



Costs associated with acute respiratory illness and select virus infections in hospitalized children, El Salvador and Panama, 2012–2013



Jorge H. Jara^{a,*}, Eduardo Azziz-Baumgartner^b, Tirza De Leon^c, Kathia Luciani^d, Yarisa Sujeý Brizuela^e, Dora Estripeaut^f, Juan Miguel Castillo^g, Alfredo Barahona^c, Mary Corro^d, Rafael Cazares^e, Ofelina Vergara^f, Rafael Rauda^g, Rosalba González^h, Danilo Franco^h, Marc-Alain Widdowson^b, Wilfrido Clará^b, Juan P. Alvis-Estrada^a, Christian Travis Murray^a, Ismael R. Ortega-Sanchezⁱ, Fatimah S. Dawood^b

^a Centro de Estudios en Salud, Universidad del Valle de Guatemala, 18 Avenida 11-95 Zona 15, Vista Hermosa III, Guatemala City, 01015, Guatemala

^b Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA

^c Hospital Materno Infantil José Domingo De Obaldía, David, Panama

^d Hospital De Especialidades Pediátricas Omar Torrijos, Panama City, Panama

^e Hospital San Juan De Dios, San Miguel, El Salvador

^f Hospital Del Niño, Panama City, Panama

^g Hospital San Juan De Dios, Santa Ana, El Salvador

^h Instituto Conmemorativo Gorgas de Estudios de la Salud, Panama City, Panama

ⁱ Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

ARTICLE INFO

Article history:

Accepted 29 May 2019

Available online 31 May 2019

Keywords:

Acute respiratory illness

Healthcare expenditures

Children

Hospitalized

Respiratory syncytial virus

El Salvador

Panama

SUMMARY

Background and objectives: Although acute respiratory illness (ARI) is a leading cause of hospitalization among young children, few data are available about cost of hospitalization in middle-income countries. We estimated direct and indirect costs associated with severe ARI resulting in hospitalization among children aged <10 years in El Salvador and Panama through the societal perspective.

Methods: During 2012 and 2013, we surveyed caregivers of children hospitalized with ARI about their direct medical (i.e., outpatient consultation, medications, hospital fees), non-medical (transportation, child-care), and indirect costs (lost wages) at discharge and 7 days after discharge. We multiplied subsidized hospital bed costs derived from administrative data by hospitalization days to estimate provider costs.

Results: Overall, 638 children were enrolled with a median age of 12 months (IQR 6–23). Their median length of hospitalization was 4 days (IQR 3–6). In El Salvador, caregivers incurred a median of US\$38 (IQR 22–72) in direct and indirect costs per illness episode, while the median government-paid hospitalization cost was US\$118 (IQR 59–384) generating an overall societal cost of US\$219 (IQR 101–416) per severe ARI episode. In Panama, caregivers incurred a median of US\$75 (IQR 39–135) in direct and indirect costs, and the health-care system paid US\$280 (IQR 150–420) per hospitalization producing an overall societal cost of US\$393 (IQR 258–552).

Conclusions: The cost of severe ARI to caregivers and the health care system was substantive. Our estimates will inform models to estimate national costs of severe ARI and cost-benefit of prevention and treatment strategies.

© 2019 The Authors. Published by Elsevier Ltd on behalf of The British Infection Association.

This is an open access article under the CC BY-NC-ND license.

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

Acute respiratory illnesses (ARI) are a leading cause of hospitalization and death among children aged <5 years worldwide.^{1,2}

During the past two decades, improved respiratory illness surveillance has led to a better understanding of the incidence of outpatient visits and hospitalizations for respiratory illness in many settings. Consequently, an increasing number of countries, including middle-income countries, have immunization programs and national treatment guidelines for respiratory infection.³ However, data on the economic burden of respiratory illness are limited from

* Corresponding author.

E-mail address: jjara@ces.uvg.edu.gt (J.H. Jara).

most regions of the world and particularly from middle-income countries.⁴

In Latin America, respiratory illness results in a substantial burden of hospitalization. During 2009–2012, approximately 313,500 influenza and pneumonia hospitalizations occurred annually in Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua, of which three quarters were among children aged less than 5 years.⁵ To prevent this disease burden, 40 out of 45 countries and territories in the Americas now recommend influenza vaccine for selected target groups, including children aged 6–59 months.⁶ In addition, some countries also recommend other respiratory viral prevention and treatment strategies for selected populations, including influenza antiviral medications and palivizumab, a monoclonal antibody used to prevent respiratory syncytial virus (RSV)-associated hospitalization. In El Salvador and Panama, the governments purchased 275,000 and 530,000 doses of influenza vaccine for children in 2013 (personal communication, John Fitzsimmons, Pan-American Health Organization). In addition, oseltamivir has been recommended for the treatment of patients hospitalized with influenza since the 2009-influenza pandemic,^{7,8} and tertiary care hospitals reported spending US\$250,000–342,000 per hospital on palivizumab (personal communication, Hospital del Niño and Hospital Jose Domingo de Obaldía).

