



Economic Burden of Herpes Zoster (“culebrilla”) in Latin America



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ABSTRACT

Background: Herpes zoster (HZ) is characterized by debilitating pain and blistering dermatomal rash. The most common complication of HZ is postherpetic neuralgia (PHN), a persistent pain that can substantially affect patients' quality of life. HZ has significant impact on patients' lives with considerable implications for healthcare systems and society. The purpose of this study was to evaluate the healthcare resource utilization (HCRU) and medical costs associated with HZ in Latin America.

Method: We conducted a pooled-analysis of three prospective cohort studies of HZ patients ≥ 50 years of age in Argentina ($n = 96$); Brazil ($n = 145$) and Mexico ($n = 142$). Patients were recruited at different time-points during their HZ episode and were followed for six months. The incidence of PHN was defined as a worst ZBPI pain score of ≥ 3 , persisting or appearing more than 90 days after the onset of rash. Work effectiveness was measured on a 100-point Likert scale where 100 was described as completely effective (able to work like before HZ began) and 0 as not effective at all. Direct costs included costs due to use of antiviral medications and all medical services used to treat HZ. Indirect cost was based on foregone earnings from patients due to work loss and presenteeism, and work loss by family caretakers. One-way sensitivity analysis was performed to assess the impact on total costs. All costs are reported in 2015 USD currency.

Results: 383 HZ patients were included and PHN incidence was 38.6%. The most commonly used resources were visits to the doctor's office (79.1% of patients), the emergency room (48.8%) and a specialist (37.9%); hospitalization was reported for 5.7% of patients. The overall direct cost per case was \$763.19 USD, indirect cost was \$701.40, for a total of \$1,464.59 per HZ episode in Latin America. Total cost associated with HZ in patients with PHN was markedly higher compared to patients without PHN (\$2,001.13 vs. \$867.72, respectively) with indirect costs accounting for the most part of this difference. The sensitivity analysis was generally robust to changes in the assumptions made.

Conclusion: HZ and its sequelae impose a substantial economic burden in Latin America which is expected to rise as the population ages and the number of HZ cases increases. The results support the need for early intervention, preventative strategies and improved disease management to reduce the HZ-associated disease burden in Latin America.

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Introduction

Herpes zoster (HZ) is caused by reactivation of latent varicella-zoster virus (VZV) in sensory ganglia and is typically characterized by painful, blistering dermatomal rash.¹ The most common complication of HZ is post herpetic neuralgia (PHN), which is characterized by pain persisting or appearing months after the rash heals. PHN can cause physical disability, emotional distress and

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interference with daily activities and sleep.^{2,3} The incidence, severity, and duration of PHN increases with age, particularly in adults aged 50 years and older.⁴ HZ may also cause neurological sequelae, HZ ophthalmicus (HZO) with eye involvement or disseminated disease.⁵ Complications of HZ have been reported in 13–26% of HZ cases.^{6,7}

The annual incidence of HZ has been reported to range from 1.2 to 4.8 cases per 1,000 inhabitants/year in North America, Europe and Asia-Pacific.^{5,8,9} The greatest challenge in reporting incidence rates in Latin American countries is the scarcity of available information.¹⁰ In the available literature, the incidence rate in Latin America ranges from 3.6–6.5.^{5,11–13} Suggesting a higher burden of disease in Latin American, compared to the previously mentioned countries.

However, there is a paucity of data detailing the economic burden in Latin American countries⁹ which may be due to the lack of mandatory reporting and active surveillance systems in these countries. The decision to introduce a new vaccine in a national immunization program is not only made on the basis of clinical data but is also influenced by health economic parameters. The purpose of this study is to address this literature gap and provide a better understanding of the healthcare resource utilization costs associated with HZ and its complications in Latin America.

Methods

Study Design and Population

Data from the observational prospective cohort MASTER (Monitoring and Assessing Shingles Through Education and Research) study, conducted in Argentina, Brazil and Mexico, using similar methods to those described in other MASTER studies,^{2,14,15} were pooled.

