data, we can only speculate as to why caregivers in our sample feared healthcare costs so much that they withheld treatment. As previously discussed, the published literature offers an abundance of possible explanations for a caregiver's fear of treatment costs (e.g., missing work to access medical care; transportation costs associated with seeking care; or low family socioeconomic status), but little consensus (25, 26, 32). Interestingly, we found no significant association between delays in treatment and family income. This may indicate that the self-reported income data were not accurate. Alternatively, the factors associated with fear of treatment costs may influence whether caregivers delay hospital-based care regardless of household income. For instance, some caregivers may have to miss a day of work in order to seek care. Knowing they would lose a full day's income, regardless of the specific amount, may affect their treatment decisions and lead to a delay in seeking medical care.

Strengths and Limitations

This study has several strengths and limitations. Based on our power analysis, the 495-subject data set was approximately five times larger than the minimum sample size needed to detect an effect size of 2 (i.e. odds ratio = 2.0). By recruiting these participants at six different hospitals across Bolivia, we built a diverse analysis population that was representative of the country as a whole. Also, procedures for data collection and management were meticulously followed to ensure accuracy. Some limitations should also be discussed. A downside of only recruiting participants from hospitals is that our results are biased toward caregivers who were willing and able to ultimately seek treatment at a hospital. Second, the large amount of missing data excluded a substantial number of subjects from any regression analysis. Finally, as a cross-sectional study, we could only analyze treatment-seeking behavior for the most current episode of diarrhea, which may not provide an accurate understanding of such complex and nuanced behavior.

Recommendations for Future Research

In general, this study benefits the global public health community by contributing to the growing body of research on pediatric diarrhea. More specifically for Bolivia, our results offer new insight into how adult caregivers respond to a child with diarrhea requiring medical attention. This study highlights two specific questions worthy of investigation. First, why do caregivers make different treatment-seeking decisions depending on the age of the child? Our results indicate that a caregiver's decision-making criteria may change as the child ages. Understanding this behavior would potentially allow public health officials in Bolivia to more efficiently allocate resources by identifying age-specific targets for intervention that change over time along with the concerns of the caregiver. Second, among Bolivian caregivers who have withheld treatment because of cost, what specific cost-related issues cause the greatest anxiety, and how can they be addressed prior to the onset of illness? This study can potentially help Bolivia answer both of these questions by expanding upon what is already known and by providing novel information currently unavailable in the published research.

Conclusion

In conclusion, we have demonstrated that both the age of the child as well as a caregiver's past actions can have significant influence on their current treatment-seeking behavior. While both of these topics are important, anything that contributes to an increased delay in accessing hospital-based care for a child with a severe diarrheal disease can dire consequences. Although these results do not justify making specific policy recommendations, they do suggest two specific research questions with potentially important policy implications.

PUBLIC HEALTH IMPLICATIONS

- This study helps fill a gap in existing knowledge regarding caregiver treatment-seeking behavior in Bolivia. We have demonstrated that both the age of the child as well as a caregiver's past actions can have significant influence on treatment-seeking behavior.
- We showed that Bolivian caregivers are already inclined to seek medical care differently for children of different ages. Bolivia should take advantage of this by developing age-specific treatment guidelines that caregivers can use to guide their decisions. Public health officials should consult with pediatric care providers in order to determine the most appropriate recommendations for each age category. The main focus of these guidelines should be to provide caregivers with easy-to-recognize warning signs that indicate when a child should be taken to a hospital immediately.
- This study does not indicate why Bolivian caregivers seek medical care differently for children of different ages. Prior to developing the guidelines, researchers in Bolivia should conduct a study to identify how specific characteristics of children and caregivers change over time as a child ages. The results of this study should be used to inform how policymakers define the age categories for the caregiver guidelines.
- Our findings indicated that caregivers who withhold treatment because of fear of cost are significantly more likely to delay seeking hospital-based care. As a simple and inexpensive initial intervention to address this, Bolivian pediatric

primary care providers should discuss this issue with caregivers at each well-child clinic visit.

