**ABSTRACT**

**ERYTHROMYCIN RESISTANT GROUP A STREPTOCCAL INFECTIONS IN LATIN AMERICA AND THE UNITED STATES**

by

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A**ntibiotic resistance among human pathogens is an emerging area of concern in the field of public health.** Group A streptococcus (GAS) **is commonly overlooked in the surveillance and research of antibiotic resistance. However, infections with GAS cause substantial morbidity and mortality each year worldwide. For optimal clinical outcomes, new Latin American immigrants to the U.S. who are diagnosed with GAS infection may require differential treatment depending upon the prevalence and pattern of antibiotic nonsusceptibility in their area of origin as compared to the prevalence and patterns in the U.S. There are no published studies to date that examine resistance patterns of GAS among Latin American immigrants in the U.S. A first step towards creating a foundation from which to develop antibiotic treatment guidelines for Latin American immigrants would include examination of the current literature on GAS resistance patterns in Latin America and the U.S. The goal of this literature review is to explore the body of evidence surrounding the rates of erythromycin resistant (ER) GAS within both regions and make recommendations for future studies and public health practices.** Studies for the review were found through a search of the PubMed and the Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS) databases. Forty articles met the criteria for inclusion: 20 with data from Latin America, 19 with data from the U.S., and one article with data from both regions. Isolates from six Latin American countries and the U.S. were collected over two decades, from 1990 to 2010. Prevalence rates of ER-GAS fluctuated by geographical location and over time. Substantial gaps in the literature were discovered. The public health significance of this review is to demonstrate the major challenges to constructing evidence-based GAS antibiotic treatment guidelines for Latin American immigrants to the U.S. based upon published articles without strengthening surveillance data from other sources.

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#

# 1.0 INTRODUCTION

**Antibiotic resistance among human pathogens is an emerging area of concern in the field of public health. Infections with nonsusceptible pathogens are more difficult to treat, which allows them to spread more easily through communities and may result in more severe illness [**[**1**](#_ENREF_1)**]. Policymakers require surveillance data and research in order to make recommendations and enact timely and evidence-based policies and clinical practices to limit the spread of resistant pathogen strains. Physicians and other health professionals benefit from this surveillance data and research in order to ensure the highest quality of care for their patients. With the relative ease of airline travel of both people and pathogens in the modern, globalized world, monitoring of antibiotic resistance is needed now more than ever. This is especially true for geographically adjacent regions, such as Latin America and the United States (U.S.). In the case of Latin America and the U.S., significant immigration integrates the people and pathogens of both regions to an even greater extent. As of 2010, 21.2 million Latin American immigrants were living in the U.S., accounting for 53.1 percent of the U.S. foreign-born population [**[**2**](#_ENREF_2)**].**

**With global focus on such pathogens as *Mycobacteria tuberculosis* and** *Staphylococcus aureus, Streptococcus pyogenes* or group A streptococcus (GAS) **is commonly overlooked in the surveillance and research of antibiotic resistance. However, infections with GAS cause substantial morbidity and mortality each year worldwide. For optimal outcomes, new Latin American immigrants to the U.S. who are diagnosed with GAS infection may require differential treatment depending upon the prevalence and pattern of antibiotic nonsusceptibility in their area of origin as compared to the prevalence and patterns in the U.S. In the development of such treatment guidelines, the approaches of evidence-based medicine (EBM) and evidence-based public health (EBPH) should be employed in order to minimize risk and maximize benefits for both individuals and their communities. The tenants of EBM and EBPH include making health care decisions based on the best available peer-reviewed evidence and epidemiological data [**[**3**](#_ENREF_3)**,** [**4**](#_ENREF_4)**].**

**Based on the review of the literature, there are no published studies to date that examine resistance patterns of *S. pyogenes* among Latin American immigrants in the U.S. In addition, there are no systematic reviews that compare the resistance patterns in Latin America to U.S. patterns. Therefore, a first step towards creating a strong evidence-based foundation from which to develop antibiotic treatment guidelines for Latin American immigrants would include examination of the current literature on GAS resistance patterns in both regions. The goal of this literature review is to explore the body of evidence surrounding the rates of erythromycin resistant (ER) GAS within the U.S. and Latin America and make recommendations for future studies and articulate public health implications.**

