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Economic burden of herpes zoster in Latin America: A systematic review and meta-analysis

Dario Javier Balan[a], Ariel Bardach[a], Carolina Palermo[a], Tomás Alconada[a], Macarena Sandoval[a], Javier Nieto Guevara[b], Jorge Gomez[c], and Agustin Ciapponi[a]

[a]Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina; [b]GSK, Panama City, Panama; [c]GSK, Buenos Aires, Argentina

ABSTRACT

This systematic review describes herpes zoster (HZ) economic burden in terms of healthcare resource use and cost outcomes in the Latin America and Caribbean (LAC) region. We searched online databases from 1 January 2000 to 20 February 2020 to identify eligible publications. We identified 23 publications that reported direct costs, indirect costs, and resources associated with HZ and its complications. The primary direct medical resources reported in the different studies were visits to doctors, transportation, days in the hospital, nursing, medication schedules, and physical therapy. Direct total costs per patient ranged from $99.99 to $4177.91. The highest cost was found in Brazil. Direct costs are, in average, 81.39% higher than indirect costs. The cost per patient that includes postherpetic neuralgia treatment is 115% higher on average for the directs and 73% for the indirect costs. Brazil reported a higher total cost per patient than Argentina and Mexico, while for indirect costs per patient, Brazil and Argentina had higher costs than Mexico, respectively. A meta-analysis on the number of days due to HZ hospitalization, performed on non-immunosuppressed patients over 65 years of age from three studies, resulted in a cumulative measure of 4.5 days of hospitalization. In the LAC region, the economic burden of HZ and associated complications is high, particularly among high-risk populations and older age groups. Preventative strategies such as vaccination could help avoid or reduce the HZ-associated disease economic burden in the LAC region.

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Herpes zoster; health economics; Latin America; and the caribbean; postherpetic neuralgia; direct cost; indirect cost

Introduction

Varicella zoster virus (VZV) is a herpes virus of the alphaherpesvirus subfamily and causes varicella (chickenpox) and herpes zoster (HZ). Primary infection with VZV usually occurs in childhood and causes varicella, which is characterized by a vesicular pruritic rash and fever. The disease is usually benign with complications related to skin and soft-tissue bacterial superinfection in children and pneumonia in adults. After the varicella episode, VZV can remain latent in the dorsal root ganglia or in nerve cells, where it may reactivate and cause HZ. Typically, HZ lesions consist of a group of vesicles or blisters, restricted to a small area, usually located on the trunk or face and associated with pain in the affected area.[1] Individuals may experience pain or it may be the only occurrence of the disease,[2] along with an increase in antibodies against VZV.[1,3,4] Clinical and diagnostic confirmation of HZ can be achieved through polymerase chain reaction (PCR) and the direct immunofluorescence assay tests.[1,5] Seroconversion, i.e. increased titration of specific antibodies in serum samples taken from acute and convalescent stages, may also be used to confirm HZ diagnosis.[3,6]

The lifetime risk of developing HZ is estimated to be 0%,[7] rising to 50% in individuals older than 85 years.[8] The HZ risk increases in individuals with a weakened immune system, who also have a high likelihood of severe disease.[1,9] Age is the main risk factor for VZV reactivation, as it is associated with reduced virus-specific cell immunity, with an increased risk of disease observed in the population from 50 to 60 years of age.[1–11] Other groups of individuals with an immunocompromised immune system include transplant recipients, patients with autoimmune diseases, individuals under treatment with corticosteroids or chemotherapeutic agents and those diagnosed with cancer or human immunodeficiency virus (HIV).[12,13] Other risk factors for HZ include female sex, being Caucasian, traumas, and other comorbidities, such as chronic lung and kidney diseases.[14–16] HZ complications occur in about 13–26% of all HZ cases and the most commonly observed complication is postherpetic neuralgia (PHN) (10–18% of HZ cases) which is associated with persistent pain four weeks after the appearance of skin lesions.[1,9,17] The risk of developing PHN in individuals increases after 50 to 60 years of age,[1] while the severity and length of an episode is proportional to the patient's age.[18] Other less common complications include ocular herpes, acute retinal necrosis, Ramsay Hunt syndrome, neurological impairment, as well as secondary skin and soft tissue bacterial infections.[19–21]

Several antiviral medicines are available to treat HZ as they reduce the appearance of skin lesions and relieve neuropathic pain.[22] Management of complications such as PHN depends upon patient's characteristics and include long-term treatments with anticonvulsants and tricyclic antidepressants.[23] To prevent HZ and PHN, the Zoster Vaccine Live (ZVL) was approved by

CONTACT Agustin Ciapponi aciapponi@iecs.org.ar Instituto de Efectividad Clínica y Sanitaria (IECS), Dr. Emilio Ravignani 2024 (C1014CPV), Buenos Aires, Argentina.

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the US Food and Drug Administration (FDA) in 2006 for adults over 60 years of age and later for adults over 50 years of age in 2011,[24] after which the vaccine was approved in several countries including those in the Latin America region.[25] In Argentina, the ZVL was authorized by the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) in 2013 for individuals >50 years of age.[26,27] In 2017 in the United States, a two-dose Recombinant Zoster Vaccine (RZV) became available and recommended by the United States Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) for use in immunocompetent adults >50 years of age.[28] Later, in 2021, the ACIP recommendation extended to adults immunodeficient or immunosuppressed aged ≥19 years.[29] Patients with prior ZVL are advised to receive the two doses of RZV due to its higher efficacy and length of protection and to prevent both HZ and PHN (particularly in people >70 years of age). While the best time to repeat vaccination is not fully clear, the ACIP recommends administering the first dose of RZV at least eight weeks after receiving ZVL.[30]

