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NLM Citation: Efstratiou A, Lamagni T. Epidemiology of *Streptococcus pyogenes*. 2016 Feb 10 [Updated 2017 Apr 3]. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes* : Basic Biology to Clinical Manifestations [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016-.
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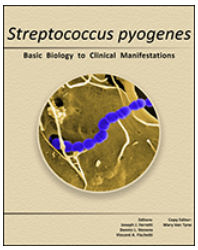

Epidemiology of *Streptococcus pyogenes*

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Created: February 10, 2016; Updated: April 3, 2017.

Introduction

While the incidence of many diseases has declined in developed countries, regions of the world with low income and poor infrastructure continue to suffer a high burden of *Streptococcus pyogenes* (group A streptococci) diseases with millions of deaths yearly (Carapetis, Steer, Mulholland, & Weber, 2005). The majority of these deaths follow the development of rheumatic heart disease (RHD), which remains a concern in both developed and developing countries. In more affluent countries, the prevalence of RHD is much lower; the majority of *S. pyogenes*-associated deaths are attributed to the clinical manifestations associated with invasive disease.

Our general understanding of the epidemiology of group A streptococci and their related diseases remains relatively poor in comparison to other infectious diseases. Many countries with established infectious disease surveillance programs undertake relatively little surveillance of diseases caused by *S. pyogenes* and other pyogenic streptococci. However, this has improved over the years with many countries establishing the presence of invasive group A streptococcal infections as a statutory notifiable disease. To fully understand the epidemiology of these diseases in terms of how they disseminate, the host and strain characteristics of importance to onward transmission, disease severity, and both inter- and intraspecies competition for ecological niches, researchers would need to undertake comprehensive investigations that follow a large cohort of individuals for a substantial period of time. Understanding these factors would also allow for the development of effective prevention strategies. The size and severity of the burden of *S. pyogenes* disease highlights the importance of epidemiologic surveillance to detect changes in disease distribution in various populations.

Since the early 1980s, there have been some remarkable changes in the worldwide epidemiology of group A streptococcal infections, particularly in the reporting of invasive group A streptococcal infections. Outbreaks of infection of both suppurative and non-suppurative *S. pyogenes* sequelae were frequently reported in the 1980s and 1990s (Efstratiou, 2000). The increase in the incidence of invasive *S. pyogenes* infections has frequently been associated with specific clones, which raises the possibility that the rise of particularly virulent clones was responsible for this re-emergence—in particular, the MT1 clone which is dominant among invasive *S. pyogenes*

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isolates in most developed countries (Luca-Harari, et al., 2009; O'Loughlin, et al., 2007). The incidence of invasive *S. pyogene*s infection varies by time and geographic region, which presumably reflects a population's susceptibility to particular strains, but also the natural variation in the predominant types (O'Brien, et al., 2002). Variation in the type distribution may also lead to fluctuations in the severity of infections and in overall mortality rates.

S. pyogenes infections may be observed in persons of any age, although the prevalence of infection is higher in children, presumably because of the combination of multiple exposures (in schools or nurseries, for example) and host immunity. The prevalence of pharyngeal infection is highest in children older than three years and has been described as a 'hazard' in school-aged children (Martin, Green, Barbadora, & Wald, 2004). Disease in neonates is uncommon, which may reflect a protective, transplacentally-acquired immunity.

For this chapter, we will focus upon the epidemiology of *S. pyogenes* infection, with emphasis on the novel molecular genomics approaches that are being applied to global epidemiology, as well as the prevention, control, and management of these devastating diseases.

Surveillance and statutory notifications

Surveillance of infectious diseases forms the bedrock of control and prevention, facilitating the identification of changes warranting investigation and implementation of control measures. Longer-term monitoring provides opportunities to assess the changes in disease burden and impact of control measures. Historical review of statutory notifications and death registrations from the UK illustrates the dramatic change in the epidemiology of *S. pyogenes* disease over the past century (Figure 1). Incidence and mortality remained high in the pre-antimicrobial (penicillin) era, although both started to fall prior to penicillin's widespread availability after the Second World War, which suggests that other host, pathogen, or environmental factors played a key role in diminishing the impact of these diseases. Modern-day surveillance programs tend to focus on invasive *S. pyogenes* disease, with legislation in place in many countries that requires statutory notification, in recognition of the importance of rapid public health action following the diagnosis of a single case (see Control and prevention). Laboratory-based surveillance systems are commonly adopted as a means to monitor invasive *S. pyogenes* infections. Surveillance case definitions vary by country but most identify cases with *S. pyogenes*-positive blood cultures, with or without inclusion of additional cases diagnosed through other sterile sites.

Surveillance systems and methods for common superficial *S. pyogenes* manifestations are more variable and sparse between countries. Primary care-based surveillance networks provide valuable means of quantifying and monitoring the burden of upper respiratory tract and skin or soft tissue infections. Although these clinical case definitions may lack specificity, they may provide sensitive measures for diseases that are not normally subject to microbiological investigation.

