Guillain-Barré Syndrome in Children Aged <15 Years in Latin America and the Caribbean: Baseline Rates in the Context of the Influenza A (H1N1) Pandemic

José Mauricio Landaverde, M. Carolina Danovaro-Holliday, Silas Pierson Trumbo, Carmelita Lucia Pacis-Tirso, and Cuauhtémoc Ruiz-Matus
Pan American Health Organization, Washington, DC

In light of the influenza A (H1N1) pandemic, the Strategic Advisory Group of Experts on Immunization of the World Health Organization requested that the acute flaccid paralysis surveillance system of Latin American and the Caribbean be used to establish Guillain-Barré syndrome incidence rates. An analysis was conducted of 10,486 acute flaccid paralysis cases diagnosed as Guillain-Barré syndrome from 2000 through 2008 in children aged <15 years in Latin America and the Caribbean countries and territories. The average incidence was 0.82 cases per 100,000 children aged <15 years in Latin America and the Caribbean countries and territories. The average incidence was 0.82 cases per 100,000 children aged <15 years (range, 0.72–0.90 cases per 100,000 children), with significant differences between northern and southern countries (1.08 vs 0.57 cases per 100,000 children). The acute flaccid paralysis surveillance system represents a useful means of monitoring Guillain-Barré syndrome during the pandemic.

As the world grapples with the influenza A (H1N1) pandemic and rushes to develop a vaccine with a safety profile that will not be well established before its use, the need to update Guillain-Barré syndrome (GBS) incidence rates has become increasingly clear. GBS is occasionally mentioned as associated with major influenza outbreaks and as a rare adverse event after influenza vaccination [1–3].

In January and February 1976, 14 soldiers in Fort Dix, New Jersey, fell ill with Hsw1N1 influenza, colloquially referred to as swine flu [4, 5]. Worried about a potential pandemic, policy makers and health officials hastily launched a nationwide vaccination campaign against the virus. A year later, no pandemic had occurred, but 30 people had died from vaccine-related complications, mainly GBS. Health officials canceled the campaign, but concerns persisted that influenza vaccinations might induce GBS [6]. One study indicated that the New Jersey influenza vaccine in 1976–1977 increased the risk of the disease nearly 6-fold [1, 7], but subsequent studies suggest that the link between influenza vaccination and an increased risk of GBS is slight or nonexistent [1, 8].

GBS is an acute disease affecting the peripheral nervous system that causes ascending paralysis and the loss of deep tendon reflexes. Although the disease is characterized by a rapidly ascending weakness, some variants present atypical clinical features. Determining the cause and epidemiology of GBS is often difficult. The disease is often preceded by respiratory and gastrointestinal infections, most frequently caused by Campylobacter jejuni [3, 8]. GBS affects children and adults worldwide, with general incidence rates varying between 1.1 and 1.8 cases per 100,000 persons per year [9]. Among children aged <15 years, GBS rates vary between 0.34 and 1.34 cases per 100,000 persons per year [9]. A systematic literature review published in 2008 indicated GBS incidence rates needed to be updated; the authors noted that “only 3 studies reported rates from 2000 onwards, and these were thought to be unreliable” [9, p 152].

On 18 May 2009, the World Health Organization’s (WHO) Ad Hoc Policy Advisory Working Group on Influenza A/H1N1 Vaccines—part of the Strategic Advisory Group of Experts on Immunization—requested that baseline frequencies of GBS be established among different populations. Because the safety of a pandemic vaccine would be unknown, the Advisory Group considered it essential to have accurate pre- and postmarketing surveillance information available. It called on WHO regions with continuing transmission of influenza A (H1N1) to make gathering GBS information a priority. In particular, it requested that the Pan American Health Organization (PAHO), the WHO Regional Office for the Americas, use its acute flaccid paralysis (AFP) surveillance system for the monitoring of polio as a source of GBS incidence rates in Latin America and the Caribbean [10]. The present analysis is in response to this WHO request.

Methods. As part of the PAHO’s polio eradication strategies, all AFP cases in children aged <15 years must be immediately reported and investigated. A stool sample must also be collected to confirm or rule out polio. National classification...
committees then review and diagnose cases discarded for polio, taking into account clinical and laboratory findings [11, 12].