# 2.0 GROUP A STREPTOCOCCUS

*S. pyogenes* is a member of the ß-hemolytic group of gram-positive, streptococci bacteria. Diseases associated with GAS infection can range from a carrier state (asymptomatic), to mild conditions such as pharyngitis, to severe disease, including acute rheumatic fever (ARF), streptococcal toxic shock syndrome (STSS), and necrotizing faciitis [[5](#_ENREF_5)]. Although the majority of cases result only in mild illness, *S. pyogenes* should not be ignored as an important pathogen. GAS infections result in significant morbidity and mortality globally each year. In 2005, severe GAS-related diseases, including ARF and invasive GAS infection, effected an estimated 18.1 million people and resulted in 517 thousand deaths worldwide [2]. Although ARF and associated complications of this illness, including rheumatic heart disease (RHD), are no longer significant problems in the U.S., Latin America still bears a significant disease burden. Although data is limited, the Brazilian Ministry of Health has reported a prevalence rate of ARF of 3 to 5 percent among children and adolescents [[6](#_ENREF_6)]. In addition to the morbidity and mortality from severe GAS-associated diseases, 616 million people experience GAS pharyngitis each year, which provides a significant burden on health systems and individuals worldwide [[7](#_ENREF_7)]. As GAS infections disproportionately affect children, the burden of disease is amplified. More years of life are lost and more years of life are spent with disability than if GAS infections primarily affected adults. GAS infection is especially important for Latin America, where the proportion of the population under the age of fifteen is approximately 30 percent, compared to only 20 percent in the U.S.[[8](#_ENREF_8)]

## 2.1 ANTIBIOTIC THERAPY

The first line of treatment for acute GAS infection in the U.S. is therapy with the penicillin-family of antibiotics, specifically oral penicillin V or injectable benzathine penicillin, and oral amoxicillin for children who cannot swallow pills and require a liquid suspension [[9](#_ENREF_9), [10](#_ENREF_10)]. In Latin America, injectable benzathine penicillin is also recommended for children, due to concerns about adherence to amoxicillin therapy and the higher burden of ARF, which can result from inadequately treated cases of *S. pyogenes* infection [[11](#_ENREF_11)]. For individuals who have experienced an episode of ARF, secondary prophylaxis with penicillin is recommended to prevent recurrent attacks [[10](#_ENREF_10)].

For individuals who are allergic to penicillin, commonly used alternatives to penicillin family antibiotics include cephalosporins, clindamycin, and macrolides [[10](#_ENREF_10), [12](#_ENREF_12)]. These alternative therapies vary in cost, effectiveness, and side effects. Macrolide family antibiotics, including erythromycin, are generally less expensive than cephalosporins.[3] This makes macrolides a suitable GAS treatment choice for low- and middle-income countries, including the majority of Latin America, that tend to spend less on healthcare than higher-income countries [[13](#_ENREF_13)]. However, patients treated with erythromycin or other macrolides tend to experience more side-effects than patients treated with cephalosporins [3]. These side effects can include diarrhea, vomiting, mild to severe skin rashes, and difficulty breathing, among other reactions [[9](#_ENREF_9)].

## 2.2 ANTIBIOTIC RESISTANCE

No penicillin or amoxicillin resistant GAS has ever been reported in a published study [[14](#_ENREF_14)]. Efforts to induce resistance in laboratory research have also been unsuccessful, with some researchers speculating that the nature of *S. pyogenes* replication eliminates the pathway for penicillin resistance in this pathogen [[14](#_ENREF_14), [15](#_ENREF_15)]. However, macrolide resistance has been reported worldwide. Prevalence of ER-GAS varies significantly over time and location, with rates as high as 72 percent in parts of Asia [[16](#_ENREF_16)]. This variation is likely to be in part due to differences in the use of erythromycin by location and over time, as multiple studies have found a positive association between greater levels of ER-GAS and elevated erythromycin consumption [[17-19](#_ENREF_17)].

The two primary mechanisms of erythromycin resistance among *S. pyogenes* are through efflux and target site modification [[20](#_ENREF_20), [21](#_ENREF_21)]. The efflux mechanism is associated with M-phenotype ER-GAS. The efflux pump, encoded by the *mef*(A) and *mef*(E) genes, produces nonsusceptibility by reducing the amount of erythromycin in the bacterial cell to subtoxic levels [[20](#_ENREF_20)]. The target site modification mechanism is associated with the macrolide, lincosamide, and streptogramin B (MLSB) phenotype ER-GAS, which produces multidrug resistance to other 14- to 16-membered ring macrolides, lincosamide, and streptogramin B [[20](#_ENREF_20), [21](#_ENREF_21)]. Encoded by the *erm* genes, ER-GAS with the MLSB phenotype have methylated macrolide-binding sites that mediate nonsusceptibility [[20](#_ENREF_20)].

Multiple methods exist for determining antibiotic resistance among bacterial pathogens, including broth microdilution, Etest, and disk diffusion. These methods vary in price and sensitivity.