- Finally, in order to further address caregivers withholding treatment because of fear of cost, researchers in Bolivia should conduct a second study to identify the specific cost-related issues that cause caregivers the greatest anxiety. The results of this study could be instrumental in designing future interventions that modify caregiver treatment-seeking behavior prior to the onset of illness.

REFERENCES

1. Parashar U, Hummelman E, Bresee J, et al. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 2003;9:565-72.

2. Widdowson M-A, Steele D, Vojdani J, et al. Global Rotavirus Surveillance: Determining the Need and Measuring the Impact of Rotavirus Vaccines. *The Journal of Infectious Diseases* 2009;200(Suppl 1):S1 - 8.

3. Dennehy PH. Rotavirus Vaccines: an Overview. *Clin Microbiol Rev* 2008;21(1):198–208.

4. Parashar UD, Burton A, Lanata C, et al. Global mortality associated with rotavirus disease among children in 2004. *J Infect Dis* 2009;200 Suppl 1:S9-S15.

5. Parashar UD, Gibson CJ, Bresee JS, et al. Rotavirus and Severe Childhood Diarrhea. *Emerg Infect Dis* 2006;12(2).

6. Grimwood K, Lambert SB, Milne RJ. Rotavirus infections and vaccines: burden of illness and potential impact of vaccination. *Paediatr Drugs* 2010;12(4):235-56.

7. Yezli S, Otter JA. Minimum Infective Dose of the Major Human Respiratory and Enteric Viruses Transmitted Through Food and the Environment. *Food Environ Virol* 2011;3(1):1-30.

8. Soares-Weiser K, Maclehose H, Bergman H, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev* 2012;11:CD008521.

9. PATH. Country National Immunization Program Introductions Of Rotavirus Vaccine. 2012. (http://sites.path.org/rotavirusvaccine/files/2013/01/Copy-of-Country-Introduction- Interactive-Spreadsheet_EN.pdf). (Accessed January 13, 2013).

10. WHO. Guidelines for estimating the economic burden of diarrheal disease with focus on assessing the costs of rotavirus diarrhea. Geneva, Switzerland: World Health Organization, 2005.

11. Rheingans RD, Constenla D, Antil L, et al. Economic and health burden of rotavirus gastroenteritis for the 2003 birth cohort in eight Latin American and Caribbean countries. *Rev Panam Salud Publica* 2007;21(4):192-204.

12. Mendelsohn AS, Asirvatham JR, Mwamburi DM, et al. Estimates of the economic burden of rotavirus-associated and all-cause diarrhoea in Vellore, India. *Tropical Medicine and International Health* 2008;13(7):934–42.

13. Rheingans RD, Antil L, Dreibelbis R, et al. Economic costs of rotavirus gastroenteritis and cost-effectiveness of vaccination in developing countries. *J Infect Dis* 2009;200:S16-S27.

14. Wilopo SA, Kilgore P, Kosen S, et al. Economic evaluation of a routine rotavirus vaccination programme in Indonesia. *Vaccine* 2009;27(Suppl 5):F67–F74.

15. Podewils LJ, Antil L, Hummelman E, et al. Projected Cost-Effectiveness of Rotavirus Vaccination for Children in Asia. *J Infect Dis* 2005;192:S133–45.

16. Bilcke J, Beutels P. Reviewing the cost effectiveness of rotavirus vaccination: the importance of uncertainty in the choice of data sources. *Pharmacoeconomics* 2009;27(4):281-97.

17. Flem ET, Latipov R, Nurmatov ZS, et al. Costs of Diarrheal Disease and the Cost-Effectiveness of a Rotavirus Vaccination Program in Kyrgyzstan. *J Infect Dis* 2009;200(Suppl 1):S195–202.

18. Isakbaeva ET, Musabaev E, Antil L, et al. Rotavirus disease in Uzbekistan: Cost-effectiveness of a new vaccine. *Vaccine* 2007;25:373–80.

19. (WHO) WHO. The World Health Report 2002: Reducing Risks, Promoting Healthy Life. 2002.

20. Plosker G. Rotavirus vaccine RIX4414 (Rotarix™): a pharmacoeconomic review of its use in the prevention of rotavirus gastroenteritis in developing countries. *Pharmacoeconomics* 2011;29(11):989-1009.

