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The economic burden of pediatric gastroenteritis to Bolivian caregivers: Predictors of catastrophic cost and overall cost burden

By

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Master of Public Health

Global Epidemiology

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Juan S. Leon, PhD, MPH

Committee Chair

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A.B., Harvard College, 2006

Thesis Committee Chair: Juan S. Leon PhD, MPH

An abstract of

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

The Economic Burden of Pediatric Gastroenteritis to Bolivian Caregivers:
Predictors of Catastrophic Cost and Overall Cost Burden
By Rachel M. Burke

Worldwide, acute gastroenteritis causes substantial morbidity and mortality in children under five years of age, with 1.4 billion episodes and 1.7 to 3 million deaths each year, with disproportionate burden in developing countries. In Bolivia, one of the poorest countries in South America, 16% of child deaths can be attributed to diarrhea, and the costs associated with this diarrhea can weigh heavily on patient families. To address this need, the study goal was to identify predictors of cost burden (diarrhea-related cost incurred as a percentage of annual income) and catastrophic cost (cost burden ≥ 1% of annual household income). From 2007 to 2009, researchers interviewed caregivers of pediatric patients (< 5 years old) seeking treatment for diarrhea in six Bolivian hospitals. Caregivers were surveyed on demographics, clinical symptoms, direct (e.g. medication, consult fees), and indirect (e.g. lost wages) costs; 551 caregivers provided complete cost data and were included in the analysis. Through multivariate logistic regression models, we determined that catastrophic cost was significantly associated ($p < 0.05$) with outpatient status (OR 0.16, 95% CI [0.07, 0.37]); seeking care at a private hospital (OR 4.12, 95% CI [2.30, 7.41]); having previously sought treatment at least once for this episode of diarrhea (OR 3.92, 95% CI [1.64, 9.35]); and the number of days the child had been ill prior to the current visit (OR 1.14, 95% CI [1.05, 1.24]). Through multivariate linear regression models, we determined that cost burden was also significantly associated ($p < 0.05$) with the same variables. These data indicate a need for further investigation into why Bolivian families seek care at private facilities, and why they may incur costs even in public facilities. Our analysis highlights the economic significance of pediatric diarrhea to Bolivian caregivers and provides insight into potential areas of intervention to reduce catastrophic cost and overall cost burden associated with pediatric diarrhea.

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Table of Contents

LITERATURE REVIEW

Pediatric Diarrheal Diseases

Worldwide, acute gastroenteritis causes substantial morbidity and mortality in children under five years of age, with 1.4 billion episodes and 1.7 to 3 million deaths each year [1]. The burden of diarrheal disease is particularly acute in developing countries, accounting for 21% of all child deaths in these areas [2]. Acute gastroenteritis is characterized by diarrhea and sometimes vomiting, and kills through dehydration. The clinical definition of acute gastroenteritis is usually phrased as "three or more watery or looser-than-normal stools within a 24-hour period or forceful vomiting" [3]. Patients may also experience fever, cramping, or abdominal tenderness (reviewed in [4, 5]). Diarrhea leads to water loss, electrolyte imbalance, and dehydration, which can be fatal [6]. Because access to healthcare and treatment such as Oral Rehydration Solution (ORS) is not as readily available in many developing countries, the risk of death from diarrhea can be much higher in these areas (reviewed in [7]).

Acute pediatric diarrhea is caused by bacterial, viral, and some parasitic agents (reviewed in [7]). Common bacterial agents causing pediatric infections in developing countries include diarrheagenic *Escherichia coli* (such as EPEC, ETEC, STEC, EAEC, and EIEC[1]), *Shigella* spp., *Salmonella enteritidis, Campylobacter* spp., and *Vibrio cholerae* (reviewed in [7]). *Yersinia, Aeromonas,* and *Vibrio parahemolyticus* may also play a role in some countries (reviewed in [8]). Viral agents have also been shown to be

[1]EPEC, enteropathogenic *Escherichia coli;* ETEC, enterotoxigenic *E. coli;* STEC, Shigatoxin-producing *E. coli;* EIEC, enteroinvasive *E. coli;* EAEC, enteroaggregative *E. coli.*

extremely common causes of diarrhea in some geographic areas [9, 10]. The most common viral etiologies of acute pediatric diarrhea are rotavirus (RV), norovirus, sapovirus, astrovirus, and enteric adenovirus (reviewed in [7]). Parasitic causes include *Giardia lamblia, Entamoeba histolytica, Cryptosporidium parvum, Cyclospora cayetanesis,* and *Isospora belli* (reviewed in [7]).

The Role of Rotavirus in Global Burden of Pediatric Diarrhea

Of diarrheal agents, rotavirus is "the most common cause of severe childhood diarrhea worldwide and of diarrheal mortality in developing countries" [11]. Each year, rotavirus causes an estimated 527,000 child deaths [12] and is responsible for a regional median of 39% of diarrhea-related hospitalizations worldwide [11]. However, the burden is concentrated in developing countries, with 80% of rotavirus-related deaths "estimated to occur in low-income countries of south Asia and sub-Saharan Africa" [13]. Part of what makes rotavirus such a "successful" virus is its high infectivity. In each gram of stool, an infected child can shed 10^9-10^{11} virions [14, 15], yet only 1.56×10^4 virus particles are necessary to cause infection in another person [16]. Patients can continue to shed virus even when they are no longer symptomatic, and infectious doses of rotavirus can survive on human hands for a few hours; virus can even be transferred from hands to inanimate surfaces (and vice versa) for up to one hour [17]. Thus, while increased access to improved hygiene and sanitation facilities may help somewhat to reduce transmission, rotavirus infection remains common within both developed and developing settings [11].

Because of its high prevalence and infectivity, rotavirus has emerged as a prime candidate for vaccination campaigns. Currently, there are two anti-rotavirus vaccines available: Rotarix® (GlaxoSmithKline) and Rotateq® (Merck). Rotarix® is a monovalent live-attenuated human strain vaccine given in two oral doses, one at two months and one at four months of age [18]. Rotateq® is a pentavalent human-bovine reassortment live-attenuated vaccine given in three oral doses, one at two months, one at four months, and one at six months of age [18]. Both vaccines are employed worldwide as part of PATH's Rotavirus Vaccine Program [19].