Investigation and reporting procedures have been standardized across Latin America and the Caribbean since the 1980s. Regional guidelines for the clinical diagnosis of AFP cases provide standardized case definitions for polio and clinical, electrodiagnostic, and laboratory criteria for the differential diagnosis of polio, including GBS, traumatic neuritis, and transverse myelitis. The PAHO Polio Eradication Field Guide, used throughout Latin America and the Caribbean for AFP surveillance, offers the following criteria for GBS: generally acute, symmetrical, and distal flaccid paralysis; absence of deep-tendon reflexes; time from paralysis to full progression ranging from hours to 10 days; low involvement of the high cranial nerves; autonomic dysfunction; cerebrospinal fluid with high protein content and relatively few cells; abnormal nerve conduction velocity at 3 weeks and demyelination; symmetrical atrophy of peroneal muscle that tends to resolve within 60 days; and cramps, tingling, and reduced sensation on the palms and soles [11, 12]. In most cases the diagnosis is established by neurologists, but when the diagnosis poses a problem, a classification committee is convened to help eliminate the possibility of polio and define the final diagnosis.

The Polio Eradication Surveillance System (PESS) is an electronic surveillance information platform and case-based database used by Latin America and the Caribbean countries since the 1980s. Approximately 33,000 notification units are required to make weekly reports to intermediate and national levels and to PAHO, even in the absence of cases. For the period 2000–2008, 92% of these notification units submitted weekly reports. To determine the rate of GBS in children aged <15 years in Latin America and the Caribbean, an analysis was conducted for the period 2000–2008. During this period, all 39 Latin America and the Caribbean PAHO member states reported AFP data. However, 14 Caribbean Islands and 4 Latin American countries were excluded from the analysis because they reported ≥1 GBS case for <2 years. Another country was excluded because of a 4-fold decrease in the number of GBS cases between the first and second halves of the study period. The countries in the analysis (Argentina, Brazil, Chile, Colombia, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, and the following English-speaking Caribbean countries: the Bahamas, Guyana, Jamaica, St Vincent and the Grenadines, Suriname, and Trinidad and Tobago) comprise 87.7% of the population in Latin America and the Caribbean.

To account for geographical variations in GBS rates, countries were divided into 2 groups, northern and southern. Northern countries included Colombia, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, and the aforementioned English-speaking Caribbean countries. Southern countries included Argentina, Brazil, Chile, and Peru. Incidence rates were calculated by dividing the number of GBS cases in PESS per year by the population aged <15 years [13]. Cases were plotted by week of onset to explore seasonality, and a Poisson distribution was used to calculate the expected number of cases by month, with 95% confidence intervals. Finally, the main clinical features of the GBS cases in PESS were analyzed. All analyses were completed using EpiInfo 2002 (Centers

Figure 1. Guillain-Barré syndrome incidence rates in children aged <15 years in Latin America and the Caribbean (LAC), 2000–2008. Northern countries included Colombia, Cuba (no Guillain-Barré syndrome cases reported in 2000), Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, and the following English-speaking Caribbean countries: the Bahamas, Guyana, Jamaica, St Vincent and the Grenadines, Suriname, and Trinidad and Tobago. Southern countries included Argentina, Brazil, Chile, and Peru.

to Disease Control and Prevention) and Stata (version 8; StataCorp) software.

Results. From 2000 through 2008, 39 countries or territories reported a total of 19,437 AFP cases, 17,182 in countries included in the analysis (88.4%). Of these 17,182 AFP cases, 10,486 (61.0%) were diagnosed as GBS. The average annual rate of GBS in children aged <15 years during this time period was 0.82 cases per 100,000 children (range, 0.72–0.90 cases per 100,000 children), with a downward trend observed in 2006–2007. There were significant differences between northern and southern countries. The annual rate in northern countries was 1.08 cases per 100,000 children (range, 0.96–1.28 cases per 100,000 children), whereas the rate in southern countries was 0.57 cases per 100,000 children (range, 0.49–0.67 cases per 100,000 children) ($P<.001$) (Figure 1). Countries with the highest annual GBS rates in children aged <15 years included El Salvador (3.86 cases per 100,000 children), Honduras (1.72 cases per 100,000 children), and Chile (1.63 cases per 100,000 children). Brazil showed the lowest annual rate of GBS in children aged <15 years (0.40 cases per 100,000 children). In Mex-
ic, the country reporting the highest number of cases, the annual GBS rate in this age range was 1.14 cases per 100,000 children.