The Latin America and the Caribbean (LAC) region is diverse in terms of socio-economic status. The economic classification of countries in the LAC region has often varied in the past two decades, but most countries were classified as 'upper middle income countries,' with only a few classified as either 'high income countries' or 'lower middle income countries' in 2021.[31]

To understand the value of preventative strategies such as vaccination in the LAC region, a complete understanding of the burden of disease is required. This will equip decision-makers with information to develop vaccine policies in a timely and relevant manner. The decision to introduce a vaccine in a national immunization program is not only made based on clinical data but is also shaped by health economic parameters. A systematic literature review (SLR) was conducted to understand the epidemiology, clinical and economic burdens of HZ in the LAC region. The epidemiology and clinical burden of HZ in the last 20 years, which imply a consistent increase in the rate of HZ incidence among high-risk populations and elderly individuals, have been reported previously.[32] Here, we cover the economic impact of HZ in the LAC region, which includes healthcare resource use and costs associated with HZ and its complications. Audio-slides summarizing this manuscipt are available on https://doi.org/10.6084/m9.figshare.21311445.v1

Methods

A systematic review was performed following the Cochrane Systematic Reviews Manual,[33] the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA)[34,35] and Meta-analyses of Observational Epidemiology (MOOSE)[36] guidelines specifically for reviews of observational studies. The study protocol is registered with the prospective international systematic review registry PROSPERO (CRD42020186586).[37]

Search sources and strategy

Online databases such as Medline (via PubMed), Latin American and Caribbean Health Sciences Literature (LILACS), Excerpta Medica Database (EMBase), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane Library, Center for Reviews and Dissemination (CRD) York, and EconLIT were searched to identify published articles relevant to the research objectives. The search strategy to identify published articles on epidemiology, clinical and economic burden of HZ, is shown in the supplementary material (File S1). Searches were time-limited to identify articles published between 1 January 2000 and 20 February 2020.

To ensure all relevant articles were found, a manual search was performed across reference lists of included publications, databases of national and international congress proceedings and doctoral theses. The websites of major local medical associations, experts and associations related to the field were visited and the authors of relevant papers were contacted about any missing or information or when a clarification was needed.

Greyliterature was searched in the following sources: generic internet and meta-search engines (Google, Google Scholar), regional Ministries of Health (Argentina, Brazil, Colombia, Chile, and Mexico), Pan American Health Organization, Virtual Health Library, and hospital reports. Information was also searched in Global Burden Disease (GBD) of the Institute for Health Metrics and Evaluation (IHME).[38]

Article selection

Publications included in this review were identified independently through peer review by the research team using predefined eligibility criteria. Discrepancies were solved with the agreement of the entire team. All screening phases of the study used COVIDENCE, an online platform used to process systematic reviews.[39,40]

Articles were qualified for inclusion in the review if the study population was comprised of individuals ≥15 years of age from the LAC region, regardless of their risk status (>60 years of age, with a transplantation, diagnosed with HIV/acquired immunodeficiency syndrome, cancer, under treatment with corticosteroids/immunosuppressants/chemotherapy). Studies were included regardless of the utilized intervention. Study designs included in this review were economic evaluations and costs or budget impact studies with full text in Spanish, English, or Portuguese, published from 1 January 2000 onwards. Case series involving ≥50 HZ cases or ≥10 HZ complications were also considered relevant for inclusion. Studies were excluded if the population was outside of the scope of the inclusion criteria, if the outcomes were other than those specified as eligible, if they were published outside of the eligible time period, if they were not reporting outcomes in countries of interest, and if they were published in a language other than the above-mentioned ones. Systematic reviews, meta-analysis, narrative reviews, interventional studies, cost-effectiveness or health economic studies, surveys, non-human data, case reports, letters to editor, newspapers, editorials, comments, opinions, molecular studies, pilot studies, protocol and pre-clinical studies, and studies with insufficient methodological details were excluded. Reference lists within systematic review and meta-analyses were screened for

additional relevant articles, as deemed necessary by the reviewer.

Data extraction

After determining the final list of eligible publications for review, the research team extracted data based on three predefined parameters. These included: study characteristics (type of publication, year published, authors, geographic location, study design including domains for the risk of bias method); participant characteristics (inclusion criteria applied, age, sex, sample size, latent immune-compromising conditions, risk evaluation for HZ); and perspective data of diagnosis and treatment (use of resources for the management of HZ, length of stay in the general ward and intensive care, direct costs – i.e., costs for outpatient visits, costs of laboratory tests, costs related to stays in the general ward and in intensive care, costs of medication schemes, costs of pain and complication management, rehabilitation – and indirect costs such as productivity, caregivers and transportation, among others).

Risk of bias assessment of included studies

To assess the risk of bias in economic studies, we applied the Consolidated Health Economic Evaluations Reporting Standards (CHEERS) checklist.[41] Based on this, the following aspects were assessed, where applicable: the population, the perspective of evaluated costs, the timeline of analysis, the clarity of direct and indirect costs, the valuation from evidence, the analytical approach utilized to estimate results (types of decision models), and the methods of cost adjustment based on inflation and discount rates. We utilized the CiCERO tool (draft version) for economic evaluations, as it assesses the most relevant parameters and criteria for such type of studies.[42] Example response options include presence, absence, no reporting and non-applicability of criteria, such as analytical perspective, establishing the target population and standardization and adjustment of costs.

The risk of bias assessment of the observational studies was done according to the United States National Heart, Lung, and Blood Institute guidelines checklists, consisting of 14 items to evaluate risk of bias in cohort and cross-sectional studies, and 9 items for case series.[43] The studies were rated as "Bad," "Poor" and "Good" for high risk of bias, uncertain risk of bias, and low risk of bias, respectively.