Cost Burden Associated with Pediatric Diarrhea

Pediatric acute gastroenteritis presents an enormous economic burden to healthcare systems [20-23]. The combined costs of pediatric diarrhea-related clinic visits, hospitalizations, and the associated medications can reach extremely high levels, particularly in developing countries where diarrheal prevalence is high. Estimates of annual healthcare system costs for rotavirus diarrhea alone range from US$2.6 million in Peru [20] and US$3.1 million in Vietnam [21] to nearly US$11 million in Kenya [23]. Diarrhea of other etiologies, of course, only increases healthcare systems costs.

Most cost-effectiveness analyses (CEAs) of rotavirus vaccination have shown it to be cost effective or potentially cost effective in developing countries [24]. An intervention is described as "cost effective" if the cost per Disability-Adjusted Life Year (DALY) averted is between one and three times GDP per capita, and "highly cost effective" if the cost per DALY averted is less than the GDP per capita [25, 26]. Several recent cross-regional analyses found that universal rotavirus vaccination would be "cost effective" or "highly cost effective" across all regions studied: Atherly *et al.* estimated that costs per DALY averted might range from US$22 in Africa to US$118 in Latin

America (provided that vaccine price decreases over time) [27]; Rheingans *et al.* reported similar findings, estimating cost per DALY averted might range US$17 – 190 globally, depending on the cost of the vaccine (additional estimates were made for specific income strata, also showing cost effectiveness) [28]. A recent study of rotavirus vaccination in Bolivia estimated that cost per DALY averted would range from cost-saving to US$172, depending on the cost of vaccination (GDP per capita US$1,758) [29]. Analyses specific to other Latin American countries have also estimated that the rotavirus vaccine would be cost effective or highly cost effective. Costs per DALY averted ranged from US$229 in Peru (GDP per capita US$2,920) [30] and US$643 in Brazil [31] up to US$1,139 in Mexico (GDP per capita US$6,121) [32] and US$11,261 (GDP per capita US$4,591) in Chile [33]. CEAs of countries with similar economic situations to Bolivia (based on GDP per capita) also indicate cost effectiveness of the rotavirus vaccine: estimated cost per DALY averted ranged US$120.46 – 361.10 in Indonesia (GDP per capita US$1,560) [34], US$40 – 192 in Vietnam (GDP per capita US$550) [21], and cost saving – US$243 in Kyrgyzstan (GDP per capita US$490) [35].

In order to combat the costs associated with rotavirus diarrhea, a number of countries have implemented the rotavirus vaccine (Rotarix® or Rotashield®) into their immunization schedules. Rotavirus vaccination has been supported by the Global Alliance for Vaccines and Immunization (GAVI) since 2006, and was recommended as a worldwide intervention by WHO in 2009 [36]. In many countries that have implemented the vaccine, there has been a reduction in the proportion of hospitalizations attributable to pediatric rotavirus diarrhea [37]. While a reduction in rotavirus-associated hospitalizations may reduce treatment-related costs to families, overall health systems costs due to rotavirus- and non-rotavirus-associated diarrhea may remain high. Brazil, for example, introduced the vaccine in 2006, and though they did note a steeper reduction in diarrhea-associated clinic visits and hospitalizations during the following year, overall health systems costs (comprising diarrhea-related treatment costs as well as vaccination costs) actually increased during this time; that is, the additional cost of the vaccine was not offset by savings from the reduction in diarrhea-associated clinic and hospital visits [38].

Despite the fact that the rotavirus vaccine has reduced diarrheal burden in many countries (reviewed in [39]), pediatric diarrhea remains common and presents a considerable economic stress to the families of affected children. Caregivers must cope with the "direct" as well as the "indirect" costs of their child's illness. Direct or "out-of-pocket" expenditures include all costs paid directly by the family, and may encompass medical costs (like medications, tests, or consult fees) as well as non-medical costs (like transportation or extra diapers) [40]. Indirect expenditures, or costs, are defined as the value of the time lost by a caregiver and their spouse from productive activities (i.e. income-generating work) during the acute episode of diarrhea [40]. In other countries, the estimated average total familial costs (direct and indirect) per episode ranged from US$19.86 for hospitalized children in Kenya [23] to US$215.88 for hospitalized children in Mexico [41]. Direct costs alone have ranged from US$12.89 per case in Brazil [38] to US$31.83 per case in Vietnam [21]. In a low-resource setting, incurred costs can represent a large proportion of a family's overall financial situation. This ratio, total incurred costs for a single diarrheal episode as a percentage of annual family income, can be termed the "cost burden," but has not been frequently studied. In one study in India, direct costs incurred per diarrheal episode ranged from 2.2% to 5.8% of the household's annual income [42].

In order to manage the overall economic burden associated with a pediatric diarrheal episode, families may employ a variety of coping strategies, including borrowing as well as selling. Borrowing money is a common coping strategy for families facing high *direct* familial costs, which can be particularly difficult for those families that are already impoverished [42, 43]. In the Indian study previously discussed, more than 80% of lower-income households reported borrowing money to cover direct costs, as compared to only 35.7% of higher-income households (significance not reported) [42]. Other coping strategies that families may employ to defray healthcare costs include selling assets ("consumables" such as rice, or "productive" assets such as livestock), re-arranging labor responsibilities within the household, hiring additional labor, acquiring another source of income (e.g. taking on an additional job), reducing spending (e.g. via decreased food intake), or simply delaying or not seeking treatment (reviewed in [44, 45]). Ironically, though they may ameliorate some short-term difficulty, many of these strategies have the potential to negatively impact the family's long-term financial situation [44-46].

In situations where a family is already living on a very narrow budget, the combined burden of direct and indirect healthcare-associated costs, and the measures that the family must take to defray these costs, can have a significant effect on the family's overall current and future economic situation (reviewed in [44, 45]). Impoverishment, defined by Russell as "household asset depletion and income loss that cause consumption levels to fall below minimum needs" [44], becomes a very real possibility for families whose healthcare costs exceed a certain level. At the point where the family is pushed into poverty, healthcare costs are termed "catastrophic." However, there is little consensus in the literature as to the exact calculations and cut-offs that are most appropriate for defining catastrophic costs, and different studies use different thresholds [47, 48]. While a cost burden of 10% is often used [48, 49], McIntyre notes that lower levels can be possibly catastrophic for very poor households [45], and still other analysts prefer to define catastrophic costs as healthcare spending greater than or equal to 40% of income remaining after accounting for subsistence needs (defined by WHO as US$1 per day per person) [46, 50].