## 2.3 SURVEILLANCE

Resistance among *S. pyogenes* to antibiotics is important to track, as antibiotic nonsusceptibility is a potential cause of treatment failure [[22](#_ENREF_22)]. Although GAS continues to be penicillin susceptible worldwide, the surveillance of *S. pyogenes* resistance to other commonly used antibiotics is of significant importance to persons allergic to penicillin. Failure to successfully treat GAS infections can result in severe complications, such as ARF. There is also evidence suggesting that more virulent strains of GAS are also more likely to be ER [[1](#_ENREF_1), [23](#_ENREF_23)]. Monitoring of ER-GAS is important for the treatment of non-allergic individuals because resistant strains are more easily spread through communities. Furthermore, treatment with erythromycin can be used in patients for whom penicillin therapy fails [[1](#_ENREF_1), [9](#_ENREF_9)].

Within the U.S., several surveillance networks track antimicrobial resistance patterns. The Active Bacterial Core (ABC) is a surveillance system operated by the Centers for Disease Control and Prevention (CDC). This is an active, sentinel surveillance network based in ten centers across the U.S. Six specific infectious pathogens are monitored by the ABC, including *S. pyogenes*. Although the ABC tracks antimicrobial resistance patterns for invasive GAS, it does not track non-invasive GAS, and patterns of resistance may differ between invasive and non-invasive GAS strains [[1](#_ENREF_1), [24](#_ENREF_24)]. The Surveillance Network (TSN) is another surveillance system, created by the company Eurofins Scientific. TSN is an international, electronic network that monitors antimicrobial resistance patterns among many pathogens, including *S. pyogenes*. TSN operates in approximately 300 U.S. clinical laboratories, but only operates in Brazil and no other Latin American countries [[25](#_ENREF_25)].

Antibacterial surveillance is less established in Latin America. The Pan American Health Organization (PAHO) operates an antibiotic surveillance network in the region (which includes the Caribbean) known as *la Red de Vigilancia de la Resistencia a los Antibióticos*. Although this system tracks ER-GAS, often the data groups *S. pyogenes* with *S. agalactiae*, or group B streptococcus (GBS), another species ß-hemolytic streptococcus. Although ER-GBS patterns are similar to those of ER-GAS, they are not identical [[26](#_ENREF_26)]. Therefore, monitoring GAS separately from GBS would be beneficial for a better understanding of resistance trends. Additionally, sample sizes used by this network tend to be small. In 2010, the number of isolates sampled per country ranged from 1 to 1763, with a median of 117 [[27](#_ENREF_27)].

# 3.0 METHODS

A literature search was conducted using PubMed and the Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS) databases. Data from published Pan American Health Organization (PAHO) reports on antibiotic resistance was also reviewed. The following MeSH and keyword terms were used in the PubMed search: “(group A streptococcus OR streptococcus pyogenes OR rheumatic fever OR scarlet fever) AND (erythromycin resistance OR erythromycin resistant)”. Two filters were created and applied separately to this search to narrow results by region. The following terms were used to create the Latin American region filter: “Latin America OR Mexico OR Central America OR Caribbean OR South America”. The search term “United States” was used to create the U.S. region filter. In the LILACS database search, the following terms were used: “(erythromycin OR eritromicina) AND streptococcus”. The results were filtered by pathogen, *S. pyogenes.* Articles were selected if they were written in English or Spanish, studied a human population in Latin America or the continental U.S., and contained a prevalence or incidence estimate of ER-GAS. Articles were excluded if they were published prior to the year 1997 or if they did not contain original data.

From each article, the following information was extracted: year of publication, years during which GAS isolates were collected, country and local region where GAS isolates were collected, number of isolates, rate(s) of resistance, method(s) of resistance testing, age of subjects, whether isolates were invasive or non-invasive and whether the study was an outbreak investigation. Resistance was defined according to Clinical and Laboratory Standards Institute (CLSI) standards. Isolates were considered resistant with a minimum inhibitory concentration (MIC) ≥ 1 mg/L [[28](#_ENREF_28)]. Intermediate susceptibility was considered susceptible for the purposes of this review, as the majority of the studies did not provide data on this variable. All methods of resistance testing were considered acceptable, as long as CLSI standards for MIC were followed.

After data was collected, information from each region was arranged in a table, with both tables aligned in the same way, in order to facilitate comparison between the data from Latin America and the U.S. So that trends in ER-GAS prevalence over time and space could be observed, the tables included columns for year(s), country and region within each country from which the GAS samples were collected. A geographical area smaller than a country (e.g. province, city, multi-state cluster) was classified as a "region" for this literature review.

Outbreak investigations were included in the literature review, as they can demonstrate the ability of ER-GAS to spread rapidly in a community. However, the rate of ER during an outbreak may not be reflective of the background prevalence of ER-GAS in a location. An outbreak was defined as the occurrence of a number of cases of GAS in excess of what would normally be expected for the defined geographical area. For consistency, information from outbreak investigations was not included in the tables. Data regarding mechanisms of resistance were also not included in this analysis, as any will result in ER and factoring the mechanisms into the analysis was beyond the scope of this review.