Analyses and reporting

In this paper, we provide a descriptive overview of healthcare resource use and cost outcomes as of 2019 together with the risk of bias results of the economic studies. In addition to a descriptive overview of the main findings, a meta-analysis on the number of days due to HZ hospitalization was performed on non-immunosuppressed patients over 65 years of age. This meta-analysis used a random effects model due to the heterogeneity of the studies. For studies reporting total direct and indirect costs per patient, an adjustment was made for comparison across countries. First, study-reported costs were converted to the local currency in the country where costs were reported. The exchange rate reported in the original study was used whenever possible, otherwise the exchange rate reported by the World Bank was used.[44] Second, the sums in the local currency for each year until 2018 were adjusted based on inflation to allow for comparison through the subsequent conversion to International Dollars ($). Inflation rates were developed from the information provided by the World Bank for all countries where data were available.[45] Finally, to make costs across countries comparable, $ was used by implementing the adjustment coefficient published by the World Bank.[46]

Results

Finding from the systematic review

Overview of included studies

A total of 1,278 studies were identified after duplicates were removed from the initial search of publications. From these, 102 studies were selected for a full-text review based on the review eligibility criteria. Lastly, 23 studies were included for a descriptive analysis of the healthcare resource use and costs (direct or indirect) associated with HZ or its complications (Figure 1 and Table 1).[47–69] None of the included studies mention the vaccination status of participants.

The 23 studies reported data for Brazil (n = 7),[53–58–65] Argentina (n = 5),[47,48-50–52,] Colombia (n = 4),[59–61–64] Mexico (n = 3),[63,66,68] Costa Rica (n = 1),[62] Nicaragua (n = 1),[69] and Latin America [including Brazil, Mexico and Argentina] (n = 1)[49] whereas one multi-regional study provided aggregate results for Latin America (n = 1),[67] with the same countries included (Table 1).

The majority of studies included in this review were case series (n = 11) followed by cohort studies (n = 7), cost-effectiveness evaluations (n = 3), pooled cost-analysis (n = 1) and budget impact analysis (n = 1) (Table 1). While all the studies provide data health-care resource use,[47–69] direct and indirect medical costs were reported in two studies (Mexico,[63] and Latin America including Brazil, Mexico and Argentina)[49] and 1 study (Latin America including Brazil, Mexico and Argentina),[49] respectively (Table 1).

Health care resource use

Table 1 provides an overview of direct and indirect costs and resource use reported in the studies. Across the studies, the type of direct use of resources comprised doctor visits, transportation, hospitalizations, nursing, medication, and physical therapy. The indirect use of resources included missed days at work for the patient, missed days at work for the relative, impaired labor capacity and the need for caretakers.

From the studies identified within the scope of the epidemiological search,[32] the number of patients requiring hospitalization ranged from 4 to 7,042,[52,68] with a frequency of hospitalization from 3% to 35.7%.[50,57] With regard to treatment pattern, a total of 3,046 patients received systemic antiviral treatment, with acyclovir being the most prescribed treatment (34.7%), followed by valacyclovir (6%), brivudine (0.6%), and famciclovir (0.5%). Patients received non-steroid anti-inflammatory drugs (NSAIDs), anticonvulsants, tricyclic antidepressants, and topical pain-relieving drops for the management of pain. A few patients were even prescribed corticosteroids (71 patients) and antibiotics