While estimates are now available about the burden of ARI and the effectiveness of some prevention and treatment strategies in Latin America,^{9,10} the economic costs of ARI remain largely unknown which precludes assessments of the cost effectiveness of existing and emerging respiratory virus prevention and treatment strategies.⁴ To inform future analyses of the cost effectiveness of ARI interventions, we estimated the hospitalization costs from the societal perspective of all-cause ARI and ARI associated with common respiratory viral pathogens among children aged <10 years participating in a clinical trial of empiric oseltamivir treatment in El Salvador and Panama.¹¹ In addition, to inform future discussions of the value of maternal RSV vaccination to protect young infants in both countries if an RSV vaccine is licensed for pregnant women, we also estimated costs of severe ARI resulting in hospitalization specifically among children aged <6 months with laboratory-confirmed RSV.

Patients and methods

Setting

This study was conducted in five tertiary care public sector hospitals: two in El Salvador (Hospital San Juan de Dios de Santa Ana and Hospital San Juan de Dios de San Miguel) and three in Panama (Hospital del Niño, Hospital de Especialidades Pediátricas, and Hospital José Domingo de Obaldía).

El Salvador has public and private health-care systems. The two main public health-care sector providers are the Ministry of Health, which covers 41% of the population, and the El Salvadorian Institute of Social Security, which covers 7% of the population; 9% of health care is provided by the private sector and the remaining 43% remains uncovered by insurance.¹² Although medical care in the public sector is provided free of charge, there are some cost-sharing mechanisms in place that rely on volunteer payments at secondary and tertiary level hospitals through a program designed to recover health care costs.¹³ In 2014, government health-care expenditures were 7% of the Gross Domestic Product (GDP); 66% of all healthcare expenditures were public sector expenditures, 29% were out-of-pocket expenditures, and 5% were other private sector expenditures.¹⁴

Panama also has public and private health-care systems. The two main providers in the public sector health-care sector are the

Ministry of Health and Social Security System. The Ministry of Health is largely financed by the state, while the Social Security System is financed by beneficiaries, employers, and the state.¹⁵ The Ministry of Health and the Social Security System combined cover 90% of the population. Health-care is provided free of charge to Panamanians, with some cost-sharing mechanisms in place based primarily on the ability of the patient/family to pay. In 2014, government health-care expenditure was 6% of the GDP; 73% of all healthcare expenditures were public sector expenditures, 22% were out-of-pocket health expenditures, and 5% were other private sector expenditures.¹⁶

Study design and data collection

We surveyed families of hospitalized children with severe ARI who were participating in a concurrent randomized placebo-controlled trial of empiric oseltamivir, an influenza antiviral medication, to estimate direct and indirect costs associated with severe ARI using a WHO recommended approach.¹⁷ The trial was conducted during at two tertiary level hospitals in El Salvador and three tertiary level hospitals in Panama. Children were enrolled during September–October 2012 and April–October 2013 to coincide with the typical influenza season in both countries. National respiratory virus surveillance data for both countries for 2013 when the large majority of children were enrolled indicate that the period of enrollment also captured peaks in circulation of respiratory syncytial virus (RSV), parainfluenza viruses (PIV), human metapneumovirus (hMPV), and adenoviruses; national surveillance reports did not provide data on rhinovirus detection.¹⁸ Trial methods have previously been described in detail.¹¹

Children were enrolled if they were <10 years of age and hospitalized <7 days after symptom onset with severe ARI defined as cough or sore throat plus age-specific tachypnea, did not meet any exclusion criterion applied in the original trial, and if their parents/legal guardians granted informed consent.

At enrollment, study physicians administered a questionnaire designed for this study to collect data about participant demographics, medical history, history of illness, and cost of any medical consultations prior to hospitalization. Nasal and oropharyngeal swabs were also collected from each participant and tested by singleplex real-time reverse transcription polymerase chain reaction at the Gorgas Memorial Institute for Health Sciences according to US CDC protocols for respiratory syncytial virus (RSV), parainfluenza viruses (PIV) 1–3, adenovirus, human metapneumoviruses (hMPV), rhinoviruses, and influenza viruses, including influenza A/H1N1pdm09, A/H3N2, and B.¹⁹

At discharge, study physicians administered a questionnaire to the participants' families to collect data about direct costs (i.e., hospital bed and outpatient visit fees, medications, diagnostic procedures, and transportation) and indirect costs (days of work lost or wages lost because of disruption in normal work routine) associated with the illness episode. Seven to 9 days after hospital discharge, study physicians administered a second telephone questionnaire on additional direct or indirect costs incurred as a result of the illness episode during the 7 days after discharge.

Since none of the study hospitals recorded itemized cost data by individual hospitalizations, we asked each hospital finance department to complete a standardized questionnaire about monthly personnel, supply, and infrastructure costs incurred by the hospital on wards where children with severe ARI were hospitalized for study months during 2013. Hospitals provided data about monthly subsidized costs for personnel, supplies and infrastructure separately for regular wards and intensive care units (ICU), number of hospitalizations per month, and average length of hospitalization per month. Cost data provided varied by hospital.