Because few studies have attempted to identify predictors of cost burden to caregivers of pediatric diarrheal patients, there are little data on risk factors. As discussed above, one study in India did show that direct costs were significantly different for different types of hospitals (urban referral vs. community) and for different types of appointments (emergency room vs. outpatient) [42]. This same study also showed that cost burden varied by hospital location, and that families that had to borrow money to pay costs had a significantly higher cost burden than those that paid out of their savings [42]. A previous thesis investigating the present Bolivian data identified the following as potential predictors of overall cost burden: treatment city, child's gender, child's family lives on less than US$2 per day, number and type of previous visits, and number of days in the hospital [51]. Previous theses also identified the following as potential predictors of catastrophic cost, defined as a cost burden greater than or equal to 1%: treatment city, child's gender, number and types of previous visits, household daily income per family member, caregiver occupation, presence of a working spouse ("protective"), withholding of treatment due to the perceived costliness of the health care treatment, whether ORS had been administered to the child, and number of days in the hospital [51, 52]. The present study will investigate these as well as other risk factors.

The situation in Bolivia

Bolivia, with a population of approximately 10.1 million people [53] and an area of 424 thousand square miles (slightly less than three times the area of Montana) [53, 54], is one of the poorest countries in South America. The per-capita GDP of Bolivia was measured as US$4,800 in 2010, ranking it as 150 in the world [53]. In 2009, it was estimated that approximately 30% of Bolivians live on less than US$2 per day (the international standard poverty line) [53]. On the Human Development Index, which takes into account health, education, and income, Bolivia ranked 95 out of 169 countries and was below the average for the Latin America and Caribbean region [55]. Within this index, Bolivia especially lagged behind other countries in the region with respect to income, though measures of health were also much lower than in other countries in the region [55].

Child mortality in Bolivia is high, and diarrheal illness makes up a large proportion of this burden. Out of every 1,000 live births in Bolivia, 51 children die before the age of five, with an estimated 16% of these deaths attributable to diarrheal illness [56]. Rotavirus is responsible for the bulk of diarrheal morbidity in Bolivia: from 2004 to 2007, surveillance indicated that 38% of children hospitalized for diarrhea were infected with RV [57]. Without vaccination, rotavirus is estimated to cause over 47,000 outpatient visits, more than 9,000 hospitalizations, and in excess of 500 deaths each year in Bolivia [57].

The magnitude of the disease burden associated with rotavirus in Bolivia has prompted ongoing surveillance and management programs. In 2005, the Pan-American Health Organization (PAHO) initiated the Rotavirus Surveillance Program (RVSP) in Bolivia to track the disease [58]. In 2008, Bolivia introduced the Rotarix® vaccine into the country's vaccination schedule with assistance from PAHO and the Global Alliance for Vaccines and Immunization (GAVI) [58-60]. RVSP continues to actively monitor RV epidemiology in Bolivia, reporting results periodically to PAHO [60]; these surveillance activities are partly supported by PAHO, PATH, and GAVI [61].

In another effort to decrease child mortality, Bolivia introduced "Seguro Universal Materno Infantil" (SUMI, Universal maternal and infant insurance) in 2002 [62]. SUMI allows for free healthcare services for children under five years of age, when seen in publicly run healthcare facilities (private facilities are not required to accept SUMI, though some do so under agreements with the government) [62, 63]. Additionally, SUMI benefits pregnant women and women up to six months post-partum [62]. SUMI is funded through municipal, departmental, and national sources, and has successfully increased coverage of routine care for under-fives since its inception [64]. However, there is mixed evidence on the impact of SUMI on the health of women of childbearing age, and the quality of overall coverage (which tends to be better in urban areas as compared to rural locations) [65]. Worries about quality may decrease utilization of SUMI. Although in theory 37% of the population should be covered by SUMI, actual utilization may be much lower: of total consults in Bolivia, only about 52% are in the public or social security sectors (leaving 48% of consults potentially non-eligible for SUMI coverage) [63]. The Ministry of Health and Sports has made efforts to promote communication with the indigenous community, in an effort to improve perceptions of and advance the provision of culturally appropriate care in SUMI-accepting facilities [66].

Under SUMI, publicly run Bolivian healthcare facilities provide standardized diarrhea treatment without charge to families [29]. The choice of treatment "Plan" is based on the degree of dehydration with which the child presents. Plans A and B are given orally over the course of a few hours, while Plan C is administered intravenously throughout two days of hospitalization. In addition to these Plans, health care professionals may also choose to prescribe additional medications based on the patient's diagnosis.

Despite the fact that SUMI provides free health care to children suffering from diarrhea, Bolivian caregivers still face substantial cost burdens when caring for infants with gastroenteritis. Additionally, costs may be incurred in privately as well as publicly run facilities. A recent analysis of the present data showed that even a single episode of pediatric diarrhea has the potential for catastrophic financial consequences: more than 40% of families were found to have cost burdens of at least 1% [67]. While the bulk of these costs were direct, indirect costs accounted for nearly a third of total costs incurred by the study population as a whole [67]. This indicates the importance of addressing both direct and indirect costs in any analysis relating to familial incurred costs.

Previous analyses of Bolivian caretakers have identified several potential risk factors for incurred costs of higher (absolute or relative) magnitude. Most recently, analysis showed that familial incurred costs may vary by appointment type and hospital or hospital location (city) [67]. Other variables that have been identified as potential risk factors for overall and catastrophic costs include those related to the severity of the disease, parental socioeconomic status, child demographics, previous treatment behavior, and caregiver perceptions of cost. Therefore, the present analysis will seek to determine the effects of these factors and of others on the relative magnitude of incurred costs (cost burden) and the risk of catastrophic cost.

Need

Though various studies have undertaken to quantify costs associated with pediatric diarrhea from the state (health care system) perspective, very few studies have examined costs from the perspective of the caregiver. In an impoverished country such as Bolivia, where families already have little disposable income, these treatment costs can weigh heavily on the caregivers of children suffering from diarrhea, presenting a significant economic burden and in some cases leading to economic hardship. In order to better serve the people of Bolivia, it is necessary to better characterize these costs and to understand the different factors that may predispose families towards experiencing greater costs and economic hardship associated with pediatric diarrhea.

