

RESEARCH PAPER



## Varicella healthcare resource utilization in middle income countries: a pooled analysis of the multi-country MARVEL study in Latin America & Europe

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### ABSTRACT

Varicella is a mild and self-limited illness in children, but can result in significant healthcare resource utilization (HCRU). To quantify/contrast varicella-associated HCRU in five middle-income countries (Hungary, Poland, Argentina, Mexico, and Peru) where universal varicella vaccination was unimplemented, charts were retrospectively reviewed among 1–14 year-olds. Data were obtained on management of primary varicella between 2009–2016, including outpatient/inpatient visits, allied healthcare contacts, tests/procedures, and medications. These results are contrasted across countries, and a regression model is fit to extrapolated country-level costs as a function of gross domestic product (GDP). A total of 401 outpatients and 386 inpatients were included. Significant differences between countries were observed in the number of skin lesions among outpatients, ranging from 5.3% to 25.4% of patients with  $\geq 250$  lesions. Among inpatients, results were less variable. Average ambulatory medical visits ranged from 1.1 to 2.2. Average hospital stay ranged from 3.6 to 6.8 days. Use of tests/procedures was infrequent in outpatients, except in Argentina (13.3%); among inpatients, a test/procedure was ordered for 81.3% of patients, without regional variation. Prescription medications were administered in 44.4% of outpatients (range 9.3%–80.0%), and in 86% of inpatients (range 70.4%–94.9%). Total estimated spending on varicella treatment in the absence of vaccination was predicted from income levels (GDP) with an exponential function ( $R^2 = 0.89$ ). This study demonstrates that substantial HCRU is associated with varicella resulting in significant public health burden that could be alleviated through the use of varicella vaccination. Differences observed between countries possibly reflect treatment guidelines, healthcare resource availabilities and physician practices.

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### Introduction

Varicella, more commonly referred to as chickenpox, is a self-limiting, yet highly contagious disease caused by the varicella zoster virus (VZV) that typically occurs during childhood. Following a 10- to 21-day incubation period, the symptoms of viral infection start to appear, which include a characteristic pruritic vesicular rash, fever, malaise, headache, and/or abdominal pain.<sup>1</sup> At times, complications may emerge and result in secondary bacterial infections, such as skin and soft tissue infections, and pneumonia, or neurologic complications, including cerebellitis, and encephalitis.<sup>2–4</sup> The care associated with varicella, whether acute or long-term, therefore, puts a significant economic burden on national health systems. Furthermore, in the absence of vaccination, most countries found in the temperate zone demonstrate a pediatric population that is over 90% seropositive for VZV.<sup>5,6</sup>

The use of vaccination to prevent varicella has become an important strategy in reducing the morbidity and mortality associated with this disease. This strategy has subsequently

diminished the healthcare and economic burden caused by varicella.<sup>7,8</sup> Varicella vaccines have been available for several decades, and include both monovalent and combination (e.g. MMRV: measles, mumps, rubella, and varicella) vaccine formulations. The vaccines are licensed for use in immunocompetent children over the age of 12 months. In both controlled and observational settings, studies have demonstrated that varicella vaccines are not only effective at preventing viral transmission, but also have a high degree of tolerability.<sup>9,10</sup>

Regardless of the availability of effective vaccines, and the understanding that they significantly reduce the burden associated with varicella, many industrialized countries have still not included varicella in their national immunization programs. The purpose of this post-hoc pooled analysis of 5 Latin American/European studies was to assess the real-world burden to healthcare systems by evaluating varicella-related HCRU, prior to the implementation of a universal varicella vaccination program.

Since the individual studies in this paper were conducted, Argentina (1 dose in 2015), Peru (1 dose in 2018), and Hungary

(2 doses in 2019) have all introduced universal varicella vaccination, highlighting the importance of understanding the local burden of disease, to help guide policies concerning the introduction of new vaccines.

## Results

### Patient disposition

The total pooled analysis included 787 patients, comprised of 401 outpatients and 386 inpatients (Table 1).

### Patient demographics/baseline disease characteristics

Patient demographics and baseline disease characteristics by patient status and country are presented in Table 1. Overall, demographics were comparable across countries. Argentina and Mexico were the only countries to report an immunocompromised outpatient (1.3% of outpatients for both), whereas Mexico reported 6.5%, Hungary 4.9%, and Argentina and Peru each 1.3% of inpatients as being immunocompromised.

The CDC and WHO routinely classify the severity of varicella based on the number of lesions reported.<sup>11,12</sup> This classification system has been used to assess disease in vaccinated and unvaccinated individuals.<sup>13–15</sup> The severity of disease is usually classified into 4 categories – mild (<50 lesions), average (50–299 lesions), moderate (250–499), and severe ( $\geq$ 500 lesions and/or complications). In this study, disease severity, as measured by the maximum number of skin lesions during rash, was significantly different between countries among outpatients ( $p < 0.001$ ). Argentina had the highest percentage (25.4%) of outpatients with moderate-severe disease ( $\geq$ 250 skin lesions) compared to Mexico, which saw the least (5.3%); Poland, Hungary, and Peru reported proportions at 18.7%, 10.6%, and 9.9%, respectively. Even though there was no statistically significant difference between countries for the inpatient group, a considerably higher proportion from Peru (90.8%) had moderate-severe disease ( $\geq$ 250 skin lesions), compared to the other countries which reported a range of 13.0% (Mexico) to 34.7% (Argentina).

### Outpatient care

Visits to any outpatient care facility, reported by patient status and country, are presented in Table 2. Statistically significant differences were observed between countries for the proportions of inpatients who had at least one ambulatory care visit, and for the proportions of both outpatients and inpatients who had visits to a doctor's office, ER, or hospital outpatient clinic (all  $p < 0.001$ ).

There was a large disparity between countries concerning the proportion of inpatients with an ambulatory care visit. Peru and Mexico had the highest proportions (100.0% and 96.1%, respectively); the other three countries had proportions ranging between 30% and 60% of inpatients, with Argentina reporting the lowest at 33.3%. Despite having the lowest proportion of inpatients with ambulatory care visits, Argentina had the highest frequency of visits/patient among users (mean: 2.2 [95% CI: 1.7–2.9]) compared to the four other countries (range: 1.1–1.6).