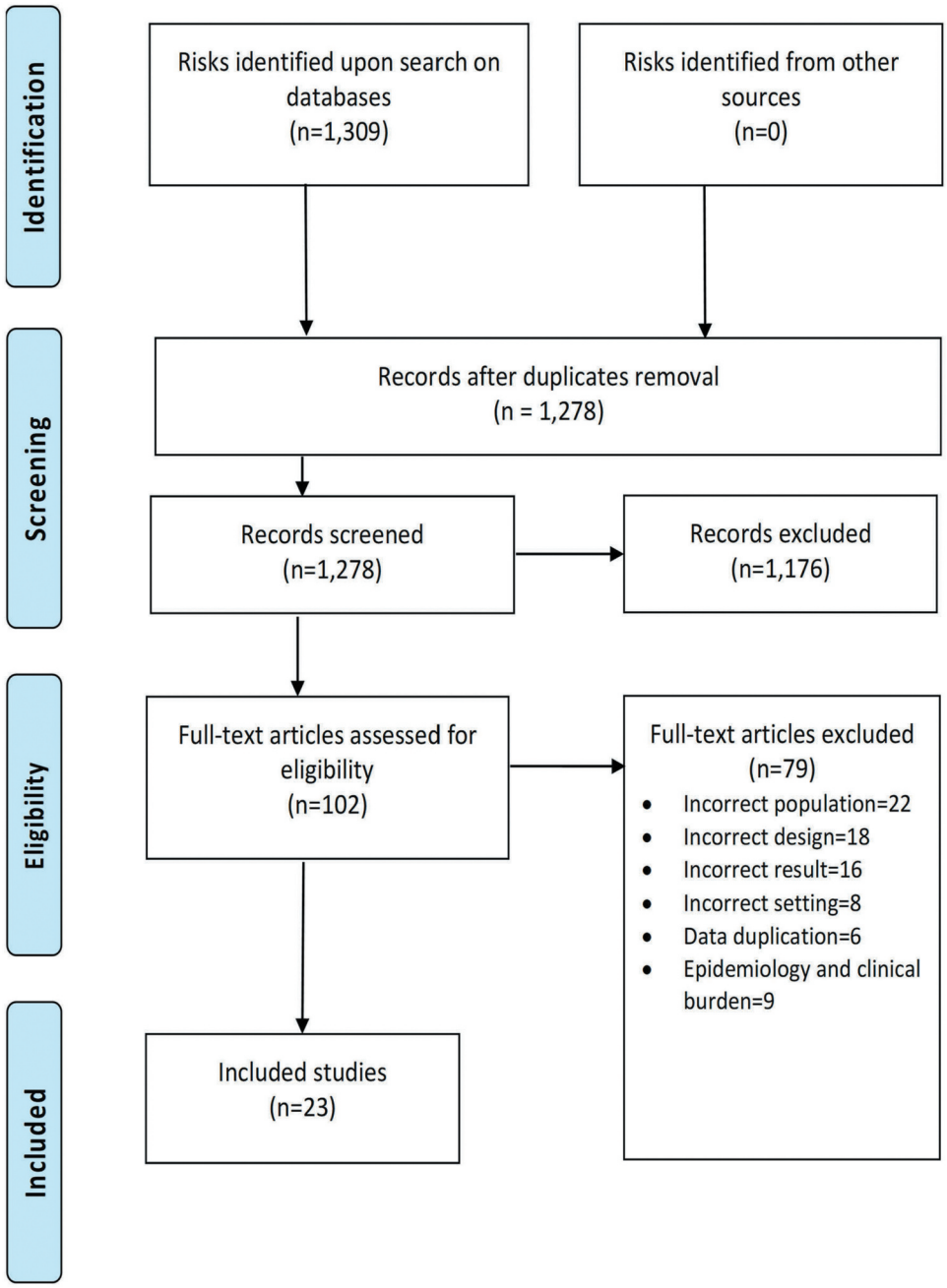

Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses.

(14 patients). In addition, the use of topical medication such as drying agents, antivirals, antibiotics, steroids, or analgesics were given to 570 patients (Table 2).

A meta-analysis on the number of days due to HZ hospitalization which was performed on non-immunosuppressed patients over 65 years of age from three studies,[52,58,62] resulted in a cumulative measure of 4.5 days of hospitalization (95%CI = 3.9 to 5.2; I^2: 49%) (Figure 2).

Cost burden

Table 1 provides an overview of cost per patient data. Studies reported different perspectives when estimating costs such as social perspective (n = 3),[49,59,60] third-party payer perspective (n = 1)[64] and the public perspective (n = 1).[65] Out-of-pocket expenses were reported in two studies.[52,58]

Total direct and indirect cost per patient were estimated based on the corresponding categories of reported resource use. In one study, costs were reported per country and as a whole, and differentiated according to the presence or absence of PHN for Argentina, Brazil and Mexico.[49] When total costs were compared in 2018 $,[49] a higher total cost was reported for HZ patients from Brazil than for patients from Argentina and Mexico. Including patients with and without PHN; this cost is observed to be 2.24 times higher than the cost accrued by patients in Argentina and 1.76 times higher than Mexico. Upon comparison of indirect medical costs, both Brazil and Argentina had higher costs versus Mexico for PHN, non-PHN and the total population. Argentina had a higher cost than Brazil in terms of total indirect medical costs, but Brazil had higher indirect costs for the PHN population (Table 1).

Table 1. Use of resources and costs per patient, as reported in reviewed studies (N = 23). Costs in 2018 international dollars ($).

Study	Study design	Country	Perspective	PHN	Type of resources reported	Direct use of resources	Total direct cost per patient	Indirect use of resources	Total indirect cost per patient
Bollea-Garlatti 2017[47]	Case series	Argentina	NA	Yes	NR	Medication, laboratory tests	NR	NR	NR
Corti 2015[48]	Case series	Argentina	NA	NR	NR	Laboratory tests, medication	NR	NR	NR
Rampakakis 2017[49]	Pooled cost analysis	Argentina	Social	Total[a] Yes No	Direct and indirect	Visits to doctor, transportation, hospitalizations, nursing, medication, physical rehabilitation	$1,124.98 $1,583.22 $1,189.53	Missed days at work for the patient, missed days at work for the relative, impaired labor capacity	$1,328.34 $1,489.67 $837.18
Rozenek 2017[50]	Case series	Argentina	NA	Yes	NR	Medication, emergency visits, visits to doctor	NR	NR	NR
Vujacich 2008[51]	Case series	Argentina	NA	Yes	NR	Medication	NR	NR	NR
Vujacich 2016[52]	Cohort	Argentina	Out-of-pocket expense	Yes	Direct and indirect	Visits to doctor, transportation, hospitalizations, nursing, medication, physical rehabilitation	NR	Missed days at work for the patient, missed days at work for the relative, impaired labor capacity, caretakers	NR
Álvarez 2007[53]	Case series	Brazil	NA	Yes	NR	Medication	NR	NR	NR
Andrade 2019[54]	Case series	Brazil	NA	NR	NR	Medication	NR	NR	NR
Antoniolli 2019[55]	Case series	Brazil	NA	Yes	NR	Emergency visits, hospitalizations, medication	NR	NR	NR
Borba 2010[56]	Cohort	Brazil	NA	Yes	NR	Medication	NR	NR	NR
Gormezano 2015[57]	Case series	Brazil	NA	Yes	NR	Medication	NR	NR	NR
Rampakakis 2017[49]	Pooled cost analysis	Brazil	Social	Total Yes No	Direct and indirect	Visits to doctor, transportation, hospitalizations, nursing, medication, physical rehabilitation	$2,528.06 $4,177.91 $1,417.37	Missed days at work for the patient, missed days at work for the relative, impaired labor capacity	$1,151.80 $1,956.82 $1,151.80
Toniolo-Neto 2018[58]	Cohort	Brazil	Out-of-pocket expense	Yes	Direct and indirect	Visits to doctor, transportation, hospitalizations, nursing, medication	NR	Missed days at work for the patient, missed days at work for the relative, caretakers	NR
Ordoñez Molina 2013b[59]	Budget impact analysis	Colombia	Social	Yes	Direct and indirect	Medication, visits to doctor, physical rehabilitation	NR	NR	NR
Ordoñez Molina 2013[60]	Cost-effectiveness evaluation	Colombia	Social	Yes	NR	Medication	NR	NR	NR
Rampakakis 2019[61]	Cohort	Colombia	NA	Yes	Direct	Visits to doctor, emergency visits, medication	NR	NR	NR
Rampakakis 2017b[62]	Cohort	Costa Rica	NA	Yes	Direct	Visits to doctor, transportation, hospitalizations, nursing, medication, physical rehabilitation	NR	NR	NR
Rampakakis 2017[49]	Pooled cost analysis	Latin America	Social	Total[a] Yes No	Direct and indirect	Visits to doctor, transportation, hospitalizations, nursing, medication, physical rehabilitation	NC NC NC	Missed days at work for the patient, missed days at work for the relative, impaired labor capacity	NC NC NC
Ortiz-Covarrubias 2015[63]	Cohort	Mexico	NR	Yes	Direct	Visits to doctor	$99.99	No	No
Rampakakis 2017[49]	Pooled cost analysis	Mexico	Social	Total[a] Yes No	Direct and indirect	Visits to doctor, transportation, hospitalizations, nursing, medication, physical rehabilitation	$1,435.51 $2,690.95 $1,247.82	Missed days at work for the patient, missed days at work for the relative, impaired labor capacity	$797.23 $869.08 $511.33
Acosta 2017[64]	Cost-effectiveness evaluation	Colombia	Third-party payer	NR	NR	Medication	NR	No	No