Cost analysis

Children with laboratory-confirmed influenza who were randomized to receive oseltamivir in the clinical trial were excluded because we assumed that this treatment might impact hospitalization costs. We assumed that study-provided empiric oseltamivir treatment of children without laboratory-confirmed influenza did not impact hospitalization costs because a prior analysis of data from this trial demonstrated no difference in adverse events between oseltamivir and placebo recipients.¹¹ Cost per illness was estimated from the societal perspective: our analyses included costs to both households and to the health-care system. Costs to households were grouped into three categories: direct medical costs (i.e., out-of-pocket expenses for medications, hospital, and outpatient consultation fees), direct non-medical costs (i.e., out-of-pocket expenses for transportation, childcare cost and other related expenses such as food and diapers), and indirect costs (i.e., self-reported income lost because of missed work and school days). For each category, we estimated the total cost per case as the sum of the itemized costs. When caregivers reported having made a payment but could not recall the amount paid, we imputed the average cost paid for the same item by other caregivers in the same site. All costs were estimated in 2013 USD in El Salvador and 2013 Balboas in Panama (1 Balboa=1 USD). Since most inpatient participants were enrolled in 2013, we adjusted all cost estimates from 2012 to 2013 values using an annual inflation rate of 3%.

We estimated hospitalization costs to the health-care system for each study participant by multiplying the length of the hospital stay in days by the estimated unit cost per hospital bed-day. For children admitted to the ICU, costs were calculated separately for days spent in the ICU versus the regular ward and then summed to calculate total cost of hospital stay. Unit costs per hospital bed-day accrued by the health-care system and not billed to patients were estimated using administrative data collected from study hospitals. Average cost per hospital bed-day was calculated by adding monthly reported costs in personnel, supplies and infrastructure and then dividing the total by the product of the total number of admissions and the average length of hospital stay per ward and month provided by each hospital; calculations were done separately for the general ward and ICU. The estimated cost per ICU bed day at one hospital in Panama was an outlier (more than five-fold higher than costs at the other two hospitals), so we substituted the cost per ICU bed day from the closest other study hospital for this hospital.

Total financial costs per severe ARI episode from the societal perspective were estimated by summing the costs accrued by caregivers and the health-care system. Since data were not collected on the setting of reported outpatient visits, WHO-CHOICE estimates of outpatient visit costs could not be used. Therefore, costs of outpatient consultations paid by the health-care system were not included. All costs were stratified by country and by whether children were admitted only to the general ward or admitted to the ICU for at least part of the hospitalization. We also calculated overall costs for all inpatient participants as the average of hospital bed costs for participants with and without ICU admission in each country weighted for the proportion of hospitalizations that included ICU admissions. For each category of cost, we calculated means, medians and inter-quartile ranges (IQR).

To evaluate whether the costs of hospitalization varied by the etiology of the respiratory illness, costs were stratified by type of virus; participants with co-detection of more than one virus type were included in the overall cost analysis but excluded from the analysis by virus type. We conducted a separate cost analysis using the same methods for children aged <6 months hospitalized with RSV illness.

We compared total household costs to the average monthly household income in each country (US\$556 in El Salvador and US\$1278 in Panama) and compared total costs from the societal perspective to the 2013 World Bank average health expenditure per capita in El Salvador (US\$277) and Panama (US\$906).²⁰

Ethics statement

The study protocol No. 062-03-2012 was reviewed and approved by the national ethical review committee of El Salvador and the Gorgas Memorial Institute for Health Studies in Panama. The Centers for Disease Control and Prevention and The Universidad del Valle de Guatemala relied upon the review of the ethical committees in El Salvador and Panama.

Results

Respondent characteristics

Of 688 children hospitalized with ARI and enrolled in the clinical trial, 19 (3%) were excluded from this analysis because they had laboratory-confirmed influenza and were treated with oseltamivir. Of the remaining 669 children, 638 (95%) had caregivers that completed both the discharge and post discharge surveys (367 in El Salvador and 271 in Panama) and were included in the analysis. For both the discharge and post-discharge cost surveys, the mother was the respondent in most cases (91% and 85%, respectively).

Participant characteristics

Of the 638 participants, 331 (52%) were infants aged <1 year, 281 (44%) were 1–4 years of age, and 26 (4%) were 5–9 years of age; 382 (60%) were male and 536 (84%) were of mixed race (Table 1). Twenty-one percent of children had at least one underlying medical condition. Of the 638 participants, 166 (26%) were vaccinated against influenza, of whom 134 (81%) had influenza vaccination status verified by inspecting their vaccine cards. In El Salvador, 41% (141/340) of participants who provided monthly household income information, reported an income \leq \$350 USD (average national monthly household income in 2013=US\$556).²¹ In Panama, 53% (127/241) of participants with reported household incomes had an income \leq \$500 USD (average provincial monthly household income in 2013 for Chiriquí Province=US\$861). The most commonly detected respiratory viruses among participants were RSV (50%), followed by rhinovirus (22%), human metapneumovirus (6%), and parainfluenza viruses 1–3 (6%) (Table 1).