In all countries except Argentina, doctor's office visits were the most common type of outpatient visit (range: 72.0%–92.0%); in Argentina the most common type was outpatient clinics (86.7%). Among inpatients, the most common type of outpatient visit was ER in Peru (96.2% of inpatients), Mexico (94.7%), and Argentina (26.7%); the most common in Hungary and Poland was doctor office visits (44.4% and 57.3%, respectively). Mexico had a considerably higher proportion of outpatients with visits to an ER, specifically 34.7%, compared to 0.0%–13.9% of patients reported in other countries.

As was observed with total ambulatory care visits, Argentina had the highest mean number of doctor's office visits/patient among users for both outpatients (2.2 [95% CI: 1.4–3.3]) and inpatients (3.0 [1.4–5.4]), at almost twice the amount reported for the other countries (ranges: 1.1–1.3 and 1.0–1.3, respectively), even though Argentina had the lowest utilization rate in both groups. The frequency of ER visits was similar between countries and patient groups (range: 1.0–1.1). All countries with patients who visited a hospital clinic reported a mean of 1.0–1.2 visits/patient for both patient groups, except Argentina, which reported 2.1 (95% CI: 1.8–2.5) visits/outpatients and 1.5 (0.5–2.3) visits/inpatients.

### Inpatient care

Visits to an inpatient setting, specifically hospitalization and ICU stay, are presented by country in Table 2. There were significant regional differences in the mean number of hospitalization days and the proportion of inpatients who required admission to the ICU ( $p < 0.001$  for both). Hungary reported the shortest mean hospital duration (3.6 [95% CI: 3.2–4.1] days), whereas Mexico and Peru reported the longest (6.7 [95% CI: 5.4–8.3] and 6.8 [5.8–8.0], respectively). In addition, Mexico had the highest proportion of inpatients requiring ICU admission compared to all the other countries (19.5% vs. 0.0%–8.0%). The mean number of days spent in the ICU ranged between 4.8 [95% CI: 1.6–14.1] days in Argentina to 7.0 days in Peru, for an overall average of 5.3 [3.9–7.2] days.

### Use of tests/procedures

The use of tests/procedures related to varicella and its complications is reported by patient status and country in Table 3. Significant regional variation was observed in the proportion of patients who had at least one test/procedure for both outpatients and inpatients (both  $p < 0.001$ ).

Argentina had the highest proportion of outpatients (13.3%) with at least one test/procedure, yet the lowest proportion among inpatients (70.7%). Aside from Peru and Poland, which had 0.0% of outpatients with any tests/procedures, Hungary had the lowest proportion (4.0%), while having the highest proportion of inpatients who reported the use of tests/procedures (97.5%). Approximately 5.3% of outpatients in Mexico had at least one test/procedure. In Mexico, Peru, and Poland, approximately 87.0%, 80.8%, and 69.3% of inpatients, respectively, had any tests/procedures. Furthermore, there was a significant difference between countries for the mean number of tests/procedures per outpatient and inpatient ( $p = 0.001$  and  $p < 0.001$ , respectively). Argentina (6.8 [95% CI: 6.1–7.5]) and Mexico (5.0 [4.5–5.6]) had

Table 1. Patient demographics and disease characteristics by patient Status and Country.

	Outpatients						Inpatients					
	Argentina N = 75 (18.7%) <sup>‡</sup>	Hungary N = 75 (18.7%) <sup>‡</sup>	Mexico N = 75 (18.7%) <sup>‡</sup>	Peru N = 101 (25.2%) <sup>‡</sup>	Poland N = 75 (18.7%) <sup>‡</sup>	Total Outpatient N = 401	Argentina N = 75 (19.4%) <sup>‡</sup>	Hungary N = 81 (21.0%) <sup>‡</sup>	Mexico N = 77 (19.9%) <sup>‡</sup>	Peru N = 78 (20.2%) <sup>‡</sup>	Poland N = 75 (19.4%) <sup>‡</sup>	Total Inpatient N = 386
<b>Gender, n (%)</b>												
Female	35 (46.7%)	42 (56.0%)	44 (58.7%)	43 (42.6%)	34 (45.3%)	198 (49.4%)	29 (38.7%)	36 (44.4%)	38 (49.4%)	35 (44.9%)	29 (38.7%)	167 (43.3%)
Male	40 (53.3%)	33 (44.0%)	31 (41.3%)	58 (57.4%)	41 (54.7%)	203 (50.6%)	46 (61.3%)	45 (55.6%)	39 (50.6%)	43 (55.1%)	46 (61.3%)	219 (56.7%)
<b>Race, n (%)</b>												
Caucasian	4 (5.3%)	75 (100.0%)	2 (2.7%)	N/A	75 (100.0%)	156 (38.9%)	6 (3.6%)	81 (48.5%)	3 (1.8%)	2 (1.2%)	75 (44.9%)	167 (43.3%)
Hispanic/Latino	71 (94.7%)	N/A	61 (81.3%)	90 (89.1%)	N/A	222 (55.4%)	65 (36.1%)	N/A	69 (38.3%)	46 (25.6%)	N/A	180 (46.6%)
Mestizo/Indigenous	N/A	N/A	12 (52.2%)	11 (47.8%)	N/A	23 (5.7%)	N/A	N/A	5 (14.3%)	30 (85.7%)	N/A	35 (9.1%)
Missing	N/A	N/A	12 (16.0%)	11 (10.9%)	N/A	N/A	4 (100%)	N/A	N/A	N/A	N/A	4 (1.0%)
<b>Area of residence, n (%)</b>												
Rural	4 (5.3%)	4 (5.3%)	13 (17.3%)	4 (4.0%)	7 (9.3%)	32 (8.0%)	12 (11.8%)	28 (27.5%)	16 (15.7%)	23 (22.5%)	23 (22.5%)	102 (26.4%)
Urban	70 (93.3%)	71 (94.7%)	62 (82.7%)	97 (96.0%)	64 (85.3%)	364 (90.8%)	62 (22.0%)	53 (18.8%)	61 (21.6%)	55 (19.5%)	51 (18.1%)	282 (73.1%)
Missing	1 (1.3%)	N/A	N/A	N/A	4 (5.3%)	5 (1.2%)	1 (50.0%)	N/A	N/A	1 (50.0%)	1 (50.0%)	2 (0.5%)
Age, years, mean (SD)	3.8 (2.4)	4.4 (2.0)	3.0 (3.2)	3.3 (3.3)	3.9 (2.6)	3.6 (2.8)	2.9 (2.2)	3.7 (2.1)	2.6 (3.5)	2.4 (3.4)	4.2 (2.3)	3.1 (2.8)
BMI, Kg/m <sup>2</sup> , mean (SD)	17.6 (2.9)	15.3 (2.0)	16.4 (2.9)	16.7 (2.8)	17.5 (1.6)	16.6 (2.7)	16.5 (2.7)	15.8 (2.6)	15.7 (3.4)	16.8 (3.8)	16.4 (2.1)	16.1 (3.0)
Immunocompromised, n (%)	1 (1.3%)	N/A	1 (1.3%)	N/A	N/A	2 (0.5%)	1 (1.3%)	4 (4.9%)	5 (6.5%)	1 (1.3%)	N/A	11 (2.8%)
<b>Maximum number of skin lesions during rash, n (%)<sup>†</sup></b>												
<50	20 (26.7%)	51 (68.0%)	27 (36.0%)	56 (55.4%)	25 (33.3%)	179 (44.6%)	3 (6.8%)	2 (4.5%)	20 (45.5%)	1 (2.3%)	18 (40.9%)	44 (11.4%)
50–249	36 (48.0%)	16 (21.3%)	44 (58.7%)	35 (34.7%)	36 (48.0%)	167 (41.6%)	50 (25.3%)	59 (29.8%)	45 (22.7%)	7 (3.5%)	37 (18.7%)	198 (51.3%)
250–500	17 (22.7%)	7 (9.3%)	4 (5.3%)	9 (8.9%)	14 (18.7%)	51 (12.7%)	14 (13.1%)	20 (18.7%)	11 (10.3%)	50 (46.7%)	12 (11.2%)	107 (27.7%)
> 500	2 (2.7%)	1 (1.3%)	N/A	1 (1.0%)	N/A	4 (1.0%)	8 (21.6%)	N/A	1 (2.7%)	20 (54.1%)	8 (21.6%)	37 (9.6%)