# 4.0 RESULTS

The PubMed search identified 804 articles prior to the application of either region filter. Twenty-two articles were captured by the Latin American region filter and 61 were captured by the U.S. filter, including one study which was caught by both filters. The LILACS database search identified 17 articles after the results were filtered for *S. pyogenes*. Forty articles met the criteria for inclusion: 20 with data from Latin America, 19 with data from the U.S., and one article with data from both regions. A flow diagram with detailed exclusion and inclusion criteria is provided in Figure 1.

Information from the published literature was summarized in two tables, grouped by region (Table 1, Table 2). The reviewed studies varied considerably in age, methods, and ER-GAS rates. The oldest article was published in 1997 and the most recent in 2012. Isolates were collected over two decades, from 1990 to 2010. Methods for participant selection and eligibility requirements differed among the studies. Among the articles that reported participant age, nine included adults and children (age 0 to 18 years), one included only adults, and nine included only children. Isolate collection methods also varied. Two studies collected specimen from normally sterile sites (e.g. blood), 13 collected specimen from non-sterile sites (e.g. throat), and 14 collected specimen from sterile and non-sterile sites. Additionally, 30 studies recruited cases of GAS infection, while one study examined background colonization (i.e. not all participants were infected) and two studies examined both cases and background colonization. The percentage of GASisolates that were nonsusceptible to erythromycin ranged from zero to 48 percent, excluding one outlier that reported 70 percent.



Figure 1: Literature review flow diagram

## 4.1 ERYTHROMYCIN RESISTANCE IN LATIN AMERICA

Data from the selected Latin American studies are summarized in Table 1. The isolates sampled in the studies were collected between 1990 and 2009, with a peak occurring between 1999 and 2001. Number of isolates sampled from 10 to 2621, with a median of 169. Only six Latin American countries were represented in the published literature: Argentina, Brazil, Chile, Costa Rica, Cuba, and Mexico. The majority of the articles included city or local region (e.g., district, state) specific data. ER-GAS prevalence from four of the articles were presented as composite rates from multiple regions of a single country (Argentina, Brazil, or Mexico) and one article presented an aggregate rate for Latin America as a whole based on isolates collected from Argentina, Brazil, and Mexico [[29-33](#_ENREF_29)]. Notably, there was only one study each from Costa Rica and Cuba, and both included a small number GAS of isolates: 10 and 40, respectively [[34](#_ENREF_34), [35](#_ENREF_35)]. The Costa Rican study was a pilot to demonstrate the broader need for antibiotic surveillance of GAS in the country. Of the 10 GAS isolates, 7 (70 percent) were erythromycin resistant [[34](#_ENREF_34)]. However, the small sample size and the collection methods used may account for this very high rate, especially as only people who had recently been treated with erythromycin were eligible to participate.

Among the three Latin American countries with the most data points, some trends emerge. In Argentina, ER-GAS rates range from 0 to 12.0 percent. The lowest rates were reported in Bariloche in 2001 and Buenos Aires from 2002 to 2006, and the highest rates occurred in Cipolletti and Neuquén in 1998 and Esquel in 2001 [[36-39](#_ENREF_36)]. Reported ER-GAS rates in Brazil ranged from 1.6 to 5.5 percent, with the low occurring in Rio de Janeiro from 1994 to 1999 and the high reported from multiregional data from 1999 to 2000 [[29](#_ENREF_29), [32](#_ENREF_32), [40](#_ENREF_40)]. In Curitiba, Brazil, one study found that ER-GAS prevalence increased from 1.9 percent during 1993 to 1999 to 4.0 percent during 2000 to 2009 [[41](#_ENREF_41)]. Reported ER-GAS rates in Chile all came from data from Santiago and ranged from a low of 0.7 in 1999 to a high of 9.8 percent in 1997 [[42](#_ENREF_42)].

Among the Latin American articles, 6 collected specimen from non-sterile sites and 9 collected specimen from sterile and non-sterile sites. No studies collected specimen from normally sterile sites only. Among the articles that reported participant age, six included adults and children (age 0 to 18 years), one included only adults, and four included only children.

Two of the studies from Mexico were scarlet fever outbreak investigations, with both outbreaks taking place in Mexico City. One of the outbreaks occurred from December 1999 to January 2000 and isolates were collected from patients age 3 to 17 years. Of the 47 GAS isolates collected, 6 of them (12.7 percent) were resistant to erythromycin [[43](#_ENREF_43)]. The other outbreak occurred in a daycare center in March 2000, among children aged 40 to 46 months. Isolates from nine of the children were found to be GAS, and all of them (100 percent) were resistant to erythromycin [[44](#_ENREF_44)]. This is in contrast with ER-GAS rates from multiple regions of Mexico during the same time period (1999 to 2000), at 11.1 percent [[29](#_ENREF_29), [32](#_ENREF_32)].