21. Atherly DE, Lewis KDC, Tate J, et al. Projected health and economic impact of rotavirus vaccination in GAVI-eligible countries: 2011–2030. *Vaccine* 2012;30:A7-A14.

22. de Soarez PC, Valentim J, Sartori AM, et al. Cost-effectiveness analysis of routine rotavirus vaccination in Brazil. *Rev Panam Salud Publica* 2008;23(4):221-30.

23. Kim SY, Goldie SJ, Salomon JA. Cost-effectiveness of Rotavirus vaccination in Vietnam. *BMC Public Health* 2009;9:29.

24. Tu HA, Woerdenbag HJ, Kane S, et al. Economic evaluations of rotavirus immunization for developing countries: a review of the literature. *Expert Rev Vaccines* 2011;10(7):1037-51.

25. Rheingans R, Kukla M, Adegbola RA, et al. Exploring household economic impacts of childhood diarrheal illnesses in 3 African settings. *Clin Infect Dis* 2012;55 Suppl 4:S317-26.

26. Burton DC, Flannery B, Onyango B, et al. Healthcare-seeking behaviour for common infectious disease-related illnesses in rural Kenya: a community-based house-to-house survey. *J Health Popul Nutr* 2011;29(1):61-70.

27. Kristiansson C, Gotuzzo E, Rodriguez H, et al. Access to health care in relation to socioeconomic status in the Amazonian area of Peru. *Int J Equity Health* 2009;8:11.

28. Rheingans R, Kukla M, Faruque AS, et al. Determinants of household costs associated with childhood diarrhea in 3 South Asian settings. *Clin Infect Dis* 2012;55 Suppl 4:S327-35.

29. Page AL, Hustache S, Luquero FJ, et al. Health care seeking behavior for diarrhea in children under 5 in rural Niger: results of a cross-sectional survey. *BMC Public Health* 2011;11:389.

30. Patil AV, Somasundaram KV, Goyal RC. Current health scenario in rural India. *Aust J Rural Health* 2002;10(2):129-35.

31. Biritwum RB, Asante A, Amoo PK, et al. Community-based cluster surveys on treatment preferences for diarrhoea, severe diarrhoea, and dysentery in children aged less than five years in two districts of Ghana. *J Health Popul Nutr* 2004;22(2):182-90.

32. Rheinlander T, Samuelsen H, Dalsgaard A, et al. Perspectives on child diarrhoea management and health service use among ethnic minority caregivers in Vietnam. *BMC Public Health* 2011;11:690.

33. CIA. CIA World Factbook - Bolivia. 2012. (https://www.cia.gov/library/publications/the-world-factbook/index.html). (Accessed March 5, 2013).

34. Bank TW. World Bank List Of Economies. 2012. (http://siteresources.worldbank.org/DATASTATISTICS/Resources/CLASS.XLS). (Accessed July 26, 2012).

35. Bank TW. Bolivia At A Glance. 2012. (devdata.worldbank.org/AAG/bol_aag.pdf). (Accessed March 5, 2013).

36. Bank TW. World Development Indicators 2012. 2012.

37. Congress LO. Country Profile: Bolivia. 2006. (http://lcweb2.loc.gov/frd/cs/profiles/Bolivia.pdf). (Accessed March 5, 2013).

38. (UNDP) UNDP. Bolivia (Plurinational State of) Country Profile: Human Development Indicators 2011. (http://hdrstats.undp.org/en/countries/profiles/BOL.html). (Accessed March 5, 2013).

39. (WHO) TWHO. Bolivia (Plurinational State Of): Health Profile. 2012. (http://www.who.int/gho/countries/bol.pdf). (Accessed March 5, 2013).

40. Atherly D, Dreibelbis R, Parashar UD, et al. Rotavirus Vaccination: Cost-Effectiveness and Impact on Child Mortality in Developing Countries. *The Journal of Infectious Diseases* 2009;200(Suppl 1):S28-38.

41. (WHO) WHO. WHO Vaccine-Preventable Diseases: Monitoring System. 2013 Global Summary. 2013. (http://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=BOL). (Accessed July 26, 2013).