\*Patients were considered immunocompromised if they had at least one of the following conditions: HIV/AIDS, congenital immunodeficiency, received systemic steroids, or had any other immunocompromised condition listed in their medical history.

<sup>†</sup>Between-country comparison: Outpatients:  $p < 0.001$ ; Inpatients:  $p = 0.476$ .

<sup>‡</sup>Proportions based on total outpatients/inpatients.

**Table 2.** Ambulatory and inpatient visits by patient Status and Country.

	Outpatient					Inpatient					
	Argentina N = 75	Hungary N = 75	Mexico N = 75	Peru N = 101	Poland N = 75	Argentina N = 75	Hungary N = 81	Mexico N = 77	Peru N = 78	Poland N = 75	Total Inpatient N = 386
Any outpatient visit, n (%)*	75 (100.0%)	75 (100.0%)	75 (100.0%)	101 (100.0%)	75 (100.0%)	401 (100.0%)	39 (48.1%)	74 (96.1%)	78 (100.0%)	45 (60.0%)	662 (84.1%)
Number of visits, mean <sup>†</sup> (95% CI)	2.2 (2.1, 2.4)	1.1 (1.0, 1.1)	1.5 (1.2, 1.8)	1.3 (1.1, 1.6)	1.2 (1.1, 1.3)	1.5 (1.4, 1.5)	1.4 (1.0, 1.8)	1.6 (1.3, 1.9)	1.1 (0.9, 1.4)	1.2 (0.9, 1.6)	1.4 (1.3, 1.6)
Visits to doctor's office, n (%) <sup>†</sup>	9 (12.0%)	65 (86.7%)	54 (72.0%)	85 (84.2%)	69 (92.0%)	282 (70.3%)	36 (44.4%)	25 (32.5%)	11 (14.1%)	43 (57.3%)	118 (30.6%)
Number of visits, mean <sup>†</sup> (95% CI)	2.2 (1.4, 3.3)	1.1 (0.9, 1.4)	1.3 (1.0, 1.7)	1.1 (0.9, 1.3)	1.3 (1.0, 1.6)	1.4 (1.2, 1.5)	1.2 (0.9, 1.6)	1.3 (0.9, 1.8)	1.0 (0.6, 1.8)	1.2 (0.9, 1.5)	1.4 (1.1, 1.7)
Visits to ER, n (%) <sup>†</sup>	8 (10.7%)	0 (0.0%)	26 (34.7%)	14 (13.9%)	9 (12.0%)	57 (14.2%)	2 (2.5%)	71 (94.7%)	75 (96.2%)	4 (5.3%)	172 (44.6%)
Number of visits, mean <sup>†</sup> (95% CI)	1.1 (0.5, 2.0)	N/A	1.0 (0.7, 1.4)	1.0 (0.6, 1.7)	1.1 (0.6, 1.9)	1.1 (0.8, 1.4)	1.0 (N/C)	1.1 (0.8, 1.3)	1.0 (0.8, 1.3)	1.0 (N/C)	1.0 (0.7, 1.5)
Visits to hospital outpatient clinic, n (%) <sup>†</sup>	65 (86.7%)	15 (20.0%)	12 (16.0%)	25 (24.8%)	13 (17.3%)	130 (32.4%)	13 (17.3%)	5 (6.5%)	3 (3.8%)	0 (0.0%)	27 (7.0%)
Number of visits, mean <sup>†</sup> (95% CI)	2.1 (1.8, 2.5)	1.1 (0.6, 1.7)	1.0 (0.5, 1.7)	1.1 (0.8, 1.6)	1.0 (N/C)	1.2 (1.0, 1.5)	1.2 (0.5, 2.3)	1.0 (0.4, 2.2)	1.0 (0.3, 3.1)	N/A	1.2 (0.8, 1.7)
Inpatient visits**											
Number of days, mean <sup>†</sup> (95% CI)							3.6 (3.2, 4.1)	6.7 (5.4, 8.3)	6.8 (5.8, 8.0)	4.7 (4.1, 5.3)	5.3 (4.9, 5.8)
ICU stay, n (%) <sup>††</sup>							2 (2.5%)	15 (19.5%)	1 (1.3%)	0 (0.0%)	24 (6.2%)
Number of days, mean <sup>†</sup> (95% CI)							6.0 (N/C)	5.4 (3.7, 7.8)	7.0 (N/C)	N/A	5.3 (3.9, 7.2)

\*Between-country comparison: Inpatients:  $p < 0.001$ . Includes doctor's office, ER, and hospital outpatient clinic visits.