Resource utilization

Of the 638 participants, 511 (80%) had at least one outpatient consultation associated with their illness episode either prior to hospitalization or during the 7 days after hospitalization (86% in El Salvador and 72% in Panama) (Table 2). Fourteen (2%) participants required ICU admission. The median length of hospitalization was 4 days (interquartile range, IQR, 3–6) among children without an ICU admission and 16 days (IQR 13–22) among children admitted to the ICU for at least part of their hospitalization, with a median of 5 days (IQR 4–8) spent in the ICU (Table 2).

Cost to households

Overall, 368 (58%) participants' caregivers paid for medications and 245 (39%) paid outpatient consultation fees for visits before or after hospitalization. Almost all caregivers (94%) paid transportation costs and 81% paid for other expenses such as diapers, phones calls, or lodging. Only 9% paid childcare costs. Overall, 40% reported

Table 1

Characteristics of children aged <10 years with severe acute respiratory illness requiring hospitalization at five hospitals, El Salvador and Panama, 2012–2013, N=638.

	El Salvador n=367 n (%)	Panama n=271 n (%)	Total N=638 n (%)
Age			
0–11 months	202 (55)	129 (47.6)	331 (52)
1–4 years	154 (42)	127 (46.9)	281 (44)
5–9 years	11 (3)	15 (6)	26 (4)
Sex			
Male	211 (58)	171 (63)	382 (60)
Ethnicity			
African	0 (0)	16 (6)	16 (3)
White	0 (0)	8 (3)	8 (1)
Indoamerican	0 (0)	75 (28)	75 (12)
Mixed	367 (100)	169 (62)	536 (84)
Other [‡]	0 (0)	3 (1)	3 (1)
Underlying medical condition (≥ 1)	45 (12)	91 (34)	136 (21)
Reported influenza vaccination	80 (22)	86 (32)	166 (26)
Monthly income per household (2013 only) [†]			
≤175 USD	67/340 (20)	22/241 (9)	-
176–350 USD	74/340 (22)	53/241 (22)	-
351–500 USD	38/340 (11)	52/241 (22)	-
≥501 USD	80/340 (24)	82/241 (34)	-
Viral detection at admission			
At least one respiratory virus at admission	294 (80)	229 (85)	523 (82)
Single virus	278 (95)	205 (90)	483 (92)
More than 1 virus	16 (5)	24 (10)	40 (8)
Type of virus			
Respiratory syncytial virus	217 (59)	101 (37)	318 (50)
Rhinovirus	56 (15)	89 (33)	145 (23)
Human metapneumovirus	8 (2)	32 (12)	40 (6)
Parainfluenza viruses 1–3	19 (5)	21 (8)	40 (6)
Adenovirus	7 (2)	5 (2)	12 (2)
Influenza A/B	3 (1)	7 (3)	10 (2)

[‡] Ngäbe–Buglé, Kuna Yala ethnics.

[†] In El Salvador and Panama, 81 and 32 participants did not provide monthly household income data, respectively. In Panama, official mean reported monthly income for 2013 was \$861.00 (Ministry of Economic and Finance for Chiriquí Province). For El Salvador, official mean reported monthly income for 2013 was \$556.16 (General Directorate of Statistics and Census for rural areas).

Table 2

Resource utilization for severe acute respiratory illness requiring hospitalization in children aged <10 years at five hospitals, El Salvador and Panama, 2012–2013, N=638.

	El Salvador n=367 n (%)	Panama n=271 n (%)	Total N=638 n (%)
Had ≥1 outpatient visit before hospitalization or during the 7 days after hospitalization	316 (86)	195 (72)	511 (80)
1 consultation before hospitalization	183 (50)	111 (41)	294 (46)
≥ 2 consultations before hospitalization	133 (36)	84 (31)	217 (34)
≥1 visit for routine follow-up care after hospitalization	17 (5)	6 (2)	23 (4)
Required intensive care unit (ICU) stay	7 (2)	7 (3)	14 (2)
Median (IQR) days of hospitalization			
Without ICU stays	4 (3–5)	4 (3–7)	4 (3–6)
With ICU stays	17 (15–24)	13 (10–16)	16 (13–22)
Days in the ICU	5 (4–9)	4 (4–8)	5 (4–8)

that at least one member of the household missed time at work because of the illness (Table 3) for a median of three work days missed (IQR 2–5) (Table 4).

In El Salvador and Panama, medication costs were the largest cost drivers of direct medical costs. In El Salvador, the median total cost to caregivers was US\$38.4 (21.5–72.4) or 7% of the average national monthly household income. In Panama, the median total cost to caregivers was US\$74.6 (IQR 39.2–134.5) or 6% of the average monthly household income and approximately 26% of the average monthly household income for those in the lowest national income quintile (Table 4).

Cost to the health-care system

The median cost to the health-care system per hospitalization weighted for the proportion of hospitalizations that included ICU admissions was US\$117.9 (IQR 59.0–383.9) in El Salvador and

US\$280.1 (IQR 150.2–420.1) in Panama. The median costs for hospitalizations that included ICU admissions were at least 8-fold higher than hospitalizations without ICU admissions in both countries (El Salvador US\$2414 vs. US\$121; Panama US\$2508 vs. US\$286) (Table 4).