Male and female patients aged ≥ 50 years at the date of onset of the HZ rash, with a physician-confirmed diagnosis of HZ, and capable of completing the study questionnaires were eligible for the study. Of the 383 patients included, 96 were from Argentina, 145 from Brazil and 142 from Mexico. Patients were recruited at different time-points during their HZ episode and were followed for up to 6 months to assess HZ-associated burden of illness. PHN was defined as a “worst pain in the last 24 hours” score of ≥ 3 , as assessed with the Zoster Brief Pain Inventory (ZBPI),¹⁶ appearing or persisting after ≥ 90 days since rash onset. All patients signed an informed consent form and the study was approved by local Institutional Review Boards in each country.

Health Care Resource Utilization and Cost Sources

The societal perspective was utilized comprising HZ-related direct costs associated with outpatient care, hospital expenditures, and drug/treatment use, and indirect costs associated with work days lost by the patients and/or family caregivers and patient work effectiveness.

Patient reported healthcare resource utilization associated with HZ and impact on employment were assessed with a customized questionnaire and the work and productivity questionnaire, respectively. The following healthcare resources were considered in estimating direct costs: visit to a general practitioner/family doctor or specialist, use of ambulance services, visit to the emergency room, hospitalization, admission to a long-term care facility, use of nursing services, visit to a physiotherapist/rehabilitation, consultation of a psychiatrist/psychologist/counselor, and use of medications or non-pharmacological treatments to treat HZ. Work effectiveness was measured on a 100-point Likert scale; patients were asked to rate their work effectiveness during a

shingles episode, 100 being completely effective (able to work like before shingles began) and 0 not effective at all.

The unit costs for the medical care services and pharmaceuticals (Supplemental Table 1) were obtained from country specific official registries in Argentina,^{17–19} Mexico²⁰ and Brazil.^{21,22} If costs were not available, information was obtained from literature searches with service fee data and was validated by local expert opinion. The cost per unit of antivirals was derived by taking the mean unit cost of treatment for HZ using the generic acyclovir (200 mg, 25 capsules), valacyclovir (500 mg, 10 capsules), and famciclovir (125 mg, 10 capsules) in the respective countries. The unit cost for famciclovir was unavailable for Mexico, therefore the unit cost of acyclovir was applied as 96.3% of patients took acyclovir. In addition, the weighted unit cost of government reimbursed non-generic valacyclovir and government reimbursed generic acyclovir was used for Mexico. Unit costs from previous years were converted to current costs using the Consumer Price Index (CPI) for the respective countries²³ and were converted, for the purpose of the analysis, from local currencies to USD using current exchange rates on October 23, 2015 as follows; 1 Brazilian real = 0.258 USD, 1 Argentine peso = 0.105 USD and 1 Mexican peso = 0.060 USD. No discount rate was applied, as the mean disease duration and follow-up period were less than 1 year.²⁴

The unit cost of work/productivity loss by patients was based on the national average salary at each country; for Argentina, the age-weighted national average salary for the age groups 50–59, 60–69 and ≥ 70 years was used as age-specific information was available. No transfer payments for work days lost were applied. The cost of family caregiver lost work days was calculated using the unit costs based on the overall national average salary. Mean productivity loss of the 6-month follow-up period was assessed on a 0–100% productivity scale (100% being completely effective; able to work like before shingles began).

Statistical Analysis

All results are reported for the overall population and by PHN status. Summary statistics were utilized to describe the study sample including measures of central tendency (mean) and dispersion (standard deviation) for continuous variables, and frequency distributions and odds ratios (OR) with the respective 95% confidence intervals (CI) for categorical variables (patients experiencing PHN as compared to those without). A one-way sensitivity analysis was performed by increasing and reducing the direct and indirect unit costs by 25% to determine the impact on total cost per HZ case. Statistical analyses were carried out using SPSS 21.0 (SPSS Inc., Chicago, IL) and SAS 9.4 (SAS Institute, Cary, NC).