42. (PAHO) PAHO. Immunization In The Americas: 2012 Summary. 2012.

43. Sethi D, Cumberland P, Hudson MJ, et al. A study of infectious intestinal disease in England: risk factors associated with group A rotavirus in children. *Epidemiol Infect* 2001;126(1):63-70.

44. Faul F, Erdfelder E, Lang AG, et al. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39(2):175-91.

45. Kleinbaum DG, Klein M, Pryor ER. *Logistic regression : a self-learning text*. 3rd ed. New York: Springer; 2010.

46. Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 2013;382(9888):209-22.

47. Sreeramareddy CT, Sathyanarayana TN, Kumar HN. Utilization of health care services for childhood morbidity and associated factors in India: a national cross-sectional household survey. *PLoS One* 2012;7(12):e51904.

48. Nasrin D, Wu Y, Blackwelder WC, et al. Health care seeking for childhood diarrhea in developing countries: evidence from seven sites in Africa and Asia. *Am J Trop Med Hyg* 2013;89(1 Suppl):3-12.

49. Quadri F, Nasrin D, Khan A, et al. Health care use patterns for diarrhea in children in low-income periurban communities of Karachi, Pakistan. *Am J Trop Med Hyg* 2013;89(1 Suppl):49-55.

TABLES

Table 1. Characteristics of the Analysis Sample

Demographics	n	Frequency (%) or Median (IQR)
Age of Child (months)	468	11 (6, 17)
Male Sex	494	273 (55.3%)
Rural Home Environment	402	73 (18.2%)
Caregivers Reported Difficulty Paying for Treatment	476	345 (72.5%)
Caregivers Reported Having Withheld Treatment b/c of Fear of Cost	396	83 (21.0%)
Household Monthly Income	495	1300 (800, 2000)

Table 2. Multivariable binary logistic regression model of the associations between risk factors and caregivers seeking treatment for acute diarrhea in a child under 5 prior to presenting at a study hospital, Bolivia 2007-2009

	Full Model (n=355)			
Risk Factor	Frequency (%)	OR	95% CI	
Age				
≤ 6 Months	98 (27.6)	1.01	0.78	1.31
7 - 12 months	99 (27.9)	1.00	0.88	1.15
>12 months (referent)	158 (44.5)	1.00		
Male Sex	193 (54.4)	0.98	0.64	1.50
Rural Home Environment	63 (17.7)	1.21	0.69	2.13
Caregivers Reported Difficulty Paying for Treatment	266 (74.9)	1.13	0.68	1.88
Caregivers Reported Having Withheld Treatment b/c of Fear of Cost	74 (20.8)	1.39	0.80	2.40
Household Monthly Income (quartiles)				
1st Quartile -- 0-800	77 (21.7)	1.24	0.90	1.69
2nd Quartile -- >800-1300	88 (24.8)	1.15	0.94	1.42
3rd Quartile -- >1300-2000	103 (29.0)	1.07	0.97	1.19
4th Quartile -- >2000 (referent)	87 (24.5)	1.00		

Table 3. Multivariable polytomous logistic regression models of the associations between risk factors and the setting in which caregivers sought treatment for acute diarrhea in a child under 5 prior to presenting at a study hospital, Bolivia 2007-2009