Total financial costs

From the societal perspective, the median total cost per severe ARI requiring hospitalization was US\$218.7 (IQR 101.3–416.0) in El Salvador and US\$393.3 (IQR 258.4–551.6) in Panama, equal to 79% and 43% of health-care expenditure per capita in each country. Caregivers bore 20% of average total costs in El Salvador and 23% of total costs in Panama. Cost of severe ARI did not differ significantly by virus type for children with single detection of RSV, rhinovirus, hMPV, PIV 1–3, influenza, or adenovirus detection (Fig. 1, Supplemental Table 1).

Table 3

Caregiver out-of-pocket expenses associated with severe acute respiratory illness requiring hospitalization among children aged <10 years in El Salvador and Panama, 2012–2013, N=638.

	El Salvador n=367 n (%)	Panama n=271 n (%)	Total N=638 n (%)
Paid for ≥1 outpatient consultations	140 (38)	105 (39)	245 (39)
Paid hospital fees	40 (11)	114 (42)	154 (24)
Purchased medication	180 (49)	188 (69)	368 (58)
Paid for transportation to/from hospital	351 (96%)	244 (91%)	595 (94%)
Median number of trips* from home to hospital (IQR)	4 (2–6)	4 (2–8)	4 (2–6)
Median minutes per trip* from home to hospital (IQR)	45 (30–60)	60 (30–120)	60 (30–90)
Paid for childcare costs	19 (5%)	37 (14%)	56 (9%)
Paid for other items associated with illness episode**	292 (80%)	220 (81%)	512 (81%)
At least one household member missed scheduled work	107 (29%)	147 (54%)	254 (40%)
Child missed school	11 (3%)	24 (9%)	35 (6%)

* Trips were reported separately for each direction (e.g., two trips per one roundtrip).

** Included food and personal items such as diapers, phone calls, lodging etc.

Table 4

Estimated caregiver and public hospital costs in United States Dollars[†] per child with severe acute respiratory illness requiring hospitalization in El Salvador and Panama, 2012–2013, N=638.

	El Salvador (n=367)				Panama (n=271)			
	Cases (n)	Mean	Median	IQR	Cases (n)	Mean	Median	IQR
Direct Medical Costs	367	23.7	9.8	0–30.0	271	40.1	26.0	10.0–51.0
Outpatient consultations fee	367	8.7	0	0–5.2	271	7.8	0	0–10.0
Hospital fee	367	1.8	0	0–0	271	10.5	0	0–15.0
Medication cost	367	13.1	0	0–18.0	271	21.5	12.0	0–30.0
Direct Non-Medical Costs	367	25.3	18.4	10.0–34.0	271	48.8	33.0	13.6–61.0
Transportation cost	367	9.5	4.5	1.6–11.4	271	18.8	8.8	3.0–20.0
Childcare cost	367	0.8	0	0–0	271	6.3	0	0–0
Other non-medical expense*	367	15.1	10.3	4.1–22.0	271	23.7	16.0	5.0–34.0
Indirect Costs								
Wages lost by household members due to child illness	367	10.9	0	0–12.0	271	13.4	0	0–0
Work days missed per household due to child illness [‡]	145	4.1	3.0	2.0–5.0	157	3.7	3.0	2.0–5.0
School days missed by child**	11	8.1	6.0	2.0–11.0	25	7.6	7.0	4.0–10.0
Total Caregiver Costs***	367	59.9	38.4	21.5–72.4	271	102.3	74.6	39.2–134.5
Medical Costs to the Health-care System for Hospitalization[‡]								
With ICU admission	7	2122.9	2414.0	1151.0–2571.0	7	2294.6	2422.0	2014.4–2633.7
Without ICU admission	360	229.6	120.6	60.3–314.0	264	325.5	286.4	153.6–409.8
All admissions ^{††}	367	241.3	117.9	59.0–383.9	271	336.5	280.1	150.2–420.1
Total Costs^{‡‡}								
With ICU admission	7	2286.4	2585.7	1212.8–2883.2	7	2452.1	2546.8	2204.1–2867.7
Without ICU admission	360	287.5	212.3	101.2–420.0	264	426.3	388.0	260.1–541.4
All hospitalized children ^{†††}	367	301.1	218.7	101.3–416.0	271	438.8	393.3	258.4–551.6

ICU: Intensive care unit; IQR: Interquartile range.

* Included food and personal items such as diapers, phone calls, lodging, etc.

** Of children who regularly attend school.

*** Total caregiver costs were calculated for each participant as the sum of their direct medical costs, direct non-medical costs and indirect costs.

† Costs from 2012 were adjusted to 2013 by increasing by 3%.

‡ Calculated for each participant as the product of days of hospitalization on the general pediatric ward multiplied by median hospital-bed cost for the general ward summed with the product of days of hospitalization in the ICU multiplied by median hospital-bed cost for the ICU. Average cost per hospital bed-day was calculated separately for the general ward and the ICU at each hospital by adding personnel, supply and infrastructure costs and then dividing the total by the product of total admissions and the average length of hospital stay per ward (general ward vs. ICU). Costs to the health-care system for outpatient consultations were not available and were not included in this analysis.

†† Weighted average of hospital bed costs for participants with and without ICU admission.