<sup>†</sup>Between-country comparison: Outpatients:  $p < 0.001$ ; Inpatients:  $p < 0.001$ .

<sup>††</sup>Between-country comparison: Outpatients:  $p < 0.001$ ; Inpatients:  $p < 0.001$ .

<sup>†††</sup>Denotes the average number of visits among patients with at least one visit.

\*\*Between-country comparison:  $p < 0.001$ .

<sup>††††</sup>Between-country comparison:  $p < 0.001$ .

**Table 3.** Use of tests/procedures, consultations, and medications by patient Status and Country.

	Outpatient					Inpatient					
	Argentina N = 75	Hungary N = 75	Mexico N = 75	Peru N = 101	Poland N = 75	Argentina N = 75	Hungary N = 81	Mexico N = 77	Peru N = 78	Poland N = 75	Total Inpatient N = 386
Tests/Procedures											
≥ 1 test/procedure, n (%) <sup>*</sup>	10 (13.3%)	3 (4.0%)	4 (5.3%)	0 (0.0%)	0 (0.0%)	17 (4.2%)	79 (97.5%)	67 (87.0%)	63 (80.8%)	52 (69.3%)	314 (81.3%)
Number of tests/procedures, mean <sup>†</sup> (95% CI)	2.4 (1.6, 3.5)	1.0 (N/C)	5.7 (3.8, 8.7)	N/A	N/A	2.4 (1.6, 3.7)	3.8 (3.4, 4.2)	5.0 (4.5, 5.6)	2.9 (2.5, 3.4)	1.8 (1.5, 2.2)	3.7 (3.5, 3.9)
Consultation of Allied Medical Professionals											
≥ 1 consultation of allied medical professionals, n (%) <sup>*</sup>	1 (1.3%)	2 (2.7%)	9 (12.0%)	0 (0.0%)	0 (0.0%)	12 (3.0%)	25 (30.9%)	47 (61.0%)	31 (39.7%)	18 (24.0%)	145 (37.6%)
Number of consultations, mean <sup>†</sup> (95% CI)	1.0 (N/C)	2.5 (0.9, 5.4)	1.0 (0.5, 1.8)	N/A	N/A	1.4 (0.7, 3.0)	1.6 (1.1, 2.1)	8.2 (7.4, 9.1)	1.5 (1.1, 1.9)	1.1 (0.7, 1.6)	2.5 (2.2, 2.9)
Treatment Use											
≥ 1 prescription medication, n (%) <sup>*</sup>	20 (26.7%)	7 (9.3%)	60 (80.0%)	31 (30.7%)	60 (80.0%)	178 (44.4%)	57 (70.4%)	73 (94.8%)	74 (94.9%)	70 (93.3%)	332 (86.0%)
Number of prescriptions, mean <sup>†</sup> (95% CI)	1.8 (1.3, 2.5)	1.1 (0.5, 2.1)	1.2 (0.9, 1.4)	1.2 (0.8, 1.6)	1.2 (0.9, 1.4)	1.2 (1.1, 1.4)	2.0 (1.7, 2.4)	2.9 (2.6, 3.4)	2.3 (1.9, 2.6)	2.1 (1.8, 2.5)	2.4 (2.2, 2.5)
≥ 1 antibiotic prescription, n (%) <sup>†</sup>	17 (22.7%)	2 (2.7%)	6 (8.0%)	17 (16.8%)	9 (12.0%)	51 (12.7%)	45 (55.6%)	57 (74.0%)	67 (85.9%)	43 (57.3%)	266 (68.9%)
Number of prescriptions, mean <sup>†</sup> (95% CI)	1.8 (1.2, 2.5)	1.0 (0.2, 3.1)	1.5 (0.7, 2.7)	1.1 (0.7, 1.7)	1.1 (0.6, 1.9)	1.4 (1.1, 1.7)	1.7 (1.4, 2.1)	2.5 (2.1, 2.9)	2.2 (1.9, 2.6)	1.5 (1.2, 1.9)	2.0 (1.9, 2.2)
≥ 1 antiviral prescription, n (%) <sup>*</sup>	5 (6.7%)	6 (8.0%)	57 (76.0%)	14 (13.9%)	54 (72.0%)	136 (33.9%)	33 (40.7%)	60 (77.9%)	21 (26.9%)	56 (74.7%)	188 (48.7%)
Number of prescriptions, mean <sup>†</sup> (95% CI)	1.2 (0.5, 2.4)	1.0 (0.4, 2.0)	1.0 (0.8, 1.3)	1.0 (0.6, 1.6)	1.0 (0.8, 1.3)	1.0 (0.9, 1.2)	1.1 (0.8, 1.5)	1.1 (0.8, 1.3)	1.0 (0.6, 1.5)	1.5 (1.2, 1.8)	1.2 (1.0, 1.4)
≥ 1 OTC treatment, n (%) <sup>*</sup>	44 (58.7%)	72 (96.0%)	60 (80.0%)	73 (72.3%)	60 (80.0%)	309 (77.1%)	43 (53.1%)	55 (71.4%)	70 (89.7%)	61 (81.3%)	300 (77.7%)
Number of treatment, mean <sup>†</sup> (95% CI)	1.4 (1.1, 1.8)	1.9 (1.6, 2.3)	1.7 (1.4, 2.0)	1.6 (1.3, 1.9)	1.7 (1.3, 2.0)	1.7 (1.5, 1.8)	2.5 (2.0, 3.0)	4.0 (3.5, 4.6)	1.9 (1.6, 2.2)	1.8 (1.5, 2.1)	2.5 (2.3, 2.7)

\*Between-country comparison: Outpatients:  $p < 0.001$ ; Inpatients:  $p < 0.001$ .

<sup>†</sup>Between-country comparison: Outpatients:  $p = 0.002$ ; Inpatients:  $p < 0.001$ .

<sup>††</sup>Denotes the average utilization number among patients who had at least 1 test/procedure, allied medical professional consultation, or treatment with medication.

substantially higher means compared to the other countries, which ranged between 1.8 [1.5–2.2] tests/procedures per inpatient in Poland, to 3.8 [3.4–4.2] in Hungary. Outpatients in Mexico (5.7 [3.8–8.7]) had the highest mean tests/procedures per patient compared to Argentina (2.4 [1.6–3.5]) and Hungary (1.0).