**Table 1:** Prevalence of ER-GAS in Latin America, 1990-2009

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country** | **Region** | **Year(s)** | **ERY Resistance** | **Source** |
| **%** | **Resistant/Total** |
| Argentina | Bariloche | 2000-2003 | 2.4 | 26/1068 | [[37](#_ENREF_37)] |
| 2003 | 5.0 | 20/398 | [[37](#_ENREF_37)] |
| 2002 | 1.8 | 5/278 | [[37](#_ENREF_37)] |
| 2001 | 0.0 | 0/223 | [[37](#_ENREF_37)] |
| 2000 | 0.6 | 1/169 | [[37](#_ENREF_37)] |
| 2000-2001 | 0.5 | 2/395 | [[36](#_ENREF_36)] |
| Buenos Aires | 2002-2006 | 0.0 | 0/152 | [[39](#_ENREF_39)] |
| 1998-2001 | 7.0 | 183/2621 | [[36](#_ENREF_36)] |
| Cipolletti | 1999-2001 | 4.2 | 1/24 | [[36](#_ENREF_36)] |
| Cipolletti & Neuquén | 1998 | 12.0 | 30/251 | [[38](#_ENREF_38)] |
| Córdoba | 1999-2001 | 4.3 | 2/47 | [[36](#_ENREF_36)] |
| Esquel | 2001 | 12.0 | 10/83 | [[36](#_ENREF_36)] |
| Mendoza | 1999-2001 | 5.5 | 30/544 | [[36](#_ENREF_36)] |
| Multiple regions | 1999-2000 | 12.1 | 4/33 | [[32](#_ENREF_32)], [[29](#_ENREF_29)] |
| 1994 | 0.2 | 4/1767 | [[31](#_ENREF_31)] |
| Neuquén | 2000-2001 | 8.2 | 8/98 | [[36](#_ENREF_36)] |
| Brazil | Curitiba | 1993-2009 | 2.6 | 29/1112 | [[41](#_ENREF_41)] |
| 2000-2009 | 4.0 | 15/373 | [[41](#_ENREF_41)] |
| 1993-1999 | 1.9 | 14/739 | [[41](#_ENREF_41)] |
| Multiple regions | 1999-2000 | 5.5 | 8/145 | [[32](#_ENREF_32)], [[29](#_ENREF_29)] |
| Rio de Janeiro | 1994-1999 | 1.6 | 6/357 | [[40](#_ENREF_40)] |
| Chile | Santiago | 1996-2005 | 3.5 | 45/1282 | [[42](#_ENREF_42)] |
| 2005 | 5.0 | 7/141 | [[42](#_ENREF_42)] |
| 2004 | 1.2 | 2/161 | [[42](#_ENREF_42)] |
| 2003 | 3.4 | 8/236 | [[42](#_ENREF_42)] |
| 2002 | 1.4 | 3/203 | [[42](#_ENREF_42)] |
| 2001 | 4.8 | 7/146 | [[42](#_ENREF_42)] |
| 2000 | 5.5 | 6/109 | [[42](#_ENREF_42)] |
| 1999 | 0.7 | 1/144 | [[42](#_ENREF_42)] |
| 1998 | 6.7 | 4/60 | [[42](#_ENREF_42)] |
| 1997 | 9.8 | 6/61 | [[42](#_ENREF_42)] |
| 1996 | 4.7 | 1/21 | [[42](#_ENREF_42)] |
| 1996-1998 | 7.8 | 12/153 | [[45](#_ENREF_45)] |
| 1990-1998 | 5.4 | 32/594 | [[46](#_ENREF_46)] |
| Cuba | Villa Clara | 2001 | 0.0 | 0/40 | [[35](#_ENREF_35)] |
| Mexico | Mexico City | 1992-1998 | 16.0 | 16/100 | [[47](#_ENREF_47)] |
| Multiple regions | 1999-2009 | 4.9 | 23/467 | [[33](#_ENREF_33)] |
| 1999-2000 | 11.1 | 11/99 | [[32](#_ENREF_32)], [[29](#_ENREF_29)] |
| Argentina, Brazil, Mexico | Multiple regions | 1999-2000 | 8.7 | 24/277 | [[32](#_ENREF_32)], [[29](#_ENREF_29)] |
| 1997-2000 | 2.7 | - | [[30](#_ENREF_30)] |

## 4.2 ERYTHROMYCIN RESISTANCE IN THE UNITED STATES

Data from the selected studies from the U.S. are summarized in Table 2. The studies from the U.S. generally sampled a larger number of isolates (range: 36 to 4508, median: 566)than studies from Latin America (range: 10 to 2621, median: 169). Nine of the studies provided countrywide (multiregional) data, two provided regional (e.g. north-east, south-west) data, and seven provided local data (i.e. from a city or other geographical area smaller than a state). The age of the data ranged from 1993 to 2010, but the majority of the data was collected from 1999 to 2003. Percent of GAS isolates collected that were erythromycin resistant range from 2.0 to 11.1 percent (median 5.2 percent) in the countrywide studies, with the two lowest rates (2.0 and 2.6 percent) occurring between 1993 and 1997. Among the local data, ER-GAS was found to be as high as 48.0 percent among a group of school-age children in Pittsburgh in 2000 to 2001 [[48](#_ENREF_48)].