(*Continued*)

Table 1. (Continued).

Study	Study design	Country	Perspective	PHN	Type of resources reported	Direct use of resources	Total direct cost per patient	Indirect use of resources	Total indirect cost per patient
Piedade 2017[65]	Cost-effectiveness evaluation	Brazil	Public sector	NR	NR	Medication	NR	No	No
Gonzalez 2013[66]	Case series	Mexico	NA	Yes	NR	Medication	NR	NR	NR
Kawai 2015[67]	Cohort	LAC	NA	Yes	NR	Medication	NR	NR	NR
Vazquez 2017[68]	Case series	Mexico	NA	Yes	NR	Hospitalizations	NR	NR	NR
Mendoza Rodriguez 2007[69]	Case series	Nicaragua	NA	Yes	NR	Medication, visits to doctor	NR	NR	NR

NA, not applicable; NR, not reported; NC, not calculable; PHN, postherpetic neuralgia.
[a]Average for Argentina, Brazil and Mexico.

Table 2. Hospitalizations due to HZ and treatment options.

Author and year of publication	Hospitalizations (n)	Antivirals (n and specific type)	Steroids (n)	Pain management treatment (n and specific type)	Antibiotics (n)	Prophylaxis (n)	Other treatments (n and specific type)
Bollea-Garlatti 2017[47]	NR	41 Acyclovir PO (35) Acyclovir IV (41)	NR	NR	NR	NR	NR
Corti 2015[48]	11	11 Acyclovir IV (11)	NR	NR	NR	NR	NR
Rozenek 2017[50]	38	1.177	NR	133 NSAIDs (97) Pregabalin (86)	NR	NR	NR
Vujacich 2008[51]	NR	271 Acyclovir PO (159) Valacyclovir PO (78) Famciclovir PO (3) Acyclovir IV (1) Foscarnet IV (1)	39	205 NSAIDs (94) Amitriptyline/ Carbamazepine (48) Opioids (30)	NR	NR	41 vitamin B (40) Topical acyclovir (24) Alternative therapies (5)
Vujacich 2016[52]	4	87 Acyclovir PO (49) Valacyclovir PO (32) Famciclovir PO (9)	3	127 NSAIDs (74) Anti-epileptic drugs (17) Opioids (15) Antidepressants (9) Topical medication (12)	5	NR	5 Ophthalmic drugs (3) Anxiolytics (2)
Antoniolli 2019[55]	NR	760 Acyclovir PO (320) Acyclovir IV (440)	NR	NR	NR	NR	NR
Álvarez 2007[53]	NR	NR	NR	Amitriptyline (9) Chlorpromazine (6) Gabapentin (4) Carbamazepine (3) Imipramine (2)	NR	NR	NR
Andrade 2019[54]	NR	19 Acyclovir PO (17) Valacyclovir PO (2)	NR	NR	NR	NR	NR
Borba 2010[56]	9	51 Acyclovir PO (46) Acyclovir IV (5)	NR	51 NSAIDs (51)	NR	NR	NR
Gormezano 2015[57]	25	19 Acyclovir IV (19)	NR	NR	NR	NR	NR
Toniolo-Neto 2018[58]	13	40 Acyclovir PO (33) Valacyclovir PO (8)	9	99 Analgesics (50) (Acetaminophen (23), AAS (1) Metamizole (19), Hyoscine (2), Others (16)) Anticonvulsants (13) Antidepressants (13) Opioids (12)	NR	NR	114 Topical treatments (31) Anti-inflammatory drugs (5) Benzodiazepines (3) Antihypertensive drugs (5) Vitamins (5) Others (65)
Rampakakis 2019[61]	NR	148	NR	139	NR	NR	NR
Rampakakis 2017b[62]	16	31 Acyclovir PO (27) Valacyclovir PO (4) Famciclovir PO (2)	9	46 NSAIDs (7) Acetaminophen (12) Anti-epileptic drugs (13) Opioids (11) Antidepressants (3)	NR	NR	16 Topical treatments (antivirals, antibiotics, and steroids) (16) Anxiolytics (3)
Kawai 2015[67]	NR	118 Acyclovir PO Valacyclovir PO Famciclovir PO	NR	NR	NR	NR	NR
González 2013[66]	NR	12 Acyclovir PO (12)	9	19	NR	NR	Ophthalmic drugs
Vázquez 2017[68]	7042	NR	NR	NR	NR	NR	NR
Mendoza Rodríguez 2007[69]	NR	261 Acyclovir (184) Valacyclovir PO (60) Brivudine PO (17) Isoprinosine (4)	2	102 Analgesics (71) Tricyclic antidepressants (31)	9		535 Topical drying agents (445) Topical analgesics (1) Topical antivirals (10) Topical antibiotics (4) 2 or more topical drugs (63) Neurotropic vitamins (12)

AAS, anabolic-androgenic steroids; HZ, herpes zoster; IV, intravenous injection; PO, prescribed orally; NSAID, nonsteroidal anti-inflammatory drugs; NR, not reported.