There was an even distribution (2.2%) of outpatients with imaging tests and culture assessments, while among inpatients, 37.3% and 51.3% of patients, respectively, had imaging tests and culture assessments. The type of test/procedure most commonly performed among inpatients in Argentina (65.3% of inpatients), Hungary (65.4%), Peru (60.1%), and Poland (33.3%), was a culture assessment. Of these assessments, the most common type among inpatients with  $\geq 1$  culture assessment was blood tests: Argentina (93.9% of inpatients;  $n = 46/49$ ), Hungary (75.5%;  $n = 40/53$ ), Mexico (56.0%;  $n = 14/25$ ), Peru (84.8%;  $n = 39/46$ ). Poland had almost equal distribution of inpatients with  $\geq 1$  blood test (48.0%;  $n = 12/25$ ) vs. ‘other’ culture assessment (52.0%;  $n = 13/25$ ). In Mexico, however, the most common test/procedure was an imaging test (55.8% of inpatients). For imaging tests among inpatients, the most common type was an X-ray ( $\geq 1$ ): Argentina (84.4% of inpatients;  $n = 27/32$ ), Hungary (82.8%;  $n = 24/29$ ), Mexico (83.7%;  $n = 36/43$ ). Peru and Poland had almost equal distribution of inpatients with  $\geq 1$  X-ray (40.0% [ $n = 12/30$ ] and 50.0% [ $n = 5/10$ ], respectively) vs. ‘other’ imaging tests (46.7% [ $n = 14/30$ ] and 50.0% [ $n = 5/10$ ], respectively). There were noted significant differences between countries with respect to both the mean number of culture assessments ( $p < 0.001$ ) and the mean number of imaging tests per patient ( $p = 0.004$ ). Inpatients in Hungary and Mexico had the highest mean number of culture assessments/patient (2.1 [95% CI: 1.8–2.6] and 1.6 [1.1–2.1] culture assessments/patient, respectively); in other countries, the mean ranged between 1.0 (Peru) and 1.4 (Argentina and Poland) per patient. Imaging tests were more frequently used in Argentina and Mexico, where inpatients had mean imaging tests/patient of 2.3 (95% CI: 1.8–2.8) and 1.8 (1.5–2.3), respectively; in other countries, the mean ranged between 1.1 (Poland) and 1.3 (Hungary).

Argentina (4.0%) had the highest proportion of inpatients with VZV assessments, compared to Peru, which had 0.0%. Hungary and Mexico had similar proportions (2.5% and 2.6%, respectively), while 1.3% of inpatients in Poland reported VZV assessments.

### Consultation of allied medical professionals

Patient consultations with allied medical professionals are presented by patient status and country in [Table 3](#).

Among outpatients, the proportion with allied medical professional was significantly different between countries ( $p < 0.001$ ). Mexico had notably higher proportions of outpatients (12.0%) who consulted any allied medical professional, compared to all other countries. Argentina and Hungary reported similar proportions of outpatients (1.3% and 2.7%, respectively) with consultations. No outpatient in Poland or Peru consulted any allied medical professional.

Among inpatients, significant differences were observed across countries in the rate of consultation with allied medical professionals ( $p < 0.001$ ). Similar to what was observed among

outpatients, Mexico had considerably higher proportions of inpatients (61.0%) with consultations, relative to other countries. Poland had the lowest percentage of inpatients (24.0%), while the percentages of inpatients with consultations in Argentina, Hungary, and Peru ranged between 30.9% and 39.7%. In addition, among users, the mean number of consultations with any allied medical professional/inpatient was significantly different between countries ( $p < 0.001$ ). Among inpatients having consulted an allied medical professional in Mexico and Argentina, the mean number of consultations/patient was almost 8- and 5-fold, respectively, the mean reported for all other countries; specifically, the mean number of consultations per patient was 8.2 [95% CI: 7.4–9.1] for Mexico and 5.4 [4.5–6.4] for Argentina compared to means ranging between 1.1 and 1.6 for other countries.

In Argentina and Mexico, specialized physicians (specialty not identified) were the most common type of other medical professional consulted by outpatients (1.3% and 10.7% of outpatients, respectively); in Hungary, the most common was “other” professional (2.7%) (not specified).

Among inpatients, the most common type of professional consulted was specialized physicians in each country; Mexico had the highest proportion of inpatients with specialized physician consultations (41.6%) compared to Poland, which had the least (17.3%). The differences observed between countries for the percentage of patients with this type of consultation were significant ( $p = 0.009$ ). Furthermore, statistically significant differences between countries were also observed for the mean number of specialized physician consultations/inpatient ( $p < 0.001$ ). Mexico and Argentina had the highest mean consultations/inpatient (5.8 [95% CI: 5.1–6.7] and 4.2 [3.4–5.3], respectively), and Poland had the lowest (1.1 [0.6–1.8]).

### Treatment use

Prescription and OTC medication use are presented by patient status and country in [Table 3](#).

The percentage of outpatients and inpatients with at least one overall prescription medication were significantly different between countries ( $p < 0.001$  for both). Among outpatients, Mexico and Poland had the highest proportion of patients who used prescription medication (80.0%) versus Hungary (9.3%), which had the lowest. Among users, the mean number of prescription medications/outpatient was also significantly different between countries ( $p < 0.001$ ). Argentina had the highest frequency of use (mean: 1.8 [95% CI: 1.3–2.5] prescriptions/outpatient), while Hungary had lowest (1.1 [0.5–2.1]).

Inpatients in Mexico, Peru, and Poland had substantially higher proportions of patients with at least one prescription medication use (93.3%–94.9%) compared to Argentina and Hungary (70.4%–77.3%). Furthermore, there were statistically significant regional differences among inpatients in the mean number of prescriptions/patient ( $p < 0.001$ ). The highest mean number of prescriptions/inpatient was reported in Mexico (2.9 [95% CI: 2.6–3.4]); the lowest was observed in Hungary (2.0 [1.7–2.4]).

The proportion of patients with antibiotic prescriptions, for both outpatients and inpatients, was significantly different

between countries ( $p = 0.002$  and  $p < 0.001$ , respectively). In Argentina, outpatients were reported as having the highest percentage of patients with antibiotic use (22.7%) relative to other countries, while Hungary had the lowest (2.7%).

Among inpatients, Peru had the highest proportion of patients with antibiotic use (85.9%), and, Hungary and Poland had the lowest (55.6% and 57.3%, respectively).