Among the U.S. articles, two studies collected specimen from normally sterile sites, seven collected specimen from non-sterile sites, and five collected specimen from sterile and non-sterile sites. Among the articles that reported participant age, four included adults and children (age 0 to 18 years), and five included only children. None of the articles from the U.S. were outbreak investigations.

**Table 2:** Prevalence of ER-GAS in the United States, 1993-2010

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country** | **Region** | **Year(s)** | **ERY Resistance** | **Source** |
| **%** | **Resistant/Total** |
| United States | Boston, Massachusetts  | 2002 | 7.7 | 15/196 | [[49](#_ENREF_49)] |
| Greenville, South Carolina | 2002-2003 | 11.0 | 12/106 | [[50](#_ENREF_50)] |
| New York City | 2001 | 25.2 | 41/163 | [[51](#_ENREF_51)] |
| Northern Utah | 2007-2008 | 2.4 | 18/739 | [[52](#_ENREF_52)] |
| Pittsburgh, Pennsylvania | 2001-2002 | 9.6 | 68/708 | [[53](#_ENREF_53)] |
| 2001 | 38.0 | 38/100 | [[48](#_ENREF_48)] |
| 2000-2001 | 48.0 | 153/318 | [[48](#_ENREF_48)] |
| 1998-2000 | 0.0 | 0/322 | [[48](#_ENREF_48)] |
| San Francisco bay area  | 1994-1995 | 12.7 | 39/306 | [[1](#_ENREF_1)] |
| North-central | 2001-2002 | 5.9 | 58/991 | [[54](#_ENREF_54)] |
| 2000-2001 | 5.3 | 48/903 | [[55](#_ENREF_55)] |
| North-east | 2001-2002 | 5.9 | 85/1444 | [[54](#_ENREF_54)] |
| 2000-2001 | 6.1 | 84/1376 | [[55](#_ENREF_55)] |
| North-west | 2001-2002 | 6.5 | 15/230 | [[54](#_ENREF_54)] |
| 2000-2001 | 8.2 | 15/184 | [[55](#_ENREF_55)] |
| South-central | 2001-2002 | 7.0 | 43/617 | [[54](#_ENREF_54)] |
| 2000-2001 | 5.4 | 28/521 | [[55](#_ENREF_55)] |
| South-east | 2001-2002 | 5.6 | 34/610 | [[54](#_ENREF_54)] |
| 2000-2001 | 4.4 | 19/433 | [[55](#_ENREF_55)] |
| South-west | 2001-2002 | 3.7 | 23/616 | [[54](#_ENREF_54)] |
| 2000-2001 | 3.8 | 19/501 | [[55](#_ENREF_55)] |
| Multiple regions | 2002-2003 | 6.1 | 171/2797 | [[56](#_ENREF_56)] |
| 2002-2003 | 6.8 | 128/1885 | [[57](#_ENREF_57)] |
| 2002-2003 | 3.8 | 40/1057 | [[58](#_ENREF_58)] |
| 2001-2002 | 5.7 | 257/4508 | [[54](#_ENREF_54)] |
| 2001-2002 | 4.3 | 40/939 | [[58](#_ENREF_58)] |
| 2001 | 11.1 | 4/36 | [[59](#_ENREF_59)] |
| 2000-2003 | 4.1 | 120/2937 | [[58](#_ENREF_58)] |
| 2000-2001 | 5.5 | 215/3918 | [[55](#_ENREF_55)] |
| 2000-2001 | 4.4 | 40/900 | [[58](#_ENREF_58)] |
| 1999-2010 | 5.2 | 9/174 | [[33](#_ENREF_33)] |
| 1999-2000 | 5.2 | 9/174 | [[60](#_ENREF_60)] |
| 1994-1997 | 2.6 | 8/301 | [[61](#_ENREF_61)] |
| 1993-1994 | 2.0 | 6/333 | [[62](#_ENREF_62)] |

# 5.0 DISCUSSION

The goal of this literature review was to explore rates of ER-GAS in Latin America and the U.S From this review, significant limitations and gaps in the literature were identified. This literature review demonstrates the major challenges to constructing evidence-based GAS antibiotic treatment guidelines for Latin American immigrants to the U.S. based upon the current published literature without supplementary surveillance data from other sources.