	Full Model (n=355)							Reduced Model (n=451)						
	Frequency	Informal Care		Formal Care		Both		Frequency	Informal Care		Formal Care		Both	
Risk Factor	**(Percent)**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**(Percent)**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age														
≤ 6 Months	98 (27.6)	1.22	0.77 1.93	1.22	0.91 1.64	0.43*	0.27 0.70	114 (25.3)	1.11	0.74 1.67	0.94	0.72 1.23	0.59*	0.40 0.87
7 - 12 months	99 (27.9)	1.11	0.88 1.39	1.10	0.95 1.28	0.66*	0.52 0.83	137 (30.4)	1.05	0.86 1.29	0.97	0.85 1.11	0.77*	0.63 0.93
>12 months (referent)	158 (44.5)	1.00						200 (44.4)	1.00					
Male Sex	193 (54.4)	0.75	0.36 1.59	1.23	0.75 1.99	0.64	0.31 1.29							
Rural Home Environment	63 (17.7)	1.24	0.48 3.17	1.39	0.75 2.60	0.80	0.30 2.12							
Caregivers Reported Difficulty Paying for Treatment	266 (74.9)	1.57	0.59 4.23	0.80	0.46 1.40	3.02*	1.07 8.47	325 (72.1)	1.67	0.75 3.74	0.80	0.50 1.26	3.20*	1.36 7.57
Caregivers Reported Having Withheld Treatment b/c of Fear of Cost	74 (20.8)	2.09	0.88 4.96	1.18	0.63 2.21	1.56	0.65 3.72							
Household Monthly Income (quartiles)														
1st Quartile -- 0-800	77 (21.7)	0.93	0.54 1.60	1.59*	1.12 2.27	0.74	0.44 1.24							
2nd Quartile -- >800-1300	88 (24.8)	0.95	0.66 1.37	1.36*	1.08 1.73	0.82	0.58 1.16							
3rd Quartile -- >1300-2000	103 (29.0)	0.98	0.81 1.17	1.17*	1.04 1.31	0.90	0.76 1.08							
4th Quartile -- >2000 (referent)	87 (24.5)	1.00		1.00		1.00								

* $p < 0.05$

Table 4. Multivariable ordinal logistic regression models of the associations between risk factors and longer delays in seeking treatment at a hospital for acute diarrhea in a child under 5 among caregivers who did not seek any formal medical treatment prior to presenting at a study hospital, Bolivia 2007-2009

	Full Model (n=176)			Reduced Model (n=202)		
Risk Factor	**Frequency (Percent)**	**OR**	**95% CI**	**Frequency (Percent)**	**OR**	**95% CI**
Age						
≤ 6 Months	99 (56.3)	1.00	0.72 1.38			
7 - 12 months	58 (33.0)	1.00	0.85 1.18			
>12 months (referent)	19 (10.8)	1.00				
Male Sex	93 (52.8)	0.74	0.44 1.26	107 (53.0)	0.78	0.47 1.27
Rural Home Environment	31 (17.6)	1.08	0.54 2.17			
Caregivers Reported Difficulty Paying for Treatment	133 (75.6)	1.00	0.55 1.98			
Caregivers Reported Having Withheld Treatment b/c of Fear of Cost	36 (20.5)	3.02*	1.51 6.00	41 (20.3)	3.01*	1.61 5.64
Household Monthly Income (quartiles)						
1st Quartile -- 0-800	35 (19.9)	1.12	0.76 1.65			
2nd Quartile -- >800-1300	40 (22.7)	1.08	0.83 1.40			
3rd Quartile -- >1300-2000	54 (30.7)	1.04	0.91 1.18			
4th Quartile -- >2000 (referent)	47 (26.7)	1.00				

* $p < 0.05$

APPENDIX: International Review Board Approval

EMORY UNIVERSITY | Institutional Review Board

TO: Juan Leon, PhD
Principal Investigator
Global Health

DATE: December 20, 2013

RE: **Notification of Amendment Approval**
AM13_IRB00004406
IRB00004406
Cost Assessment of Rotavirus-Induced Diarrhea in Bolivia

Thank you for submitting an amendment request. The Emory IRB reviewed and approved this amendment under the expedited review process on **12/20/2013**. This amendment includes the following:

Personnel Change only: Adding Stephen Ragan as study Coordinator; remove Michael Garber from the study.

Important note: If this study is NIH-supported, you may need to obtain NIH prior approval for the change(s) contained in this amendment before implementation. Please review the NIH policy directives found at the following links and contact your NIH Program Officer, NIH Grants Management Officer, or the Emory Office of Sponsored Programs if you have questions.

Policy on changes in active awards: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-129.html

Policy on delayed onset awards: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-130.html

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

Sincerely,

Donna Thomas
Administrative Assistant
This letter has been digitally signed

	Burke	Rachel	Dean
	Fabiszewski	Anna	Global Health
CC	Ragan	Stephen	SPH: Student Services
	Rebolledo Esteinou	Paulina	RTP

Emory University IRB
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu/
An equal opportunity, affirmative action university