Among patients prescribed an antibiotic, the mean number of antibiotic prescriptions per patient was significantly different across countries for both outpatients and inpatients ( $p = 0.004$  and  $p < 0.001$ , respectively). Outpatients in Argentina treated with an antibiotic had the highest mean number antibiotics/patient (1.8 [95% CI: 1.2–2.5]) relative to other countries, which reported means of 1.5 (0.7–2.7), 1.1 (0.7–1.7), 1.1 (0.6–1.9), and 1.0 (0.2–3.1) antibiotics/patient for Mexico, Peru, Poland, and Hungary; whereas among inpatients, Mexico had the highest mean antibiotic prescriptions/patient (2.5 [95% CI: 2.1–2.9]) and Poland the lowest frequency of antibiotic use (1.5 [1.2–1.9] prescriptions/inpatient).

A remarkably higher proportion of outpatients in Mexico and Poland were given antiviral prescriptions (76.0% and 72.0%, respectively) compared to other countries (range: 6.7%–13.9%). This difference observed in the percentage of outpatients between countries was significant ( $p < 0.001$ ). On average, outpatients in all countries were treated with between 1.0 and 1.2 antiviral prescriptions/patient. A significant difference was also noted for the proportions of inpatients with antiviral use when comparing countries. Again, Mexico and Poland had substantially higher percentages of inpatients who were treated with antiviral prescriptions (77.9% and 74.7%, respectively); Argentina, Hungary, and Peru had between 24.0% and 40.7%. Although not statistically significant, the mean use of antivirals/inpatient ranged between 1.5 in Poland to 1.0 in Peru.

OTC medications were used by over 50% of outpatients in all countries (range: 58.7%–80.0%) with significant differences observed between countries for outpatients ( $p < 0.001$ ). The mean number of OTC medications/outpatient did not vary significantly between countries, and ranged between 1.4 in Argentina to 1.9 in Hungary. Similar to outpatients, over 50%

of inpatients in all countries had OTC use; Argentina had the highest proportion at 94.7% and Hungary the lowest at 53.1%. Again, these differences were significant ( $p < 0.001$ ). Statistically significant regional differences were also observed among inpatients for the mean number of OTC medications/inpatient. In Mexico, inpatients used OTC medications at a frequency of 4.0 [95% CI: 3.5–4.6] OTC medications/patient, which was substantially higher than what was recorded for other countries. Inpatients in Peru and Poland had the lowest frequency of use (1.9 [1.6–2.2] and 1.8 [1.5–2.1] OTC medications/patient, respectively).

### Estimated annual cost of treating varicella

Based on the estimated number of children with varicella seeking care, available hospitalization rates, and published cost per varicella case,<sup>16–18</sup> the total cost for the management of varicella is estimated to range from 1.85 USD per capita in Peru to 8.85 € in Poland (Table 4). Given that seroprevalence rates are close to 100% by the time of adolescence,<sup>5,6</sup> the annual number of new varicella cases in any given country is practically equivalent to the size of its birth cohort in the absence of vaccination; therefore, it is likely that the financial burden is underestimated. Even in the presence of this underestimation, however, the amount spent on treatment of varicella ranged from 22.70 USD (Peru) to 130.32 USD (Poland), and was highly correlated with gross domestic product per capita (Table 4, Figure 1). The best fit regression equation ( $R^2 = 0.89$ ) showed an exponential relationship between GDP per capita and the total cost per immunizable child of treating varicella.

### Discussion

The current pooled analysis has demonstrated that varicella among the pediatric population in the absence of varicella vaccination is associated with considerable healthcare resource utilization, which extends well beyond consultation with the treating physician, including auxiliary use of tests and procedures, consultation of allied medical professionals, and, in some

**Table 4.** Published estimates of costs associated with varicella.

	Argentina N = 75	Hungary N = 75	Mexico N = 75	Peru N = 101	Poland N = 75
Total population 1–14 <sup>A</sup> (2015)	9,436,929	1,243,502	29,908,770	7,527,440	4,997,777
Estimated number of varicella outpatients who seek care	122,296 <sup>1</sup>	37,406 <sup>2</sup>	207,321 <sup>3</sup>	128,892 <sup>4</sup>	171,768 <sup>5</sup>
Estimated number of hospitalized varicella cases	195 <sup>1</sup>	179 <sup>2</sup>	12,718 <sup>3</sup>	1,720 <sup>4</sup>	350 <sup>5</sup>
Estimated cost per varicella outpatient	322.7 USD <sup>1</sup>	160.6 € <sup>2</sup>	240.65 USD <sup>3</sup>	97.6 USD <sup>4</sup>	245.5 € <sup>5</sup>
Estimated cost per varicella inpatient	2,947.7 USD <sup>1</sup>	736.0 € <sup>2</sup>	5,786.20 USD <sup>3</sup>	769.9 USD <sup>4</sup>	1198.1 € <sup>5</sup>
Estimated total cost for management of varicella in children 1–14	40,054,378 USD <sup>1</sup>	6,096,449 € <sup>2</sup>	123,480,000 USD <sup>3</sup>	13,907,146 USD <sup>4</sup>	42,588,385 € <sup>5</sup>
Estimated cost per capita (total cost/total population 1–14)	3.93 USD	4.59 €	3.83 USD	1.71 USD	7.97 €
Estimated cost per immunizable child (total cost/population aged 1 <sup>A</sup> ), converted to USD <sup>B</sup>	53.31 USD	76.82 USD	52.81 USD	22.70 USD	130.32 USD
2015 GDP/Capita, PPP Adjusted <sup>C</sup>	20,323 USD	25,582 USD	17,277 USD	12,402 USD	26,135 USD

<sup>1</sup>Estimate for 2015. Giglio N et al. *J Med Econ.* 2018 Apr;21(4):416–424.

<sup>2</sup>Estimate for 2015. Meszner Z et al. *BMC Infect Dis.* 2017 Jul 14;17(1):495.

<sup>3</sup>Estimate for 2017. Vasquez-Rivera M et al. *Acta Pediatr Mex.* 2018 Nov-Dec 39(6):334–348.

<sup>4</sup>Estimate for 2016. Castillo M et al. Under review at *Revista Médica Herediana.*

<sup>5</sup>Estimate for 2015. Wysocki J et al. *BMC Public Health.* 2018 Mar 27;18(1):410.

<sup>A</sup>World Population Prospects: The 2017 Revision: Special Aggregates: United Nations related groups File SA3/POP/8–1: Total population (both sexes combined) by broad age group, aggregate and constituents, 1950–2100 (thousands) Estimates and Medium variant, 1950–2100 POP/DB/WPP/Rev.2017/SA3/POP/F08–1.