## 5.1 LIMITATIONS OF THE PUBLISHED LITERATURE

One major limitation to the current body of published literature is the lack sufficient data coverage (i.e. number of data points over geographical location and time) for reliable and consistent analysis. ER-GAS prevalence data was only available for six Latin American countries and was limited even for these areas. Localities within countries were not uniformly sampled, which left some regions completely unsampled. The most notable example was Chile, for which ER-GAS data was only available for the Santiago metropolitan area. Furthermore, the countries with the most data available, Argentina, Brazil, and Chile, are not reflective of the countries from which the majority of Latin American immigrants to the U.S. originate. As of 2010, 55 percent of Latin American immigrants were from Mexico, and an additional 18 percent were from the Caribbean **[**[**2**](#_ENREF_2)**].** Although geographical coverage was better in the U.S., ER-GAS rates by city were inconsistent and statewide data was completely unavailable. Although regional data for Latin America spanned over two decades, from 1990 to 2009, countrywide and local data generally did not have this breadth. In the U.S., the same is true for state and local areas. When location and time are examined together, there are very few points that overlap to observe trends and inconsistencies in the data.

Gaps in the literature become even more pronounced when factoring for differences in methodology that could potentially mediate or moderate ER-GAS rates. Variables include age of the study participants, whether isolates were collected from sterile or non-sterile sites, and whether carriage rates for asymptomatic individuals were observed. Information on these variables was unavailable for many of the studies. Among the studies that did include this information, there was significant diversity. A majority of the research observed ER-GAS among adults and children, in varying ratios and with diverse median participant age. Studies differed in whether isolates were drawn from sterile sites, non-sterile sites, or some combination, which ranged from mostly (85 percent) sterile to mostly (92.5 percent) non-sterile [[33](#_ENREF_33), [54](#_ENREF_54)]. Even when not accounting for methodology differences, there was insufficient data to reliably observe trends or inconsistencies. If these variables are considered, no two studies examined in this review are strictly comparable.

Limitations of the published literature in terms of data coverage may arise from factors related to the research process. Pharmaceutical companies fund a significant number of bacterial resistance studies. Increased interest in research on bacterial resistance rates may explain the sharp increase in studies on this topic centered in the late 1990’s and early 2000’s. A new family of antibiotics, the ketolides, was developed in 1998, which prompted the worldwide Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) surveillance study. Once telithromycin, the new ketolide, was approved for use in Europe in 2001 and the U.S. in 2004, the number of studies on ER-GAS decreased. The inconsistent nature of funding for antibiotic resistance research may limit the potential that the published literature has for monitoring of ER-GAS prevalence. An additional limitation is the lag time between original research and publication date. On average, articles included ER-GAS rates for samples drawn two to three years prior to publication. Because the evidence gathered in this review suggests that ER-GAS prevalence may fluctuate more rapidly than this lag time, creating an evidence-base for antibiotic treatment guidelines using data from published studies may not be feasible.

## 5.2 RECOMMENDATIONS FOR IMPROVED SURVEILLANCE

Surveillance outside of published research, through inter-hospital exchange of information or the strengthening of existing surveillance networks, could provide more reliable and up-to-date prevalence estimates. Several studies found in this review suggest that individual hospitals already maintain ER-GAS surveillance efforts. However, the number of hospitals that conduct ER-GAS surveillance and the degree to which inter-hospital data exchange already occurs regionally, nationally, and internationally is unknown. Monitoring of ER-GAS in this way would result in prevalence data that was geographically specific, as it would be linked to the hospital service area. This method would also benefit from the relatively low cost associated with passive surveillance. Challenges to creating hospital networks for resistance monitoring may include communication, quality control, and added burden on health care practitioners. Surveillance through hospitals would also not be able to capture ER-GAS carriage rates among asymptomatic individuals.

Some existing surveillance networks, such as TSN and the ABC surveillance system in the U.S. and the PAHO-supported *Red de Vigilancia de la Resistencia a los Antibióticos* in Latin America, already collect data on ER-GAS prevalence. The ABC surveillance system currently tracks resistance patterns only among invasive GAS isolates. As non-invasive GAS is more prevalent in the U.S., the cost and benefits of the incorporation of monitoring non-invasive GAS isolates should be examined. Activities to strengthen the impact of these networks on clinical and public health practice would include increased dissemination of results to hospitals and through periodically published reports.

Surveillance networks could potentially provide better data coverage and comparability than research studies. A network can operate indefinitely once established, provided that funding is maintained, whereas studies have defined start and end dates, increasing the likelihood of coverage gaps. Efforts to control variables such as participant age and invasive versus non-invasive samples should be easier among several surveillance networks, which have the ability to institutionalize guidelines for GAS sample collection, than across a much larger number of research teams, working in various settings across the U.S. and Latin America. Electronic surveillance networks would also benefit from having minimal to no lag time between data collection and data dissemination.