Goal and Aims

The goal of this study is to characterize the financial effects of an episode of pediatric diarrheal disease on the caretakers of Bolivian children (under five) who sought treatment for diarrhea from 2007 through 2009. In particular, we seek to characterize predictors of incurred costs as well as identify predictors of longer-term financial impact of pediatric diarrheal disease on caretakers. Specifically, this study has the following aims: 1) To quantify the financial impact of a single episode of pediatric diarrhea on the Bolivian caregiver, in terms of indirect costs, direct costs, total incurred costs, and overall cost burden (including an assessment of catastrophic costs); and 2) To identify predictors of the financial impact of pediatric diarrheal episodes on Bolivian caregivers, specifically considering the outcomes of cost burden and catastrophic cost.

Significance

By quantifying the costs that families incur as a result of pediatric diarrhea, we can provide important evidence to motivate policy changes in Bolivia to help alleviate the substantial economic burden associated with pediatric diarrhea. Further, identification of risk factors will enable lawmakers to design appropriate policies to help Bolivian families avoid these high costs. This improved understanding of cost drivers will also support more effective programming to address the underlying risk factors driving families towards catastrophic costs in Bolivia, and will provide a foundation for designing interventions in other settings as well. Lastly, at a more global level, improving the understanding of the consequences of pediatric diarrhea in Bolivia will provide a local foundation for progress toward the first, fourth, and fifth United Nations Millennium

Development Goals (eradicating extreme poverty and hunger, reducing the under-five mortality rate, and improving maternal health, respectively).

ROLE

For this manuscript, the author was responsible for the data analysis, writing of all sections, and the development of the tables and figures. Data was collected by other researchers previously involved in the project.

MANUSCRIPT

TITLE

The economic burden of pediatric gastroenteritis to Bolivian caregivers: Predictors of catastrophic cost and overall cost burden

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ABSTRACT

Worldwide, acute gastroenteritis causes substantial morbidity and mortality in children under five years of age, with 1.4 billion episodes and 1.7 to 3 million deaths each year, with disproportionate burden in developing countries. In Bolivia, one of the poorest countries in South America, 16% of child deaths can be attributed to diarrhea, and the costs associated with this diarrhea can weigh heavily on patient families. To address this need, the study goal was to identify predictors of cost burden (diarrhea-related cost incurred as a percentage of annual income) and catastrophic cost (cost burden ≥ 1% of annual household income). From 2007 to 2009, researchers interviewed caregivers of pediatric patients (< 5 years old) seeking treatment for diarrhea in six Bolivian hospitals. Caregivers were surveyed on demographics, clinical symptoms, direct (e.g. medication, consult fees), and indirect (e.g. lost wages) costs; 551 caregivers provided complete cost data and were included in the analysis. Through multivariate logistic regression models, we determined that catastrophic cost was significantly associated ($p < 0.05$) with outpatient status (OR 0.16, 95% CI [0.07, 0.37]); seeking care at a private hospital (OR 4.12, 95% CI [2.30, 7.41]); having previously sought treatment at least once for this episode of diarrhea (OR 3.92, 95% CI [1.64, 9.35]); and the number of days the child had been ill prior to the current visit (OR 1.14, 95% CI [1.05, 1.24]). Through multivariate linear regression models, we determined that cost burden was also significantly associated ($p < 0.05$) with the same variables. These data indicate a need for further investigation into why Bolivian families seek care at private facilities, and why they may incur costs even in public facilities. Our analysis highlights the economic significance of pediatric diarrhea to Bolivian caregivers and provides insight into potential areas of intervention to reduce catastrophic cost and overall cost burden associated with pediatric diarrhea.

INTRODUCTION

Worldwide, acute gastroenteritis causes substantial morbidity and mortality in children under five years of age, with 1.4 billion episodes and 1.7 to 3 million deaths each year [1]. The burden of diarrheal disease is particularly acute in developing countries, accounting for 21% of all child deaths in these areas [2].

Acute gastroenteritis presents an economic burden to both healthcare systems and patient families [68-70]. Although health insurance in many countries may cover some costs associated with pediatric diarrhea, patient families often still incur substantial expenses. Caregivers must cope with the "direct" as well as the "indirect" costs of their child's illness. Direct or "out-of-pocket" expenditures include all costs paid directly by the family, and may encompass medical costs (like medications, tests, or consult fees) as well as non-medical costs (like transportation or extra diapers) [40]. Indirect expenditures, or costs, are defined as the value of the time lost by a caregiver and their spouse from productive activities (i.e. income-generating work) during the acute episode of diarrhea [40]. Studies have estimated average total familial costs (direct and indirect) per pediatric diarrhea episode ranging from US$19.86 for hospitalized children in Kenya [23] to US$215.88 for hospitalized children in Mexico [41]. Direct costs alone for a pediatric diarrhea episode have ranged from US$12.89 per case in Brazil [38] to US$31.83 per case in Vietnam [21]. In a low-resource setting, incurred pediatric diarrhea costs can represent a large proportion of a family's overall budget. This ratio, total incurred costs for a single diarrheal episode as a percentage of annual family income, can be termed the "cost burden," but has not been frequently studied. In one study in India, direct costs incurred per diarrheal episode ranged from 2.2% to 5.8% of the household's annual income [42].

In situations where the family is already living on a small household budget, the combined burden of direct and indirect healthcare-associated costs can have a serious effect on the family's overall current and future economic situation (reviewed in [44, 45]). Impoverishment, defined by Russell as "household asset depletion and income loss that cause consumption levels to fall below minimum needs" [44], becomes a very real possibility for families whose healthcare costs exceed a certain level. At the point where the family is pushed into poverty, healthcare costs are termed "catastrophic." However, there is little consensus in the literature as to the exact calculations and cut-offs that are most appropriate for defining catastrophic costs, and different studies use different thresholds [47, 48]. While a cost burden of 10% is typically used [48, 49], McIntyre notes that lower levels can be possibly catastrophic for very poor households [45], and still other analysts prefer to define catastrophic costs as healthcare spending greater than or equal to 40% of income remaining after accounting for subsistence needs (defined by WHO as US$1 per day per person) [46, 50]. In our study, in order to provide a sensitive analysis of catastrophic cost, we elected to use a cut-off of 1% cost burden for catastrophic cost.