Risk of bias among included studies

Quality assessment of economic studies (n = 8) is provided in Table 3. Most economic studies were of adequate quality. However, of the eight studies with economic study designs,[49–52–58–65] only one study[60] used the discount rate, while none of the studies adjusted their cost estimates based

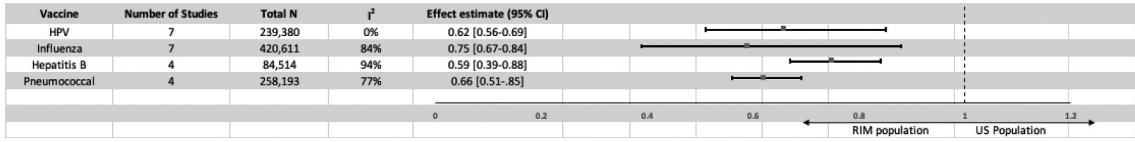

Figure 2. Meta-analysis of number of days of hospitalization due to HZ in immunocompetent patients ≥65 years of age. HZ, herpes zoster. References: Vujacich 2016;[52] Toniolo-Neto2018;[58] Rampakakis 2017.[62]

Table 3. Quality evaluation for use of resources and cost studies (n = 8).

Publication	Ordoñez Molina 2013[60]	Ordoñez Molina 2013b[59]	Ortiz-Covarrubias 2015[63]	Acosta 2017[64]	Piedade 2017[65]	Rampakakis 2017[49]	Toniolo-Neto 2018[58]	Vujacich 2016[52]
Country	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Population for analyses	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Timelines	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Perspective	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Discount rate	Yes	No	No	No	No	No	No	No
Adjustment based on inflation	No	No	No	No	No	No	No	No
Compared interventions	Yes	Yes	No	Yes	Yes	No	No	No
Direct costs	NR	Yes	Yes	NR	NR	Yes	Yes	Yes
Indirect medical costs	NR	Yes	No	No	No	Yes	Yes	Yes
Indirect costs	NR	Yes	No	No	No	Yes	Yes	Yes
Effectiveness	NR	NA	NA	NR	NR	NA	NA	NA
Treatment compliance/ adherence	NR	NR	NR	NR	NR	NR	NR	NR
Decision model used?	Yes	Yes	No	Yes	Yes	No	No	No
Does it show costs, economic and/ or health results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Uncertainty	Yes	Yes	No	Yes	Yes	Yes	No	No
Conflicts of interest and financing source	NR	NR	NR	NR	NR	Yes	Yes	Yes
Software	NR	NR	NR	NR	NR	Yes	Yes	No
Costs standardization	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cost breakdown	NR	NR	NR	NR	NR	Yes	Yes	Yes
Summary suitable for audience	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are RCT based EE results and decision models split?	NA	NA	NA	NA	NA	NA	NA	NA
Are DSA and PSA reported separately?	Yes[a]	Yes[a]	No	Yes[a]	Yes[a]	Yes[a]	No	No

NA, not applicable; NR, not reported; DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis.
Yes[a]: Reporting only deterministic sensitivity analysis.

on inflation rates. Four studies did not report any comparator, and three studies did not report any estimation of direct or indirect costs.

The risk of bias assessment of case series and cohort studies reporting resource usage has been reported elsewhere and is shown in Tables S1 and S2, respectively. Seventy-five percent of the cohort studies[49,56,61,67] and 91% of the case series/epidemiological surveillance studies[47–48–50–51–53–55–57–66–68–69] were assessed as having low risk of bias.

Country-specific burden data from department of health databases

An internet-based search for information was conducted on HZ disease burden on the websites of Departments of Health of Brazil, Chile, Colombia, and Mexico. It should be noted that it was not possible to access data for Colombia and Panama due to restricted access to the Colombia Department of Health data,[70] and no availability of free access to the Panama

Department of Health data. Cost data was only found for Brazil and has been reported.

Mexico

Two different health systems exist in Mexico, namely the Mexican Institute of Social Security (IMSS) which provides health-care services for individuals with formal employment and the 'Secretaría de Salud' serving individuals without formal employment. The IMSS reported an average in-hospital stay of 4.8 days due to HZ, and an average of 443 discharges were observed per year (2010–2017) among patients ≥15 years of age.[71] In contrast, the 'Secretaría de Salud' reported an average in-hospital stay of 3.8 days with 131 annual average hospitalizations (2018–2019) due to HZ.[71] Please refer to Fig S1 for an average number of hospital discharges per international classification of diseases, tenth revision (ICD-10) category in Mexico from 2010 to 2017.

Brazil

Health information published by the Information Department of the Unified Health System (DATASUS) was utilized.[72] The data published by DATASUS on hospital morbidity come from the Hospital Information System of the SUS (SIH/SUS), administered by the Department of Health, through the Healthcare Secretariat and the State and Municipal Health Secretariats. Hospital units that were part of the SUS sent their corresponding information on admissions to the municipal or state managers through the Authorization for Hospitalization (AIH). This information was then consolidated by DATASUS into a database which includes information related to most hospital admissions in Brazil; primary care coverage by this database is 75–80% of the general population.[73] Total cost is available in the hospital morbidity database (defined as the cost for approved AIHs in the period to be considered as the approved cost of production), also comprising hospital costs and professional service costs. Information on costs (total cost, hospital costs, and professional service costs) and on use of resources (days and mean length of stay in hospital) was obtained, and costs per hospitalization and per day of hospitalization were estimated.