‡‡ Calculated for each patient as the sum of the caregiver's out-of-pocket costs and cost to the health-care system for their hospitalization.

††† Does not include weekends, holidays, or days when persons were not otherwise scheduled to work.

Cost of RSV-associated severe ARI hospitalizations among infants aged < 6 months

Overall, there were 99 severe ARI episodes with RSV detection requiring hospitalization among infants aged <6 months. In El Salvador, the median total cost to households for these hospitalizations was US\$34.0 (IQR 21.6–68.0), the median overall cost to the health-care system was US\$230.3 (59.0–333.7), and the median total cost from the societal perspective was US\$246.1 (107.1–399.3) (Supplemental Table 2). In Panama, the median total cost to households for RSV-associated severe ARI requiring hospitalization was US\$56.8 (IQR 25.5–140.5), the median overall cost to the health-care system was US\$280.1 (200.3–534.4), and the median total cost from the societal perspective was US\$402.0 (253.0–616.2).

Discussion

In this study of >600 children hospitalized with severe ARI in El Salvador and Panama, we estimated that the median total financial cost per severe ARI episode was US\$219 in El Salvador and US\$393 in Panama equal to 79% and 43% of national health expenditure per capita in each country. The cost of hospitalizations that included ICU admissions were five to eight-fold higher than hospitalizations without ICU admission. Caregivers bore approximately one fourth of costs equal to 6–7% of average national monthly household incomes in each country and 26% of average national household income for those in the lowest income quintile in Panama. In addition, severe ARI episodes that required hospitalization frequently resulted in indirect costs of lost work days and wages for

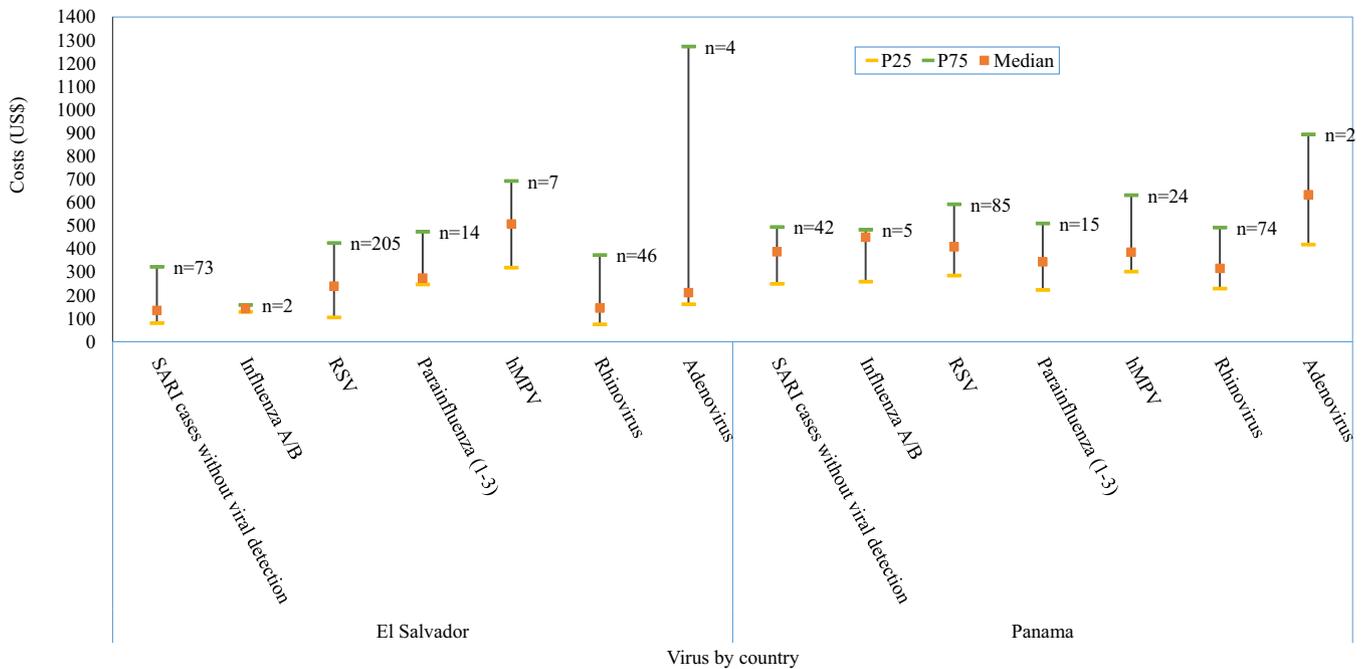


Fig. 1. Total costs in US Dollars from the societal perspective for severe acute respiratory illness requiring hospitalization among children aged <10 years, by virus type, El Salvador and Panama, 2012 and 2013, $N = 598^*$.

*Analysis excludes participants with viral co-detection.

caregivers. We also evaluated costs by virus type for common respiratory viruses and found no significant differences in costs per episode between viruses, possibly because the mainstay of treatment is supportive care.