<sup>B</sup>IRS Mid-Year Exchange Rates for 2015 (1 USD = 0.93 EUR) were used.

<sup>C</sup>The 2017 World Bank Development Indicators Online.

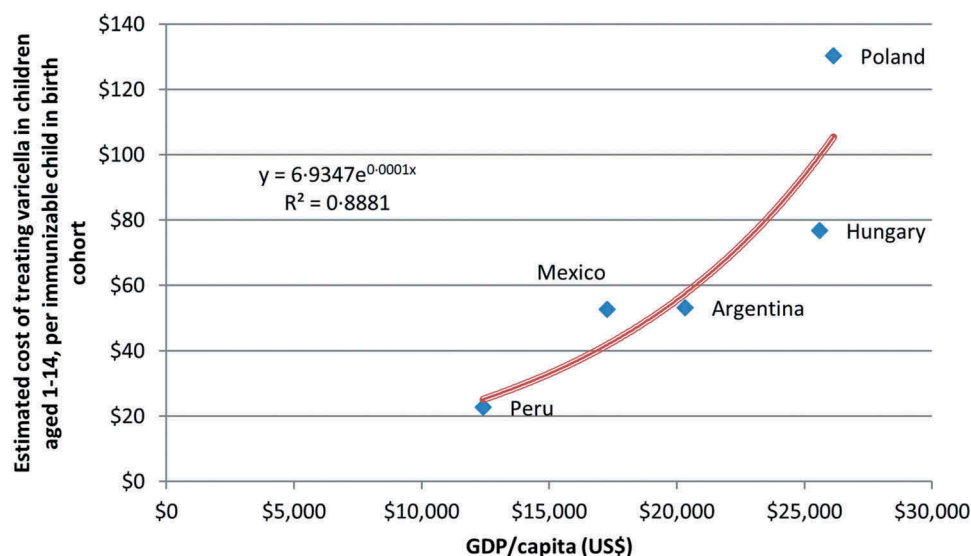


Figure 1. Regression of varicella treatment cost per immunizable child on GDP per capita (2015 PPP adjusted).

cases, hospitalization. For tests/procedures, even though utilization was low among outpatients, over 69% of inpatients in each country had at least one, with an overall mean of 3.7 (95% CI: 3.5–3.9) tests/procedures per patient. In every country assessed, at least 24% of inpatients consulted an additional medical professional, most often a specialized physician; in some countries, this percentage was as high as 61.0% (Mexico). Furthermore, in more than half of the countries outpatients also had additional medical professional consultations.

These data suggest that varicella puts a large financial burden on public health systems. Compared to prevailing prices for varicella vaccines in countries around the world, more is being spent on treatment and management of varicella disease than it would cost to implement universal varicella vaccination of one-year-olds, and the fit of the regression equation in Figure 1 suggests that this finding may potentially be extrapolatable to other middle-income countries. This is in contrast to past “common wisdom” that opined that outside high-income settings, the economic burden of varicella was unlikely to be sufficient to justify vaccination.

One reason for this may be that in the past 40 years, middle-income countries have undergone significant changes in pre-primary (i.e., daycare, preschool, and kindergarten) school participation,<sup>19</sup> in population urbanization,<sup>20</sup> and in the proportion of population under the age of 15 (Table 5),<sup>21</sup> factors which could influence not only varicella virus circulation and transmission, but lead to increased health care seeking behavior – and hence, increase the overall direct and societal costs of managing varicella.

Significant regional variation was observed in the types of ambulatory care which could be explained by differences across countries regarding access to care and health insurance coverage. In some countries, such as Argentina, a significant proportion of the population receives medical attention supported by the government where hospital networks are the main source of primary care.<sup>22</sup> As suggested by the literature, outpatients in Argentina in this study mostly visited hospital outpatient clinics. In other studies, the use of an emergency room has been reported to be

Table 5. Changes in key demographic factors that may influence varicella virus transmission and health-care seeking behaviors.

Changes from 1975–2015	Argentina	Hungary	Mexico	Peru	Poland	All Middle-Income
In pre-primary school participation <sup>1</sup>	107%	53%	432%	635%	41%	355%
In urbanization <sup>2</sup>	13%	14%	26%	28%	10%	75%
In % of population <15 <sup>3</sup>	–14%	–28%	–41%	–36%	–38%	–34%

<sup>1</sup>UNESCO Institute for Statistics.<sup>19</sup>

<sup>2</sup>United Nations Population Division. World Urbanization Prospects: 2014 Revision.<sup>20</sup>

<sup>3</sup>World Bank staff estimates based on age/sex distributions of United Nations Population Division’s World Population Prospects: 2017 Revision.<sup>21</sup>

preferable to a doctor’s office visit when there was a lack of financial coverage or certain barriers to accessing clinics;<sup>23</sup> this could potentially explain findings in Mexico where visit to the ER was the most common type of ambulatory care among outpatients. According to local expert opinion, access to an ER is however limited in Hungary and only available in larger cities, and therefore most patients will be seen by a primary care physician, if seeking care; this would explain why such a small proportion of patients in our study sought care at an ER in Hungary.

The regional variation that was observed for the use of medical tests/procedures, consultations with allied medical professionals, and use of prescription medication is likely a reflection of the differences in local physician practices. A comparison of patient management between different countries demonstrated that physicians in some countries were more likely to prescribe medication and refer patients to a specialist when treating the same patient.<sup>24</sup> Furthermore, depending on the region, differences in the number of medical tests/procedures ordered and the number of diagnostic tests have been described in the literature.<sup>25</sup>

The variability in prescription medication use between countries could be further explained by differences in national or regional guidelines for the treatment of varicella. Specifically, for antiviral use, Argentina had the lowest proportion of patients

being prescribed antivirals, while Poland and Mexico had much higher ratios. The guidelines for treatment of varicella in Argentina state that while useful in certain high-risk situations, antivirals are not recommended routinely for primary prevention.<sup>26</sup> They also mention that there is limited data on acyclovir use as a prophylaxis after viral exposure and that there are limited studies in adults, and immunocompromised patients. Furthermore, while there is dosage information provided, the guidelines are not entirely clear on when antivirals should be used. Poland and Mexico, on the other hand, have very straightforward guidelines that dictate when a physician should prescribe antivirals.<sup>27,28</sup> While acyclovir is recommended only for severe cases in Poland, or for patients belonging to high-risk groups, local expert opinion has indicated that many physicians still prescribe antivirals regularly, despite these recommendations. Availability of medications and of generic versions may also play a role in the differences observed for prescription medication use. As an example, many Latin American countries still have limited access to high-cost medications, while countries like Mexico, have grown their pharmaceutical industry by 200%, and account for close to 40% of all pharmaceutical sales in Latin America, consequently improving access.<sup>29,30</sup>