Results

A total of 383 patients were included in the analysis. Of 363 patients with available PHN information, 140 (38.6%) developed PHN. Table 1 summarizes the patient characteristics at baseline by PHN status and overall. The mean (SD) age at onset of disease was 67.7 (11.2) years and the majority of patients were female (64.2%). Approximately 50.0% of patients reported 20 lesions or less in the primary and adjacent dermatome at the time of enrolment and the majority (73.6%) had experienced severe prodromal pain (worst pain score ≥ 7). Overall, patients developing PHN were older (70.3 vs. 65.8 years) and had more severe rash at enrolment (20.2% vs. 11.4% of patients with available information had more than 50 lesions in the affected dermatomes) as compared to patients without PHN.

Table 2 describes the healthcare resource utilization associated with HZ in Latin America. The most commonly used resources used

Table 1
Patient Demographics and Disease Characteristics by PHN Status and Overall.

Patient Characteristics	PHN ²		Total (N=383) ³
	No (N=223)	Yes (N=140)	
Age (years) ¹ , mean (SD)	65.8 (10.7)	70.3 (11.3)	67.7 (11.2)
Female gender, n (%)	145 (65.0%)	86 (61.4%)	246 (64.2%)
Number of lesions in primary/adjacent dermatome, n (%)			
None	1 (0.4%)	0 (0.0%)	1 (0.3%)
1–10	69 (30.9%)	24 (17.1%)	95 (24.8%)
11–20	68 (30.5%)	22 (15.7%)	98 (25.6%)
21–50	40 (17.9%)	21 (15.0%)	63 (16.5%)
51–100	18 (8.1%)	13 (9.3%)	33 (8.6%)
>100	5 (2.2%)	4 (2.9%)	10 (2.6%)
Missing	22 (9.9%)	56 (40.0%)	83 (21.7%)
Worst prodromal pain score, n (%)			
No pain/Mild (0–2)	5 (2.2%)	6 (4.3%)	12 (3.1%)
Moderate pain (3–6)	39 (17.5%)	12 (8.6%)	55 (14.4%)
Severe pain (≥7)	163 (73.1%)	110 (78.6%)	282 (73.6%)
Missing	16 (7.2%)	12 (8.6%)	34 (8.9%)

¹ Two patients were missing age information.² Twenty patients were missing PHN information.³ Total Cohort comprises Argentina (n = 96); Brazil (n = 145), and Mexico (n = 142).

were antiviral medications (82.8% of patients); followed by visits to the doctor's office (79.1%), the emergency room (48.8%), or a specialist (37.9%), non-pharmacological treatments (19.8%), and nursing services (15.4%) with a mean (SD) frequency of utilization among users of 4.3 (8.39), 2.56 (2.61), 6.22 (6.71), 23.16 (28.00), and 3.26 (5.15), respectively. When compared with patients who did not present PHN, patients with PHN were more likely to visit the emergency room (56.4% vs. 44.8%, OR = 1.59) or a specialist (50.7% vs. 29.6%, OR = 2.45), require nursing services (25.0% vs. 10.8%, OR = 2.76), consult a physiotherapist (7.9% vs. 2.7%, OR = 3.08), or be hospitalized (8.6% vs. 4.0%, OR = 2.23), but were less likely to have been treated with antiviral medications (71.4% vs. 88.3%, OR = 0.33).

Table 2
HZ-Associated Healthcare Resource Utilization by PHN Status and Overall.