The total cost of hospitalization for varicella and HZ in patients ≥65 years of age, in the 2010–2019 period, expressed in current Brazilian real (R$) per year, was R$ 17,683,123 (total annual cost ranged from R$ 1,284,498 in 2012 to R$ 2,041,051 in 2017). The total cost of hospital services in the period was R$ 15,470,797 (annual cost of hospital services ranged from R$ 1,116,799 in 2012 to R$ 1,796,096 in 2017) and a total cost of professional services was R$ 2,212,142 (annual cost of professional services ranged from R$ 167,699 in 2012 to R$ 251,233 in 2013). Between 2010 and 2019, the average total cost per hospital stay was R$ 1,064 (ranging from R$ 888 in 2012 to R$ 1,203 in 2017), while the average cost of hospital services per hospital stay was R$ 931 (ranging from R$ 772 in 2012 to R$ 1,058 in 2017). The average cost of professional services per hospital stay was R$ 133 (ranging from R$ 116 in 2012 to R$ 152 in 2014). The average total cost per day of hospitalization was R$ 148 (range from R$ 132 in 2012 to R$ 167 in 2014), with an average cost of hospital services per day of R$ 129 (range from R$ 115 in 2012 to R $ 146 in 2014) and an average cost of professional services per day of R$ 19 (range from R$ 17 in 2012, 2018 and 2019 to R$ 21 in 2014) (Table S3).

Additionally, R$ was converted to international $ for comparison with data from different countries (Table 4). The total cost of hospitalizations per VZV in patients ≥65 years of age for each year ranged from $791,948 in 2019 to $1,324,051 in 2010. The total cost of hospital services ranged from $695,392 in 2012 to $1,152,290 in 2010, while the total cost of professional services ranged from $94,457 in 2019 to $171,762 in 2010. Between 2010 and 2019, total cost per hospital stay ranged from $455 in 2019 to $674 in 2013. The costs for hospital services per hospital stay were $401 in 2019 to $588 in 2013, and the costs for professional services per hospital stay were $54 in 2019 to $87 in 2010. Lastly, with respect to costs per day of hospitalization, the total cost per day ranged from $62 in 2019 to $100 in 2010, while the cost of hospital services per day ranged from $55 in 2019 to $87 in 2010 and the cost of professional services per day of hospitalization ranged from $7 in 2019 to $13 in 2010 and 2011. It could be observed that the hospitalization costs were lower in 2019 that in 2010, this

Table 4. Brazil. Costs of hospitalizations caused by varicella and HZ in patients ≥65 years of age in the public health system (SUS). Values in International dollars ($)[a] per year.

				Costs per hospitalization			Costs per day of hospitalization		
Year	Total cost	Hospital service cost	Professional service cost	Total cost	Hospital service cost	Professional service cost	Total cost	Hospital service cost	Professional service cost
2010	$ 1,324,051	$ 1,152,290	$ 171,762	$ 671	$ 584	$ 87	$ 100	$ 87	$ 13
2011	$ 1,122,124	$ 974,882	$ 147,242	$ 639	$ 555	$ 84	$ 95	$ 83	$ 13
2012	$ 799,812	$ 695,392	$ 104,420	$ 553	$ 481	$ 72	$ 82	$ 72	$ 11
2013	$ 1,154,579	$ 1,006,882	$ 147,697	$ 674	$ 588	$ 86	$ 88	$ 76	$ 11
2014	$ 905,426	$ 789,582	$ 115,844	$ 656	$ 572	$ 84	$ 92	$ 81	$ 12
2015	$ 853,862	$ 748,061	$ 105,801	$ 535	$ 468	$ 66	$ 75	$ 66	$ 9
2016	$ 876,809	$ 769,092	$ 107,717	$ 557	$ 489	$ 68	$ 76	$ 67	$ 9
2017	$ 935,404	$ 823,142	$ 112,262	$ 551	$ 485	$ 66	$ 73	$ 65	$ 9
2018	$ 867,152	$ 762,686	$ 104,466	$ 499	$ 439	$ 60	$ 64	$ 56	$ 8
2019	$ 791,948	$ 697,410	$ 94,457	$ 455	$ 401	$ 54	$ 62	$ 55	$ 7

HZ, herpes zoster.

[a]Exchange rates per year from Brazilian real to international dollars ($): 1.388 (2010), 1.473 (2011), 1.606 (2012), 1.701 (2013), 1.813 (2014), 1.989 (2015), 2.133 (2016), 2.182 (2017), 2.201 (2018), and 2.253 (2019).[46]

might be due to two main factors: 1) the number of patients hospitalized in 2010 was the highest for the period and 2) the Real currency devaluated against the US dollar.

Please refer to Table S4 and Fig S2 for data on hospitalizations due to varicella and HZ in patients ≥65 years of age in Brazil from 2010 to 2019.

Chile

The open-access data on hospital discharges and deaths was accessed from the official Statistics and Health Information Department' (DEIS) in Chile. Hospital discharge data was collected from 2010 to 2018.[74] Uncomplicated HZ (B029) had an average hospital discharge of 246 per year during 2010 and 2018. The rest of the ICD-10 categories ranged from 8.00 to 53.00 discharges on average per year (Table S5). Average annual in-hospital stays per ICD-10 category from the period of 2010 to 2018 show that encephalitis caused by HZ (B020) required the highest number of in-hospital days for the period of analysis (14.5 days on average) with the rest varying from 3.61 to 8.91 days. The average length of in-hospital stays as per the ICD-10 category from 2010 to 2018 for uncomplicated HZ is 6.37 days (Table S6).