Though various studies have undertaken to quantify costs associated with pediatric diarrhea from the state (health care system) perspective [20-23, 28, 29, 35, 41, 43, 71], fewer studies have specifically sought to examine costs from the perspective of the caregiver [35, 38, 42, 43, 71, 72], and most of these do not identify potential predictors of these costs. Yet these costs often represent a substantial burden for families, particularly in impoverished settings, and can be incurred even in situations where patients do have insurance coverage [73, 74].

Bolivia is one of the poorest countries in South America (per-capita GDP was US$4,800 in 2010) [53]and suffers high rates of general and diarrhea-related infant mortality: out of every 1,000 live births in Bolivia, 51 children die before the age of five, with an estimated 16% of these deaths attributable to diarrheal illness [56]. Without vaccination, rotavirus alone is estimated to cause over 47,000 outpatient visits, more than 9,000 hospitalizations, and in excess of 500 deaths each year in Bolivia [57]. The cumulative financial impact of these diarrheal episodes may be severe in a setting where 30% of the population lives on less than US$2 per day (2009 est.) [53]. In spite of a universal insurance program (Seguro Universal Materno-Infantil, SUMI, benefitting children under five, pregnant women, and women up to six months post-partum), Bolivian patient families may still face substantial out-of-pocket expenses and productivity losses associated with pediatric gastroenteritis-related hospitalizations and outpatient visits. Given its high levels of poverty and high rates of acute pediatric gastroenteritis, Bolivia is an excellent setting in which to evaluate the costs of pediatric diarrhea from the caregiver perspective.

The goal of this study was to characterize the financial effects of an episode of pediatric diarrheal disease on the caretakers of Bolivian children (under five) who sought treatment for diarrhea from 2007 through 2009, prior to full implementation of the rotavirus vaccine into the immunization schedule (introduced in late 2008) [58-60]. Thus, this study may also serve as a baseline for comparison to future studies in a post-vaccination setting. Specifically, this study has the following aims: 1) To quantify the financial impact of a single episode of pediatric diarrhea on the Bolivian caregiver, in terms of indirect costs, direct costs, total incurred costs, and overall cost burden (including an assessment of catastrophic costs); and 2) To identify predictors of the financial impact of pediatric diarrheal episodes on Bolivian caregivers, specifically considering the outcomes of cost burden and catastrophic cost. By quantifying the costs that families incur as a result of pediatric diarrhea, and identifying predictors of these costs, we plan to develop mechanisms that lead to these costs and thereby provide a foundation for interventions to prevent catastrophic costs due to pediatric diarrhea. Additionally, improving the understanding of the consequences of pediatric diarrhea in Bolivia will provide a local foundation for global progress toward the first, fourth, and fifth United Nations Millennium Development Goals (eradicating extreme poverty and hunger, reducing the under-five mortality rate, and improving maternal health, respectively).

MATERIALS AND METHODS

Sample Population and Recruitment

The study population was recruited from 2007 to 2009 in outpatient clinics, pediatric hospital wards, and emergency rooms in six healthcare settings across four cities: El Alto, La Paz, Cochabamba, and Santa Cruz. Caregivers of children suffering from diarrhea were identified by attending nurses and doctors (inpatients) or by study staff (outpatients). Study staff then explained the study to these caregivers and obtained oral consent. Caregivers were eligible to participate if they were at least 18 years of age and were responsible for a child under five who was currently receiving treatment for diarrhea. If caregivers were uncertain of the child's diagnosis, study staff confirmed whether the child had experienced three or more loose or watery stools within the past 24 hours, or had experienced forceful vomiting and fever.

The total sample size of 1,107 was estimated from the "Guidelines for Estimating the Economic Burden of Diarrheal disease with focus on Assessing the Costs of Rotavirus Diarrhea" [40]. To achieve a 10% precision and 0.5 coefficient of variation for each hospital, at least 49 records were collected from each hospital. Of this overall population, we selected 551 observations with complete cost data and sufficient sample size for analysis. Given sample size considerations, only inpatient (N=254) and outpatient (N=297) visits were considered from six hospitals (Hospital Boliviano Holandés in El Alto, Hospital Materno Infantil and Hospital del Niño in La Paz, Centro Pediatria Albino R. Patiño and Hospital German Urquidi in Cochabamba, and Hospital Mario Ortiz Suarez in Santa Cruz). Due to inappropriate sample sizes for analyses (< 10 children), for hospital German Urquidi, inpatient visits were excluded, and for Hospitals Materno Infantil and del Niño, outpatient visits were excluded.

Prior to data collection, all portions of the study, including inpatient and outpatient chart abstraction, were approved by Emory University's Institutional Review Board (Protocol IRB00004406) and the Bolivian National Bioethics Committee.

Healthcare Cost Determination

Healthcare costs were obtained from caregivers via structured interviews conducted by trained study staff. The interview guide was based on guidelines from the World Health Organization (WHO) report "Guidelines for estimating the economic burden of diarrheal disease with a focus on assessing the costs of rotavirus diarrhea" [40]. Caregivers of outpatient children were typically interviewed in the waiting room, while those of hospitalized children were typically interviewed within the first one or two days of the child's stay. Costs in Bolivianos (BOB) were converted into USD using the 2012 exchange rate of 1 BOB equal to US$ 0.146.

Data Entry and Database Management

Trained field staff collected all data and entered it using Epi Info (v. 3.4.3). To ensure the quality of the data and the fidelity of entry, data were double entered by two separate staff. The two databases were compared, and discrepancies logged and corrected according to a paper copy of the survey, in order to create a finalized clean database. As an extra measure of quality control, a random sample of 5% of the records in this new database was checked against the original data, and a 100% match was confirmed. Since no errors were found, a subsequent 100% data-check was deemed unnecessary. SAS v. 9.3 (Cary, NC) was used for all data cleaning and analysis.

Variable Definitions

Direct Medical Costs encompassed fees or costs associated with diagnostics, cost of medication, consultation fees, and any costs related to previous treatment for this episode of diarrhea.