Seasonality was apparent in Mexico and Central America (El Salvador, Guatemala, Honduras, and Nicaragua) (Figure 2). The expected monthly number of cases was highest for Mexico in August, with 43 cases (95% confidence interval, 30–56 cases), and lowest for Panama, with <1 case expected each month.

GBS was more common among boys (58.2% of cases). The median age of patients with GBS was 6 years, with the highest percentage of cases (39.5%) occurring in the 1–4-year age group and the lowest (25.3%) in the 10–14-year age group. The overall case fatality rate was 2.5%, without statistically significant differences among age groups. Honduras showed the highest case fatality rate (7.8%), and Peru had the lowest (0.3%). Regarding clinical features, paralysis was ascending in 86.3% of affected subjects, with both legs affected in 95.8% and both arms in 57.4%; all 4 extremities were affected in 56.9% of cases. Hyporeflexia or areflexia was recorded in 88.2% of cases. Cranial pairs were involved in 15.4% of cases and respiratory muscles in 18.3%. Roughly 2 months after onset of the paralysis, residual atrophy was recorded in 3.9% of cases and residual paralysis in 12.9%. Fever was recorded in 32.8% of cases, with a significantly higher incidence (36.0%) in the 0–4-year age group.

Discussion. This analysis of >10,000 GBS cases in children aged <15 years in Latin America and the Caribbean countries found a GBS incidence of 0.82 cases per 100,000 children per year (range, 0.72–0.90 cases per 100,000 children per year) for the period 2000–2008, with significant differences between northern and southern countries. These rates are consistent with those reported in other studies [1, 8, 9]. Although differences in rates between northern and southern countries may be explained by differences in seasonality, climate, or epidemiology, further research is required to determine why GBS would occur less frequently in southern countries than in Latin America and the Caribbean countries north of the equator. When GBS cases were analyzed by week, the number of cases in Mexico and Central America increased between weeks 19 and 41, a trend that may indicate seasonality. Investigators in El Salvador and Mexico have reported seasonality, in 1 report suggesting a link between increased frequency of GBS and the increased presence of gastrointestinal and respiratory pathogens during the rainy season [14, 15]. Seasonality will also be important to consider when evaluating the relationship between GBS and infectious diseases, including influenza. Furthermore, it will be interesting to contrast GBS occurrence in 2009, when influenza A (H1N1) has circulated, with that in previous years. The expected number of cases per month can be calculated from the AFP surveillance system. These estimates should facilitate GBS surveillance efforts in relation to the new influenza A (H1N1) pandemic virus and once the vaccine is introduced.

This analysis has several limitations. Although the AFP surveillance network of Latin America and the Caribbean is one of the world’s largest and best-established surveillance systems, with 92% of its >30,000 notification units reporting weekly, the system was never specifically intended to monitor GBS. Diagnostic criteria may also vary by country. Although cerebrospinal fluid and nerve conduction studies are conducted in most cases, these variables are not collected in the AFP surveillance form. Similarly, no previous infection or vaccination antecedents are recorded, except vaccination with oral polio vaccine. Nonetheless, countries follow strict guidelines, and the analysis of signs and symptoms is consistent across the region. Breakdowns of cases by sex and age group proved similar to those determined in other studies [1, 8, 16]. Data regarding paralysis, cranial pairs, hyporeflexia, areflexia, residual atrophy, and residual paralysis proved consistent with GBS. A high incidence of fever, a finding that is not well understood, has been reported elsewhere in another study conducted in Latin America and the Caribbean in 1989–1991 [16]. In spite of these limitations and in the absence of GBS surveillance, we believe that AFP surveillance can be used to monitor GBS.

The rush to develop a pandemic vaccine means that limited information about potential adverse events, including GBS, will be available when the vaccine is introduced. When a vaccine is introduced, the GBS rates and trends established using the AFP surveillance system, in the absence of specific GBS surveillance, should help health officials monitor increases of the disease that may result from the influenza A (H1N1) virus or a vaccine against it. However, there may be bias caused by a higher level of suspicion for GBS related to vaccination, leading to higher rates of diagnosis and reporting. We have provided our findings for Latin America and the Caribbean countries and other countries in the world that may benefit from a more general GBS baseline. The variation of GBS rates in this analysis, however, suggests that Latin America and the Caribbean countries should develop their own baselines with use of country-specific information. Finally, field studies should be conducted to differentiate between an increase in GBS cases that could result from pandemic influenza A (H1N1) and an increase resulting from the introduction of a pandemic vaccine.

References