Healthcare Resource Utilization (N = 383)	PHN				OR	95% CI	Total (N = 383) ⁴	
	No (N = 223)		Yes (N = 140)				n (%)	Mean (SD) ²
	n (%)	Mean (SD) ²	n (%)	Mean (SD) ²				
Direct Costs								
Ambulance	5 (2.2%)	NA	6 (4.3%)	1.00 (0.00)	1.95	0.58 - 6.52	12 (3.1%)	1.0 (0.00)
Doctor's Office	172 (77.1%)	2.65 (2.32)	113 (80.7%)	5.83 (11.45)	1.24	0.74 - 2.09	303 (79.1%)	4.3 (8.39)
Emergency Room	100 (44.8%)	2.07 (1.77)	79 (56.4%)	3.00 (3.09)	1.59	1.04 - 2.44	187 (48.8%)	2.56 (2.61)
Hospital Admission	9 (4.0%)	1.25 (0.50)	12 (8.6%)	6.83 (8.69)	2.23	0.91 - 5.44	22 (5.7%)	5.18 (7.68)
Long-Term Care Facility	1 (0.4%)	1.00 (NC)	0 (0.0%)	NC	0.53	0.02 - 13.05	1 (0.3%)	1.00 (NC)
Nursing Service	24 (10.8%)	2.09 (2.14)	35 (25.0%)	4.10 (6.41)	2.76	1.56 - 4.89	59 (15.4%)	3.26 (5.15)
Physiotherapist/Rehabilitation	6 (2.7%)	6.00 (5.66)	11 (7.9%)	9.90 (18.53)	3.08	1.11 - 8.54	18 (4.7%)	9.25 (16.91)
Psychiatrist/Psychologist/ Counsellor	9 (4.0%)	3.00 (1.41)	7 (5.0%)	4.00 (2.10)	1.25	0.46 - 3.44	16 (4.2%)	3.75 (1.91)
Specialist	66 (29.6%)	3.50 (2.64)	71 (50.7%)	8.36 (8.17)	2.45	1.58 - 3.80	145 (37.9%)	6.22 (6.71)
Non-Pharmacological Treatment	43 (19.3%)	25.03 (26.55)	30 (21.4%)	23.48 (31.07)	1.14	0.68 - 1.93	76 (19.8%)	23.16 (28.00)
Antiviral Medications ¹	197 (88.3%)	NA	100 (71.4%)	NA	0.33	0.19 - 0.57	317 (82.8%)	NA
Indirect Cost								
Employed Patients missing work/Work Days Lost	44 (53.0%) ³	39.10 (91.21)	33 (89.2%) ³	45.17 (44.67)	7.31	2.38 - 22.5	79 (62.2%) ³	41.44 (73.61)
Family Member Lost Work/Work Days Lost	43 (19.3%)	10.27 (35.29)	58 (41.4%)	11.05 (24.34)	2.96	1.84 - 4.75	105 (27.4%)	11.04 (28.09)
Employed Patients/% Work Effectiveness	83 (37.2%)	71.56 (32.44)	37 (26.4%)	51.60 (30.99)	0.61	0.38 - 0.96	127 (33.2%)	63.10 (33.49)

NC: Not calculable, NA: Not available OR: Odds Ratio. CI: Confidence Interval.

¹ Antiviral medications included acyclovir, valacyclovir and famciclovir, as available in each country. Frequency of antiviral use was not available.² Among patients who used the respective healthcare resource.³ Proportions based on the total number of employed patients: 83 without PHN, 37 with PHN, 127 overall.⁴ Total Cohort comprises Argentina (n = 96), Brazil (n = 145), and Mexico (n = 142). Twenty patients were missing PHN information.**Table 3**
Average Cost per HZ Case Based on Country-Specific and Overall Costs.

	Cost ¹	Argentina	Brazil	Mexico	Latin America ²
Total	Direct Costs	\$767.33	\$1,132.64	\$706.42	\$763.19
	Indirect Costs	\$906.04	\$516.04	\$392.32	\$701.40
	Total	\$1,673.37	\$1,648.68	\$1,098.73	\$1,464.59
PHN	Direct Costs	\$1,079.89	\$1,871.82	\$1,324.23	\$1,227.67
	Indirect Costs	\$1,016.08	\$876.71	\$427.68	\$773.46
	Total	\$2,095.97	\$2,748.53	\$1,751.91	\$2,001.13
No PHN	Direct Costs	\$811.36	\$635.02	\$614.06	\$421.52
	Indirect Costs	\$571.03	\$516.04	\$251.63	\$446.20
	Total	\$1,382.39	\$1,151.06	\$680.67	\$867.72

¹ All costs are in 2015 USD.² Latin America comprises Argentina, Brazil, and Mexico.