Direct Non-Medical Costs included the cost of transportation to and from the appointment (and previous appointments for this episode of diarrhea), cost of any food bought during the visit, cost of any extra diapers purchased during the child's stay, and cost of any childcare for the caregiver's other children while the caregiver was accompanying the sick child.

Total Direct Costs were the sum of medical and non-medical direct costs.

Indirect Costs were defined as the value of lost wages by the caregiver and his or her spouse. These lost wages were calculated based on the caregiver's report of weekly or monthly salary for herself and her spouse, as well as the caregiver's report of the number of days of work missed by herself and her spouse due to this episode of the child's diarrhea.

Total Incurred Costs were calculated by summing the direct and indirect costs for each case.

Annual Household Income was calculated by summing the reported monthly incomes for the caregiver (usually the child's mother) and his or her spouse, and then multiplying this value by 12. Where the caregiver salary was missing and the caregiver reported having no job or being a homemaker, then caregiver salary was set to zero (n=305). Where the spouse salary was missing and the caregiver reported that the spouse had no job, then spousal salary was set to zero (n=16). Otherwise, missing salaries were kept as missing data. If at least one parent reported a salary after adjustment, then the household income equaled the value reported by the salary-generating parent. However, if both parents had missing salaries, then the household income was kept as missing data.

Cost Burden was calculated by dividing the total incurred costs (sum of direct and indirect) by the annual household income. This was then expressed as a percentage. We were also interested in modeling "catastrophic cost," defined as the cost burden that may push families into poverty. There is little consensus in the literature on the exact calculations and cut-offs that are most appropriate for defining catastrophic costs, and cut-offs may range from 5% to 20% (discussed in [47]). For our study, given the high level of poverty in Bolivia (60.1% below the national poverty line in 2007) [75], we decided to define catastrophic cost as cost burden greater than or equal to 1%. This allows for a sensitive analysis of catastrophic cost. In our data, cost burden was right skewed, so we $\log_{10}$ transformed the data for regression analysis.

Statistical Methods

All analyses were completed in SAS version 9.3 (Cary, NC). We used Spearman correlation coefficients (continuous variables), chi-square tests (categorical variables), and Analysis of Variance (ANOVA) to assess relationships among catastrophic cost (defined as cost burden greater than or equal to 1%), cost burden (continuous), and potential predictors.

Multivariate logistic regression was used to examine relationships among potential predictors and the dichotomous outcome variable, catastrophic cost burden (defined as cost burden greater than or equal to 1%). Potential predictors were selected *a priori,* and the gold standard model for catastrophic cost included the following predictors: appointment type (dichotomized as outpatient vs. inpatient), Rural residence (vs. urban), Private hospital (vs. public), Number of people in the household (continuous), whether the caregiver had sought treatment for this episode of the child's diarrhea prior to the current visit (dichotomous), the number of transportations taken to this appointment (continuous), whether this was the child's first episode of diarrhea (dichotomous), the number of days the child had been ill prior to the current visit (continuous), whether the child presented with at least one complication (dichotomous; complications included electrolyte disorder, electrolyte imbalance, hypokalemia, metabolic acidosis, anemia, malnutrition, acute respiratory infection, bronchopneumonia, intussusception, dehydration, or any other unnamed complication), and the two-way interaction of number of days ill and complications. Collinearity was assessed using the Collinearity Diagnostics Using the Information Matrix macro for SAS [76], and interactions were dropped if they were non-significant ($p > 0.05$). Because all variables were potential exposures and assessment of select subsets indicated potential confounding (odds ratio estimates differed by over 10% from the gold standard), we determined not to do a full assessment of confounding. Tests of global fit (Wald, Likelihood Ratio, and score) all showed p values of less than 0.0001.

For the linear regression models, collinearity was not present because all variance inflation factors were below 10. Interaction terms were dropped one-by-one if $p > 0.05$. To determine the final linear model, we performed all-possible-regressions selection, beginning with the initial list of potential predictors identified based on *a priori* and data-driven criteria. During this process we prioritized adjusted R^2 and required all models to be hierarchically well formulated. Reduced models indicated confounding (parameter estimates differed by ≥10% from the gold standard), so the gold standard model was used as the final adjusted model.

RESULTS

Characteristics of the Study Population

In order to assess predictors of cost burden of pediatric diarrhea on Bolivian caregivers, investigators recruited a sample of infants across three geographic areas in Bolivia: La Paz and El Alto, Cochabamba, and Santa Cruz (Table 1). The study population was evenly split in terms of gender, in- versus outpatient status, and insurance status. The mean monthly income was US$243 (though income was highly skewed right, with most caregivers reporting a very low income). Most caregivers reported having sought some kind of treatment at least once prior to the current clinic or hospital visit; the mean length of time that the child had been ill prior to the current visit was five days. Approximately half the children presented with at least one complication, and 35% were experiencing their first episode of diarrhea in their lifetime. Less than a fifth of caregivers reported a rural residence, and the average number of transportations taken to arrive to the current visit was just over one. The average household size was approximately 5, and most caregivers interviewed were the mothers of the sick children and had low income.

To understand the economic burden that pediatric diarrhea places on caregivers of Bolivian infants, we collected data regarding direct (medical and non-medical) and indirect costs, in addition to data on household income (Table 2). Among those surveyed, the mean direct medical costs were US$17.17, and the mean direct non-medical costs were US$7.26. For an average Bolivian family with five members (mean household size in our population), these combined total direct costs can amount to between four and six days of food and fuel (for cooking and heating) for the household, depending on the level of food security experienced by the family [77]. Mean indirect costs (lost wages) were

US$14.85, though this sample was smaller given that not all caregivers reported salary information; this would represent between two and three and a half days of food and fuel for the same family. Total incurred costs, of US$34.31, for one pediatric diarrheal episode, could account for between five and eight days of food and fuel. The mean cost burden for the population was 1.77%, and over 40% of the sample spent at least 1% of their annual income on this single episode of pediatric diarrhea (Figure 1). For a family with the median annual income of US$2,274, a cost burden of 1% would translate into US$22.74 spent on a single episode of diarrhea. This would represent between three and five days of food and fuel for the same "average" family discussed above. Viewed through another lens, this amount is nearly twice as much as the average monthly expenditure on intra-city transportation reported for Bolivians of "moderate" poverty in 2000 [75]. Thus, cost burdens of even 1% may constitute a substantial economic burden in a setting where families use over 60% of daily per-capita expenditure for food and fuel alone, leaving little extra for healthcare, education, and housing expenses [77]. Overall, these data indicate that even a single episode of pediatric diarrhea may place a large financial burden on caregivers of Bolivian infants.