To date, among countries in Latin America, published estimates of costs of hospitalized ARI or pneumonia among children are available from Argentina, Colombia, Guatemala, Honduras, Nicaragua, Peru and Mexico, although only some studies included costs to the health-care system that are critical to policy making decisions.^{4,22–26} In Argentina, the median cost of hospitalization for respiratory illness among children aged <5 years from the societal perspective was US\$529.²⁴ In Nicaragua, the average cost of severe respiratory illness hospitalizations among children aged 6 months through 9 years from the government perspective ranged from US\$315 among patients hospitalized in the general ward to US\$ 972 for those hospitalized in the ICU.²² Costs of illness in our study were lower than those estimated in high-income Argentina but similar to those from middle-income Nicaragua.

Our findings could be used to assess the cost-effectiveness and cost-benefit of prevention and treatment strategies for influenza and RSV in Latin America. Currently, the World Health Organization recommends that countries consider influenza vaccination for young children aged <2 years and persons with underlying medical conditions. While 64% and 56% of countries in Latin America have influenza vaccine policies that target pregnant women and young children, respectively, investments in influenza vaccines are limited because of their expense and uncertainty about their value in lower income settings.⁶ Similarly, clinicians in El Salvador and Panama have access to and sporadically use influenza antiviral medications and palivizumab, but the cost-effectiveness of these interventions has not been well studied in Latin American countries. In addition, RSV vaccines are in phase 3 trials for use in pregnant women as a potential strategy to protect young infants through antenatal placental antibody transfer.²⁷ Middle-income countries, such as the majority of countries in Latin America, are poised to consider expansion or introduction of respiratory

viral vaccines for high-risk groups. Data from our study provide actual cost inputs that can be combined with data about illness incidence and intervention effectiveness to inform discussions about the cost-benefit of interventions to reduce the burden of respiratory illness.

Strengths of our study include collection of detailed data on both direct and indirect costs to caregivers among a large cohort of children from both urban and rural areas in two Latin American countries, use of administrative data on costs to the health-care system from study hospitals, and use of gold standard testing to identify respiratory viral etiologies for the majority of illness episodes allowing estimates of cost by virus type. Nevertheless, several limitations should be considered. First, because costs to the health-care system were not obtained through a micro-costing approach¹⁷, the completeness of hospital administrative data varied by hospital with some hospitals missing data for certain cost categories (e.g., amortization of equipment and facilities). Second, while, 84% of children had at least one outpatient consultation during their illness, costs to the health-care system for outpatient consultations were unavailable. Taken together, these limitations likely led to an underestimate of total costs to caregivers and the health care system. Third, systematic testing for bacterial infection was not done in our study, and we were not able to assess costs of severe ARI associated with bacterial infections. Lastly, our study only estimated costs of severe ARI resulting in hospitalization at tertiary level public hospitals which may not be representative of primary and secondary level hospitals and private hospitals in each country that may not have intensive care units and may admit lower acuity patients.

Financial disclosure statement

The authors have no financial relationships relevant to this article to disclose.

Additional disclosures

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conflict of interest statement

All authors have indicated they have no potential conflicts of interest to disclose.

Clinical trial registration

Panama and El Salvador Children's Oseltamivir Study (PECOS). This study is registered in ClinicalTrials.gov, number NCT01690637.

Acknowledgments

Thank you to Rafael Chacón, Nelson Alvis-Zakzuk, María Sotomayor and the influenza team for their support.

Funding

This study was funded by the US Centers for Disease Control and Prevention through Cooperative Agreement number RFA-GH-13-00102CONT14 with the Universidad del Valle de Guatemala.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.05.021.