The limitations of this study are inherent to its retrospective design and the use of patient charts. Specifically, only a cross-section of patient care may be captured in the charts which could lead to under-estimation of the actual HCRU associated with varicella. On the other hand, there is a chance that HCRU was slightly over estimated, due to the exclusive selection of patients who sought some type of care. Additionally, the healthcare centers recruited in this study were not categorized based on their type of sector (i.e. public, private, or unions), which could explain some of the observed differences. Finally, there is a chance that inaccuracies or discrepancies in the details recorded in patient charts may exist.

This study demonstrates that varicella is associated with considerable use of healthcare resources, resulting in substantial public health burden. Introduction of universal varicella vaccination may be a cost-effective option to minimize this burden, and several of the countries in the current study (Argentina, Peru, and Hungary) have recently decided to implement universal varicella vaccination. An important consideration that could impact the cost-savings, however, is the vaccination rate. According to the WHO,<sup>31</sup> Poland and Hungary have high rates (92%–99%) of vaccination; for Argentina, Mexico, and Peru, rates fluctuated between 62% and 94% depending on the vaccine offered. Fortunately, there are many strategies that exist to increase vaccination rates,<sup>32,33</sup> and maintain the cost-effectiveness of vaccine implementation.

The differences in healthcare resource utilization and related costs observed between countries most likely reflect treatment guidelines, healthcare resource availabilities, healthcare seeking behaviors, and local physician practices. The observed correlation between gross domestic product and the cost of varicella treatment, both per capita, and per immunizable child, in this selection of middle income countries is striking. Considering that treatment cost of varicella exceeds the cost of an immunization program, it may be true that these findings apply to other countries with similar healthcare systems.

The results of this study could serve as an important source of data for potential evaluation of the cost effectiveness of future national universal varicella vaccination programs not only in the countries studied, but in other comparable low and middle-income settings.

## Materials and methods

### Study design

MARVEL was a multi-country observational, retrospective chart review study<sup>16–18</sup> that assessed the burden of illness associated with varicella. Investigators screened patient charts from the most recent year, and went back as much as five years to identify eligible cases. Information was extracted from the date of first primary varicella diagnosis until resolution, or, if unavailable, the date of last contact. Local ethics committee approval was obtained for each study, which were conducted per the Guidelines for Good Pharmacoepidemiology Practices (GPP), and in accordance with regional laws and regulations.

This post-hoc analysis specifically evaluated the use of healthcare resources due to varicella in 5 countries between the following dates: Argentina (2009–2014), Hungary (2011–2015), Mexico (2011–2016), Peru (2011–2016), and Poland (2010–2015).

### Patient population

Patients were considered eligible for study inclusion if they were between the ages of 1 and 14 years (12 for Argentina, Hungary, and Poland) and had a primary varicella diagnosis recorded in their charts within the respective study period; both outpatients, defined as patients who visited the doctor's office (family doctor, general practitioner, pediatrician, or infectious disease specialist), outpatient clinic/department of hospital, or emergency room (ER) without hospitalization for their varicella diagnosis, and inpatients, defined as those admitted to a hospital for their primary varicella, including those with initial consults in an outpatient setting, were included. To allow for generalizability of the results to both groups, efforts were made to obtain an outpatient to inpatient ratio of approximately 1:1. Patients who had received prior varicella vaccination, or who presented with either a history of varicella, or with herpes zoster infection, were excluded from the study.

### Healthcare resources

The utilization of the following resources was evaluated: visits to the doctor's office, visits to an outpatient clinic/department of hospital, visits to the ER, hospital and intensive care unit (ICU) stays, allied healthcare consults (e.g. physiotherapist, psychologist, social worker, specialized physician, and other professional), tests/procedures performed (e.g. imaging, cultures, and VZV assessments), prescription medications (e.g. antibiotics, and antivirals), and over-the-counter (OTC) medications. For each HCRU type, the utilization rate and frequency of use (among users) are presented; for inpatients only, the duration of hospital and/or ICU stay were estimated. The overall cost of varicella per capita for each country was also evaluated, based on data from previously published studies.



## Statistical methods

Statistical analyses were stratified by outpatient vs. inpatient status and by country nested within each patient status. Descriptive statistics were produced including the mean and standard deviation (SD) or 95% confidence interval (CI) of the mean for continuous variables, and count and percentage for categorical variables. For exploratory purposes, the Chi-square test was used for the comparison of utilization rates and Poisson regression for the frequency of use.

The estimated annual costs of treating varicella in children under aged 15 are reported from the original papers, and the cost per immunizable child was regressed on GDP per capita using different functional forms.

Statistical analyses were performed using SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Disclosure of potential conflicts of interest

L.J.W. is an employee and stock shareholder of Merck & Co. Inc. M.E.C. received payment as a consultant for Merck & Co. Inc. N.G. received payment as a consultant for Merck & Co. Inc., and is a consultant for GSK. Z. Meszner received payment as consultant for Merck & Co. Inc, and is a consultant for MSD, Pfizer, and GSK. Z. Molnar received payment as a consultant for Merck & Co. Inc. M. V. received payment as a consultant, and is a speaker for, Merck Sharpe & Dohme. J.W. reports grants from Merck & Co. Inc. A.A. and B.J.K. are employees of Merck & Co. Inc. E. R. and J.R. are employees of JSS Medical Research (the hired CRO).

## Contributors

L.J.W. conceived/designed the study, analyzed the data, interpreted the results, created figures, and reviewed/revised the manuscript. M.E.C., N. G., Z. Meszner, Z. Molnar, M.V., and J.W. collected the data, interpreted the results, and reviewed/revised the manuscript. A.A. and B.J.K. interpreted the results and reviewed/revised the manuscript. J.R. analyzed the data, interpreted the results, and wrote the manuscript. E.R. conceived/designed the study, analyzed the data, interpreted the results, and wrote the manuscript. All authors reviewed and approved the final manuscript.

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