Predictors of Catastrophic Cost Burden (Cost Burden Greater Than or Equal to 1%)

In order to identify household characteristics that were associated with a catastrophic cost burden, we constructed a multivariate logistic regression model where catastrophic cost burden (outcome variable) was defined as a cost burden of at least 1% (Table 3). Through analysis of a bivariate association with the outcome, among 11 independent variables, six variables were significant: gender, rural residence, private vs. public hospital setting (Albino Patiño vs. all other hospitals), whether the family had sought treatment prior to the current visit, whether the child was an outpatient, and whether the child had presented with at least one complication. For inclusion in the full model, we also developed six biologically plausible two-way interactions: Age*Gender, Number of days ill prior to seeking treatment (numdaysill)*Complication, Age*Numdaysill, Gender*Numdaysill, Age*Complication, Age*Numdaysill. Hierarchical backwards elimination resulted in Numdaysill*Complication as the only significant interaction term. Therefore the final model included this interaction term and the aforementioned 11 variables. In this final adjusted model, we found significant ($p < 0.05$) odds ratios for the following variables: seeking treatment at Albino Patiño Hospital (4.13, [2.30, 7.41]), having sought treatment at least once prior to the current visit (3.92, [1.64, 9.35]), the number of days that the child had been ill before the current visit (1.14 [1.05, 1.24]), whether the child was an outpatient (0.16, [0.07, 0.37]), and the interaction between number of days ill and whether the child presented with a complication. The odds ratio associated with this interaction decreased with greater differences in number of days ill (comparing children with complications to those without), but did not show significance between differences of one to 14 days, though the overall term was statistically significant (Figure 2). The odds ratio associated with changes in number of days ill alone (no changes in whether or not the child had a complication) increased as the number of days ill increases (though the confidence interval also widened), and was significant throughout ($p < 0.01$). Overall, we found that treatment-seeking behaviors, along with hospitalization and seeking treatment in the private hospital, were important risk factors for a family to experience a catastrophic cost burden.

Predictors of Cost Burden

In order to determine potential predictors of cost burden, we first examined bivariate associations and then constructed a multivariate linear regression model with Log_{10} cost burden (to fulfill normality assumptions in the linear regression models) as the outcome variable (Table 4). Analysis of a bivariate association with the outcome (using ANOVA for categorical predictors and Spearman correlation coefficients for continuous predictors), among 11 independent variables, similar to the logistic regression analysis (Table 3) identified seven variables that were significantly associated: gender, rural residence, private vs. public hospital, whether the caregiver had sought treatment prior to the current visit, number of days that the child had been ill before the current visit, whether the child was an outpatient, and whether the child presented with at least one complication. Hierarchical backwards elimination allowed us to drop all interactions (as described in preceding paragraph) except for Numdaysill*Complication. The adjusted R^2 of this final model was 0.295. This model indicated the following variables as significant ($p < 0.05$), with the same directions of effects as the logistic model (Table 3): private hospital, whether the caregiver had sought treatment prior to the current visit, the number of days that the child had been ill prior to the current visit, whether the child was an outpatient, and the interaction term Numdaysill*Complication. The interaction results were slightly different from those of the logistic model (Figure 3): for those children who presented with at least one complication, each additional day increased (though, by a decreasing amount, as the days grew) cost burden until 12 days, at which point additional days actually lowered cost burden (Figure 3). Overall, we found that treatment-seeking behaviors, along with hospitalization and being treated in a private hospital, were important risk factors for increasing levels of cost burden.

DISCUSSION

The goal of this study was to characterize the financial impact of a child's pediatric diarrhea on their caregivers in Bolivia by quantifying the financial impact of a single episode of pediatric diarrhea and identifying predictors of cost burden as well as catastrophic cost. Our analyses showed that indirect costs presented a substantial burden to families. We also found an increasing cost burden and risk of catastrophic cost for children who were hospitalized (as opposed to outpatients), children whose parents had sought treatment for this episode of diarrhea at least once prior to the current visit, and children who had been sick for more days prior to the current visit. Lastly, we also saw that children seen in Albino Patiño Hospital (a private treatment setting) were more likely to report a catastrophic cost burden, and showed a higher cost burden overall as compared to children seen in other hospitals.

In our sample, indirect costs were a substantial burden on families surveyed (Table 2). Further, for families reporting lost wages, these indirect costs represented an average of 32% of their overall incurred costs (data not shown). These lost wages, associated with just a single episode of diarrhea, accounted for a median loss of 0.35% of the annual income (4.2% of monthly household income, or a little over one day of work) of these families (data not shown). This suggests that lost wages were a substantial contributor to overall cost burden in our population. While two studies of costs associated with pediatric diarrhea, in Canada and Britain, also found indirect costs to be important contributors to overall cost burden [73, 74], most studies we read from developing settings found indirect costs to be minimal if even present [35, 42, 43, 71]. Only one study in a developing setting, in China, showed indirect costs to be an important component of overall cost burden associated with pediatric diarrhea [78]. It is important to note methodological differences between our study and the above-mentioned work. The studies in Britain and Canada utilized country mean daily wages and caregiver-reported time lost from work. Additionally, parents in the British study did not incur any medical costs beyond over-the-counter medications. In contrast, the studies in developing settings mostly calculated indirect costs as we did (based on caregiver reports of average daily or monthly wages and caregiver-reported time lost from work). In the studies in developing settings where indirect costs were minimal, the authors cited two possible reasons for the low contribution of indirect costs. First, they mentioned difficulty in calculating average daily wages (e.g. because caregivers were employed informally and thus unable to estimate daily wages). Second, a low percentage of surveyed caregivers in those studies lost wages or missed work (because the caregiver who attended the sick child did not earn an income). We suspect that our study found greater indirect costs due to the seemingly higher prevalence of income-generating activities by both spouses, as opposed to just one spouse. Because we found that indirect costs were important to overall diarrhea-related costs in Bolivia, we recommend that future economic studies and cost-effectiveness analyses focusing on societal costs in other countries include indirect costs in their analyses.