Discussion

This study summarizes the available economic evidence associated with HZ resource use over the past 20 years in the LAC region. A review of 23 published studies and the country's Department of Health websites provided the data for direct and indirect costs related to HZ in the general and at-risk populations in the region. Overall, the review shows that there is a significant economic burden of HZ and PHN in the LAC region which underscores the importance of HZ vaccination in high-risk patients, especially for elderly adults who have a higher HZ risk and are more likely to suffer from chronic zoster-associated pain.

Among the 23 studies which reported direct costs, indirect costs and resource use associated with HZ and its complications, country-level results were presented for Brazil, Argentina, Colombia, Mexico, Costa Rica, and Nicaragua. In addition to the regional studies, a multi-country study was also conducted which included Argentina, Brazil and Mexico. Of the 23 studies, five studies reported the use of direct medical resources, four studies reported the use of indirect resources and only two studies reported a monetary value of utilized resources.[49,63] We found that direct costs were related to medical consultations, transfers, hospitalizations, nursing consultations, physical rehabilitation, and medication schemes. The main source of indirect resource use identified in this review was workdays lost by patient and family members, the need for caregivers and the deterioration of work capacity. Both Brazil and Argentina had higher indirect costs versus Mexico for PHN, non-PHN and the total population. Patients in Argentina accrued a higher indirect medical cost than Brazil, but Brazil had higher indirect costs for the PHN population.

Information on resource use and costs was also available from the ministerial databases of Mexico, Brazil and Chile. Data from these databases show important time trends in the burden of the disease. Hospitalizations remained stable over time in Brazil, Mexico, and Chile, and both in Mexico and in Chile the main cause of hospitalization was uncomplicated HZ. Similarly, the in-hospital length of stay remained stable in these three countries, and the main reasons for admission were uncomplicated HZ in Mexico, and HZ encephalitis in Chile. In Mexico, the mean stay in hospital was 4.8 days, relative to 443 discharges per year on average for HZ in patients over 15 hospitalized in public health-care facilities (between 2010 and 2017), and 3.8 days in the Secretaría de Salud (SS) facilities (from an average 131 annual hospitalizations for HZ between 2018 and 2019).[71] This means that Mexico had a lower mean stay in hospital versus Brazil. The difference in in-hospital stay between Mexico (average stay of 3.8–4.8 days among patients ≥15 years of age) and Brazil (average stay of 7.2 days among patients ≥65 years of age) can be explained by the fact that hospitalizations reported for Brazil correspond to patients ≥65 years of age, with 41% of hospitalizations being reported among patients ≥80 years of age while in Mexico, hospitalizations correspond to patients ≥15 years of age, with 54–56% of the hospitalizations pertaining to the group aged 15–64. Therefore, either an older age in patients might be associated with more severe cases, or cases may be more severe, or there may be a different proportion of disease complications regardless of age, and thus, a larger need to remain hospitalized in Brazil. Only Brazil reported the cost of hospitalizations associated with VZV from its ministerial database. The reported average total cost per hospitalization among patients ≥65 years of age was R$ 1,064 and the average total cost per day of hospitalization for this group was R$ 148 (annual values expressed in Brazilian reals; exchange rates to $ ranged from 1.39 in 2010 to 2.25 in 2019).[72] Hospitalization costs were lower in 2019 than in 2010 owing to the number of hospitalized patients in 2010 which was the highest during the 2010–2019 period and a devaluation in R$ during this time period.[75] Despite an absence of large population-based cohort studies in the LAC region, the costs from Brazil are comparable to the results described in previously published literature.[49]

While this is one of the most updated systematic reviews of the economic burden of HZ in the LAC region, several limitations warrant further discussion. For some of the studies included in our analysis, the design was not always meeting the highest epidemiological standards, for example, outcomes were not always clearly defined, or length of follow-up properly reported, however for the majority of them, the evaluator deemed the quality of the evidence as good, and all studies provided valuable information from the public health perspective. Due to the lack of HZ-related costs from countries other than Brazil, a comparison between countries was not feasible. None of the countries included in this review adjusted their health-care costs based on inflation rates to allow for comparison through the subsequent conversion to international dollars. To this end, it should also be noted here that fluctuations in foreign exchange rates could render difficult the comparisons. This highlights the need for more evidence-based studies of cost and resource utilization in countries of the LAC region. Additionally, there was a considerable amount of heterogeneity in the populations

included in the studies such as different age groups, at-risk populations versus general population and studies with small and large number of participants. Due to this heterogeneity, results described in this study may not be generalizable to other settings. The results described in this study might suffer from underreporting due to the lack of active surveillance systems and mandatory reporting in the region. An issue inherent in systematic review is publication bias, or the tendency to report only clinically significant findings, however we mitigated this risk by looking for outcomes of interest into gray literature such as ministry of health websites. Further research on the economic burden of HZ in the LAC region is needed to better understand HZ related impact on the patients, society, and health-care systems. In future studies, it would be helpful to report separately costs incurred by VZV and costs incurred by HZ, and to report the HZ vaccination status of participants. Further research may also provide relevant insights to health-care policymakers in the region.

Conclusion

This review demonstrates that although evidence is limited, HZ and its sequelae suggests a substantial economic burden in the LAC region, which is expected to rise as the population ages and the number of HZ cases increase. The results support the need for preventative strategies such as vaccination and improved disease management to avoid or reduce the HZ-associated economic disease burden in the LAC region.

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Author's contributions

AB, AC, JNG and JG participated to the conception/design of the review; AB, AC, TA, CP, MS, JG and DB and FA participated to the collection/assembling of the data; AB, AC, TA, CP, MS, and DB performed/supervised the analysis; AB, AC, TA, CP, MS, and DB participated to the interpretation of the data in the application of the methodology. All authors agreed to the publication of the present work.

Data availability

All relevant data are within the manuscript.

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