## 5.3 RECOMMENDATIONS FOR FUTURE RESEARCH

Because erythromycin resistance among GAS fluctuates considerably over time and geography, the published literature can only offer a glimpse into resistance trends. Although surveillance networks may provide more consistent and reliable monitoring of ER-GAS prevalence, there is still an important role for research on the topic. Studies analyzing the ER-GAS prevalence of Latin American immigrants and their communities in the U.S. could potentially provide a better basis for evidence-based clinical care within this steadily increasing U.S. population. Latin American populations in the U.S. can vary significantly in a number of community level factors that may influence guidelines for antibiotic therapy. These factors may limit the length of time after immigration for which ER-GAS prevalence in the country of origin is relevant, the degree of impact of this prevalence, or both.

For example, communities may differ in the homogeneity of the country and local region of origin of individuals. Among a heterogeneous population of immigrants, one might hypothesize that the ER-GAS rate in the place of origin of an individual would have less relevance than it would in a community in which everyone shared the same exposure to ER-GAS in their region of origin. Another factor that could influence antibiotic therapy guidelines is the relative amount of interactions individuals of an immigrant community have with members of the broader U.S. community. ER-GAS rates in the areas of origin of members of a community that is more closed off may have more impact for a longer period of time, as individuals would have less exposure to local American people and their bacteria. Other community factors that may impact ER-GAS prevalence among Latin American immigrant populations in the U.S. include income, education, and gender ratio, availability of primary care, health beliefs, and age of the population. ER-GAS prevalence among Latin American populations living in the U.S. may be better understood within local contexts if more research is conducted on how these factors influence rates of antibiotic nonsusceptibility.

ER-GAS rates are of special importance to individuals who are allergic to penicillin, for which the first-line treatment for GAS is erythromycin. Because of this, the prevalence of penicillin-allergy in a population is important for determining how highly ER-GAS surveillance should be prioritized. Research could estimate these allergy rates, which may differ among Latin American countries and the U.S., and therefore also among immigrant populations within the U.S.

## 5.4 RECOMMENDATIONS FOR PUBLIC HEALTH PRACTICE

Continued research and surveillance of ER-GAS and other strains of resistant pathogens are important for guiding public health best practices and policies to limit the spread of resistance and ensure the continued effectiveness of antibiotic therapy against infectious diseases. Infection with GAS results in substantial mortality and morbidity, along with economic costs, each year. Monitoring of ER-GAS is especially important for the unknown number of individuals who are allergic to penicillin. Furthermore, GAS exists in a context of other bacterial pathogens that are also influenced by the appropriate use of erythromycin and other antibiotics. The cost of susceptibility testing using basic methods, such as disk diffusion, should be small in comparison to the costs associated with the loss of life and reduced health outcomes due to continued antibiotic resistant pathogens.

Best public health practices should include consistent monitoring of ER-GAS in the U.S. and Latin America so that evidence-based guidelines for antibiotic therapy among immigrant populations living in the U.S. can be developed. Surveillance networks should be strengthened and allow healthcare providers access to ER-GAS data. Healthcare facilities should also incorporate antibiotic resistance monitoring into routine practice in order to determine local nonsusceptibility trends. This may involve a larger role for physicians, nurses, physician assistants, pharmacists, and other healthcare professionals in the monitoring and control of antibiotic resistance.

Clinical-based surveillance could be enacted through continuous quality improvement (CQI) programs, which have effectively controlled antibiotic use and stabilized antibiotic resistance in the past [63]. The plan, do, study, act (PDSA) model would compliment the CQI approach. PDSA acts as a cycle in which operational changes are defined in terms of specific objective, then data on key indicators is collected and analyzed to determine the success of the changes and whether modifications are needed, before the cycle restarts [64]. In terms of ER-GAS and other antibiotic resistant pathogens, primary measures may include prevalence of resistant strains, clinical outcomes, and expenditures, including cost of susceptibility testing. With CQI and PDSA, clinical practices, which may include continuing education programs for healthcare professionals in antibiotic nonsusceptibility of GAS and other common pathogens, could be evaluated, improved, and tailored to specific healthcare facilities.

**APPENDIX: LIST OF ACRONYMS**

ABC Active Bacterial Core

ARF Acute rheumatic fever

CDC Centers for Disease Control and Prevention

CLSI Clinical and Laboratory Standards Institute

CQI Continuous quality improvement

EBM Evidence-based medicine

EBPH Evidence-based public health

ER Erythromycin resistant

ERY Erythromycin

GAS Group A streptococcus

GBS Group B streptococcus

LILACS Literatura Latino Americana e do Caribe em Ciências da Saúde

MIC Minimum inhibitory concentration

MLSB Macrolide, lincosamide, and streptogramin B

PAHO Pan American Health Organization

PDSA Plan, do, study, act

PROTEKT Prospective Resistant Organism Tracking and Epidemiology for the Ketolide

 Telithromycin

RHD Rheumatic heart disease

STSS Streptococcal toxic shock syndrome

TSN The Surveillance Network

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