With respect to employment, 62.2% of all patients reported missing an average of 41 work days while the caregivers of 27.4% of patients reporting missing an average of 11 days of work. In addition, the work effectiveness of the employed patients was reduced, on average, to 63.1% during the 6-month follow-up period due to their HZ. In the subgroup analysis by PHN, patients developing PHN were more likely to report work loss by their caregiver (41.4% vs. 19.3%) and on their behalf (89.28% vs. 53.0%). No remarkable differences were observed between PHN groups in the average number of days missed among patients/caregivers missing work.

Table 3 summarizes the average cost per HZ case based on the local unit costs in each country and the average unit costs in the three countries (Latin America). Based on the latter, the average direct cost per case was \$763.19 and the indirect cost was \$701.4, for a total of \$1,464.59. Total cost associated with HZ in patients with PHN was markedly higher (\$2,001.13 vs. \$867.72) with indirect costs accounting for the most part of this difference. Based on the local unit costs, the average total cost per HZ case was estimated at \$1,673.37 for Argentina, \$1,648.68 for Brazil, and \$1,098.73 for Mexico. Direct costs accounted for 45.9%, 68.7%, and

Table 4
One-Way Sensitivity Analysis of Total Costs per HZ Case.

Unit Costs Used	Value (Variation)	Average Total Cost		
Argentina	Base Case	\$1,673.37		
	±25% Direct Cost	\$ 1,481.54	–	\$ 1,865.21
	±25% Indirect Cost	\$ 1,446.86	–	\$ 1,899.88
Brazil	Base Case	\$1,648.68		
	±25% Direct Cost	\$ 1,365.52	–	\$ 1,931.84
	±25% Indirect Cost	\$ 1,519.67	–	\$ 1,777.69
Mexico	Base Case	\$1,098.73		
	±25% Direct Cost	\$ 922.13	–	\$ 1,275.33
	±25% Indirect Cost	\$ 1,000.65	–	\$ 1,196.81
Latin America²	Base Case	\$1,464.59		
	±25% Direct Cost	\$ 1,273.79	–	\$ 1,655.39
	±25% Indirect Cost	\$ 1,289.24	–	\$ 1,639.94

¹All costs are in 2015 USD.

² Latin America comprises *Argentina, Brazil, and Mexico*.

64.3% of the total average cost per HZ case in Argentina, Brazil and Mexico, respectively. The sensitivity analysis results were generally robust to changes in assumptions shown in Table 4.

Discussion

To our knowledge, this is the first study prospectively assessing the financial HZ burden of illness in Latin America. Economic burden of illness studies for HZ in Latin America are scant or non-existent despite the expected increase in incidence as the population ages.^{5,8} The pooled cost associated with HZ in Latin America has been evaluated and the direct cost is \$763.19 USD, the indirect cost is \$701.40 USD, and the total cost is \$1,464.59 USD per HZ episode of care. In the country-specific subgroup analysis, considerable differences in the cost per HZ case were observed between-countries (Argentina, Brazil, Mexico) probably reflecting the differences in the cost of life.

The most commonly used healthcare resource were visits to the doctor's office, the emergency room and a specialist, while among hospitalized cases (5.7%) the mean hospital length of stay was 5 days. These results are comparable to other reports with similar sample parameters.^{28,29} Moreover, the proportion of patients (82.8%) reporting taking an antiviral treatment for HZ is analogous to other studies.^{25,26} The mean number of work days lost per employed patient was 41 days, which was higher than other studies reporting between 7–15 days.^{27,28} Ultsch et al. reported that absenteeism from work is typically longer for patients ≥50 years of age and those developing PHN who reported an average of 60 days of absence.²⁹ Within almost all direct and indirect cost parameters studied, a higher rate of utilization was observed for patients with PHN compared to non-PHN patients. Consistent with increased disease severity, patients with PHN were more likely to miss work (89.2% vs. 53.0%) and to have a family member miss work to act as a caregiver (41.4% vs. 19.3%) compared to non-PHN patients, but the mean number of work days lost were comparable between groups. Furthermore, PHN patients reported a lower % work effectiveness than non-PHN patients; 51.60% vs 71.56%, respectively. This is consistent with other studies reporting greater HCRU and a higher economic and social burden of disease associated with PHN.^{27,30–32}