As significant ($p < 0.01$) predictors of catastrophic cost and overall cost burden, our study identified inpatient status, previous treatment for this episode, and increasing number of days the child had been ill prior to the current visit. A higher cost burden for inpatients is consistent with other published literature from studies in India and China [42, 72, 78], and, in Bolivia, may also reflect the overall higher costs associated with hospitalization as compared to outpatient visits [29]. A hospitalization, compared to an outpatient visit, may result in a higher cost burden due to additional medication costs or fees, as well as an increased need for the caregiver to take time off work. Though there has been no analysis of the impact of prior treatment-seeking behavior in the published literature, several mechanisms may explain this phenomenon. The higher cost burden and risk of catastrophic associated with previous treatment may have reflected payments made for medication or to providers seen before the current visit. In our analyses, patients experiencing catastrophic cost tended to have paid significantly more on average for prior analysis, medication, and consults (data not shown). While there also has been no analysis in the published literature of the association between catastrophic cost and the number of days the child had been ill prior to the current visit, we believe that this variable captures an important element of illness severity both independently and as modified by complications. Children who are sick for a long time before their parents seek hospital treatment may develop illness of a greater severity, which may incur higher treatment costs (both prior to and during the current visit). Additionally, these children may come from families which are less equipped or inclined to utilize hospital care. We hypothesize that these parents may delay seeking to treatment due to a greater *fear* of incurring costs, which may be independent of their actual ability to pay. Data was not collected on the fear of incurring costs, but we found no significant association of number of days ill with income per capita, monthly household income, or perceptions of how the current diarrheal episode affects the household finances (data not shown). Overall, these results point to the importance of caregiver treatment-seeking behavior as well as the severity of the child's illness to overall caregiver-incurred cost burden associated with pediatric diarrhea in Bolivia. Based on these findings, we recommend interventions targeted at modifying caregiver treatment behavior for episodes of pediatric diarrhea.

Though few other studies address the specific impact of hospital or hospital type on familial-incurred cost, we found this to be a significant predictor. Caregivers whose children were seen in the private hospital (Albino Patiño) were significantly more likely to incur a catastrophic cost burden, and had an overall higher cost burden. This is generally consistent with other research findings: One study in Vietnam found indirect costs to be significantly higher in a private urban clinic, as compared to public and rural hospitals and clinics, but did not further characterize the impact of this variable [21]. In Bolivia, families whose children are seen at private hospitals may have a greater risk of catastrophic cost because they are unable to take advantage of SUMI (universal insurance), and therefore incur higher direct medical costs. Private hospitals may also have higher baseline costs than public facilities. Additionally, families who went to the private hospital in our study had significantly higher average costs for previous treatments (data not shown). Perhaps these families sought care at the private hospital because they felt like they had exhausted other options. However, our data did not show significant differences between the private hospital and other hospitals in terms of indirect costs, which we might have expected if we believed that families had to take off more time from work to go to a private hospital, or transportation costs to the current appointment, which we might have expected if we believed that families were traveling farther to get to the private hospital. Given the greater cost of privately provided care, it is important to understand how and why patients choose to seek care at these facilities, as opposed to publicly run facilities (which accept insurance). Use of private facilities is not limited to wealthy families: Up to 40% of healthcare utilization in Bolivia occurs in the private sector, with 75% of these patients uninsured [66]. Other countries also show use of private services across wealth strata [79]. Families may elect to pay for private consultations based on a belief that the quality of care is better in the private setting, as found in one study in Kenya [80], or for other reasons not yet explored. Overall, these data indicate a need for further investigation into why parents take their children to private practitioners instead of public facilities, and why they may incur direct costs even in public facilities, where they should theoretically be covered by SUMI.

This study has several strengths. One strength was the representativeness of its results to Bolivia because of the wide breadth of health care sites, covering multiple geographic regions of Bolivia and two types of health care settings (outpatient and inpatient). A second strength was the detail (i.e. multiple types of costs) and care (e.g. double data entry) with which data were collected. A third strength is the consistency of the significant results in our logistic and linear models, which lends confidence to our analysis. One limitation was that our cost estimates were likely an underestimate of the true cost estimates because the caregiver sometimes refused or was unable to provide specific cost information. A second limitation was that we had only one private treatment setting in our sample, which makes it difficult to generalize conclusions about private versus public treatment locations.

In addition to demonstrating the substantial financial impact of even a single episode of pediatric diarrhea, our study shows the importance of hospital choice, caregiver treatment behavior, and illness severity in the consideration of the financial impact of an episode of pediatric diarrhea on Bolivian caregivers. These results shed light into potential areas of intervention for reducing societal burden from pediatric diarrhea. Increased caregiver education may be necessary regarding home treatment of diarrhea and when to take children to the hospital for care. The quality and availability of publicly funded healthcare may need to be emphasized to the population. Further research is also needed in Bolivia to understand why parents are still incurring treatment costs despite accessing public hospitals (where they should be covered by SUMI), and why some elect private over public facilities for treatment of pediatric diarrhea. Overall, our study implies that universal insurance programs alone may be insufficient to protect families from costs associated with pediatric diarrhea, and may need to be accompanied by educational campaigns or other systemic improvements in order to be fully effective.

In conclusion, we have shown that hospital, caregiver treatment behavior, and appointment type were significant predictors for overall cost burden and catastrophic cost associated with episodes of pediatric diarrhea in Bolivia. These costs can represent five to eight days of food for an average family, and even a cost burden of 1% can be important in a setting where the median expenditure on food and fuel amounts to over 60% of per capita daily expenditure, leaving little for housing, education, and incurred medical costs [77]. We have also demonstrated that indirect costs represented a substantial portion of overall cost burden for most of these families. Our data serve as a baseline for societal diarrheal costs in Bolivia before and immediately following the implementation of the rotavirus vaccine into the national immunization schedule in 2008. Overall, our analysis highlights the economic significance of pediatric diarrhea to Bolivian caregivers and also provides a more general framework for considering potential areas of intervention to reduce catastrophic cost and overall cost burden associated with pediatric diarrhea.

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