References

- Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the sustainable development goals. *Lancet* 2016;**388**:3027–35.
- Nair H, Simoes EA, Rudan I, Gessner BD, Azziz-Baumgartner E, Zhang JS, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 2013;**381**:1380–90.
- Ortiz JR, Perut M, Dumolard L, Wijesinghe PR, Jorgensen P, Ropero AM, et al. A global review of national influenza immunization policies: analysis of the 2014 WHO/UNICEF Joint Reporting Form on immunization. *Vaccine* 2016;**34**:5400–5.
- Peasah SK, Azziz-Baumgartner E, Breese J, Meltzer MI, Widdowson MA. Influenza cost and cost-effectiveness studies globally – a review. *Vaccine* 2013;**31**:5339–48.
- Descalzo MA, Clara W, Guzman G, Mena R, Armero J, Lara B, et al. Estimating the burden of influenza-associated hospitalizations and deaths in Central America. *Influenza Other Respir Viruses* 2016;**10**:340–5.
- Ropero-Alvarez AM, El Omeiri N, Kurtis HJ, Danovaro-Holliday MC, Ruiz-Matus C. Influenza vaccination in the Americas: progress and challenges after the 2009 A(H1N1) influenza pandemic. *Hum Vaccin Immunother* 2016;**12**:2206–14.
- El Salvador M de SP y AS. *Lineamientos actualizados para el manejo del virus pandémico (H1N1) 2009 en humanos*. San Salvador: El Salvador; 2009.
- Ministerio de Salud Ministerio, de Desarrollo Agropecuario, Autoridad Nacional del Ambiente P. Plan estratégico integrado MINSA-MIDA-ANAM ante las amenazas de la Influenza aviar y la pandemia de influenza. Panama City, 2006.
- El Omeiri N, Azziz-Baumgartner E, Clara W, Guzman-Saborio G, Elas M, Mejia H, et al. Pilot to evaluate the feasibility of measuring seasonal influenza vaccine effectiveness using surveillance platforms in Central-America, 2012. *BMC Public Health* 2015;**15**:673.
- El Omeiri N, Azziz-Baumgartner E, Thompson MG, participants RE-in, Clara W, Cerpa M, Palekar R, et al. Seasonal influenza vaccine effectiveness against laboratory-confirmed influenza hospitalizations – Latin America, 2013. *Vaccine* 2017.
- Dawood FS, Jara J, Gonzalez R, Castillo JM, De Leon T, Estripeaut D, Luciani K, Sujey Brizuela Y, Barahona A, Cazares RA, et al. A randomized, double-blind, placebo-controlled trial evaluating the safety of early oseltamivir treatment among children 0–9 years of age hospitalized with influenza in El Salvador and Panama. *Antiviral Res* 2016;**133**:85–94.
- Organización Panamericana de la Salud, Organización Mundial de la Salud. Estrategia de Cooperación con el País El Salvador 2012 2015 (Accessed 3 April 2018) https://www.paho.org/els/index.php?option=com_docman&view=download&alias=820-estrategia-de-cooperacion-2012-2015&category_slug=reforma-del-sector-salud&Itemid=364.
- Acosta M, Saenz Mdel R, Gutierrez B, Bermudez JL. The health system of El Salvador. *Salud Publica Mex* 2011;**53**(Suppl 2):s188–96.
- Health expenditure, Total (% of GDP), El Salvador. (Accessed February 28, 2018) <https://data.worldbank.org/indicator/SH.XPD.TOTL.ZS?locations=SV>.
- Análisis de Situación de Salud (ASIS). (Accessed 28 February 2018) <http://www.minsa.gob.pa/informacion-salud/analisis-de-situacion-de-salud-asis>.
- Health expenditure, total (% of GDP), Panama. (Accessed 28 February 2018) <http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS?locations=PA>.
- WHO Manual for estimating the economic burden of seasonal influenza. (Accessed 3 April 2018) <http://apps.who.int/iris/bitstream/handle/10665/250085/WHO-IVB-16.04-eng.pdf;jsessionid=A479FB9244C203EAAFA01CA76CA1558?sequence=1>.
- PAHO Influenza regional report. (Accessed 22 May 2019) <https://www.paho.org/hq/dmdocuments/2013/influenza-2013-Regional-Update-EW-49.pdf>.
- Kim C, Ahmed JA, Eidex RB, Nyoka R, Waiboci LW, Erdman D, et al. Comparison of nasopharyngeal and oropharyngeal swabs for the diagnosis of eight respiratory viruses by real-time reverse transcription-PCR assays. *PLoS One* 2011;**6**:e21610.
- Health Expenditure Per Capita. (Accessed 28 February 2018), <https://data.worldbank.org/indicator/SH.XPD.PCAP?end=2014&start=2013&view=chart>.
- Encuesta de Hogares de Propósitos Múltiples 2013. (Accessed 28 February 2018) www.digestyc.gob.sv/index.php/temas/des/ehpm/publicaciones-ehpm.html.2013.
- Chittaganpitch M, Supawat K, Olsen SJ, Waicharoen S, Patthamadilok S, Yingyong T, et al. Influenza viruses in Thailand: 7 years of sentinel surveillance data, 2004–2010. *Influenza Respir Viruses* 2012;**6**:276–83.
- Alvis-Guzman N, Orozco-Africano J, Paternina-Caicedo A, Coronell-Rodriguez W, Alvis-Estrada L, Jervis-Jalabe D, et al. Treatment costs of diarrheal disease and all-cause pneumonia among children under-5 years of age in Colombia. *Vaccine* 2013;**31**(Suppl 3):C58–62.
- Marcone DN, Durand LO, Azziz-Baumgartner E, Vidaurreta S, Ekstrom J, Carball G, et al. Incidence of viral respiratory infections in a prospective cohort of outpatient and hospitalized children aged </=5 years and its associated cost in Buenos Aires, Argentina. *BMC Infect Dis* 2015;**15**:447.
- Porrás-Ramírez A, Alvis-Guzman N, Rico-Mendoza A, Alvis-Estrada L, Castaneda-Orjuela CA, Velandia-Gonzalez MP, et al. Cost effectiveness of influenza vaccination in children under 2 years old and elderly in Colombia. *Rev Salud Publica (Bogota)* 2009;**11**:689–99.
- Alvis-Guzman N, Marin-Correa C, Castaneda-Orjuela C, Sanchez-Ruiz C, Carrasquilla SM, Sanchez-Largaespada F. Hospitalization costs due to severe acute respiratory infection (SARI) in three Central American countries. *Infectio* 2018;**22**:159–66.
- Giersing BK, Karron RA, Vekemans J, Kaslow DC, Moorthy VS Meeting report: WHO consultation on Respiratory Syncytial Virus (RSV) vaccine development, Geneva, 25–26 April 2016. *Vaccine*, 2017.