In the absence of no similar studies in Latin American reporting the economic burden of HZ in patients aged 50 years or older, we have attempted to evaluate how our cost estimates compare to those from other regions. Scott et al. found that the average overall cost of HZ at any age in the first 6 months of diagnosis was £524.00 per patient in England.³³ When looking at

studies using a similar age group, the average cost per case reported was approximately \$550 Australian dollars in Australia (direct cost only),³¹ €376 (€1,645 for PHN cases) in Germany,²⁹ €722 (€1,355 for PHN cases) in Italy,²⁷ and €419.87 (€672.76 for PHN cases) in France.³⁴ Comparison of our results with other published economic evaluations, most of them conducted in industrialized countries, requires caution, as the methodologies for determining the burden of disease, perspective, resource utilization and variables used to determine direct and indirect cost vary greatly between countries. Studies may vary in terms of duration of follow-up, HZ and PHN definition, immunocompetent vs. immunocompromised populations, inpatient vs outpatient cases, age, geographic location and associated particularities in patient management, source of data and estimates to determine direct and indirect costs. Panatto et al. conducted a systematic review of the economic burden of HZ which provides empirical evidence of the differences in methodologies and cost outcomes for a variety of studies worldwide.³⁵ The cost of hospitalized HZ cases adjusted to January 2013 inflation values ranged from €774.66 to €31,026.22 in Europe and from €9041.36 to €23,219.82 in the United States (US). Moreover, even within the same geographic location, the review confirmed that differential methodologies can influence the findings of the total costs. For instance, the outpatient and consultations costs in the US ranged from a mean ± SD €621.51 ± 2,654.81 in the commercially insured and Medicare patients and from €899.36 ± 1,566.75 in the Medicaid patients. These differences highlight the need to use local data and comparable parameter estimates to calculate total costs.

Our current study has several limitations. Firstly, the study population included older patients (>50 years) who sought care for HZ episodes, which may have resulted in the inclusion of more severe cases of HZ than present in the general population. The severity of HZ cases is positively associated with treatment costs, particular in the elderly.^{31,33,36–39} Secondly, the data presented was based on the best unit cost data available, the lack of actual medical costs being a major limitation in this study. The few medical costs which were unavailable were interpolated using information from the other countries. As seen in previous economic analyses by Ultsch et al.²⁹ and Luce et al.,⁴⁰ sick-pay would be considered a transfer payment and ascribed to the payer perspective. Since sick pay in Latin America for HZ associated illness is not reported, we calculated foregone earnings for the portion of our sample that was actively working. Moreover, the sample is over 50 years of age and no official data was found to support old age security payments in these countries, therefore we omitted sick pay as a transfer payment. In addition, a small proportion of the population in Latin America have private health insurance; 26% in Brazil and less than 10% in both Argentina and Mexico.^{41,42} The HZ antiviral medications used in this study are not covered by the public health insurance plan in the studied countries, therefore including co-payments or reimbursement costs for drug and medical services would not be required.

Conclusion

The current analysis has demonstrated that HZ and its sequelae impose a substantial economic burden in Latin America, as documented in other regions, which, in the absence of boosting, is expected to rise as the population ages and the number of HZ cases increases. The results provide a basis for evaluating the cost associated with HZ and support the need for early intervention, preventative strategies and improved disease management to reduce the HZ-associated disease burden in Latin American countries. Despite the availability of a safe and efficacious vaccine,^{43,44} HZ vaccination is not included in the national

immunization programs in the majority of Latin American countries. The results presented here call for careful model-based evaluations of the cost-effectiveness of HZ immunization programs.

Conflict of Interest

K. Johnson and H. Monsanto are employed by Merck & Co. Inc. Alejandro Ortiz has received honorarium fees as speaker for Bayer Health Care, MSD and Silanes Labs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijid.2017.02.021>.

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