Epidemiology of invasive disease

Disease incidence

With the establishment of surveillance systems for invasive *S. pyogenes* infections in many developed countries, data are being accumulated to allow researchers to assess longitudinal patterns in disease incidence. While concerns about the escalation in invasive disease have been widespread since the 1980s, evidence from surveillance systems to substantiate these claims is more elusive. (Steer, Lamagni, Curtis, & Carapetis, 2012a). Recent surveillance data from Utah do point to worrying trends of sustained increase in disease incidence, with rates rising to reach a surprising 9.8 per 100,000 population in 2010 (Stockmann, et al., 2012). Short-lived periods of intensification of disease incidence have been reported in many countries (Steer, Lamagni, Curtis, & Carapetis, 2012a). These may represent natural cycles driven by an accumulation of susceptible individuals as result of waning immunity and an influx of unexposed birth cohorts. Historical time series document such

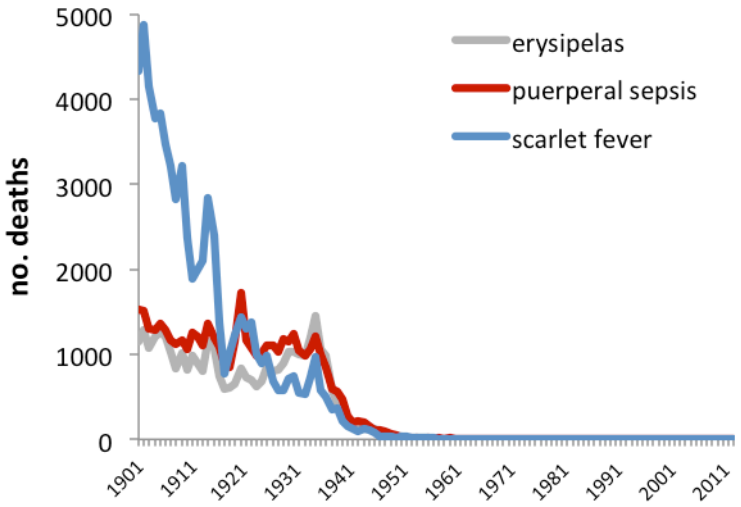

Figure 1: Certified deaths attributed to erysipelas, puerperal sepsis and scarlet fever, England and Wales, 1901-2012

epidemic cycles for scarlet fever and other formerly severe *S. pyogenes* manifestations (Figure 1). The introduction of novel strains within a population has long been demonstrated as a cause of upsurge in *S. pyogenes* disease incidence, and the advancement of whole genome sequencing is beginning to provide evidence for this phenomenon (Al-Shahib, et al., 2014; Beres, et al., 2004; Tyrrell, et al., 2010; Turner, et al., 2015). Periodic upsurges may also be the result of intensified transmission within specific risk groups: for example, increases in the incidence of *S. pyogenes* disease may follow the introduction of unfamiliar strains within drug-injecting communities (Lamagni, et al., 2008c; Sierra, et al., 2006), or may occur during an influenza epidemic (Zakikhany, et al., 2011).

The dynamic nature of *S. pyogenes* infection notwithstanding, contemporary data suggest an invasive *S. pyogenes* infections incidence of around 2 to 4 per 100,000 population in developed countries (Steer, Lamagni, Curtis, & Carapetis, 2012a). Considerably higher rates are observed in developing countries and within indigenous populations in developed countries, such as the USA and Australia, which range from 12 to 83/100,000 (see the below section on Demographic risk factors).

Seasonal patterns of disease

A distinct seasonal pattern of invasive *S. pyogenes* disease incidence can be noted in many temperate climates within Europe and North America (Lamagni, et al., 2008a; Lamagni, et al., 2009b). While cases occur throughout the year in these countries, disease incidence is typically lowest in the autumn and then steadily rises towards its peak incidence in December through to April (Figure 2). The drivers for this seasonal pattern remain unexplained to date, and may reflect an interplay between climatic factors, behavioral patterns, and the incidence of predisposing viral infections (Lamagni, et al., 2008a; Lamagni, et al., 2009b; Zakikhany, et al., 2011).

Demographic risk factors

Numerous epidemiological studies have identified high rates of invasive *S. pyogenes* infection in men rather than women, a pattern that can be observed for many other invasive bacterial infections and one that is not fully understood. Age-specific incidence rates show a typical J-shaped distribution, with highest rates in the elderly, followed by infants. Assessment of rates of disease according to patient ethnicity show generally higher rates of disease in individuals of non-white European descent. These observations have been made in a diverse range of populations, including indigenous populations of Australia, New Zealand, the Pacific Islands, and circumpolar regions of the northern hemisphere. The reasons behind these excesses in risk are poorly understood and could

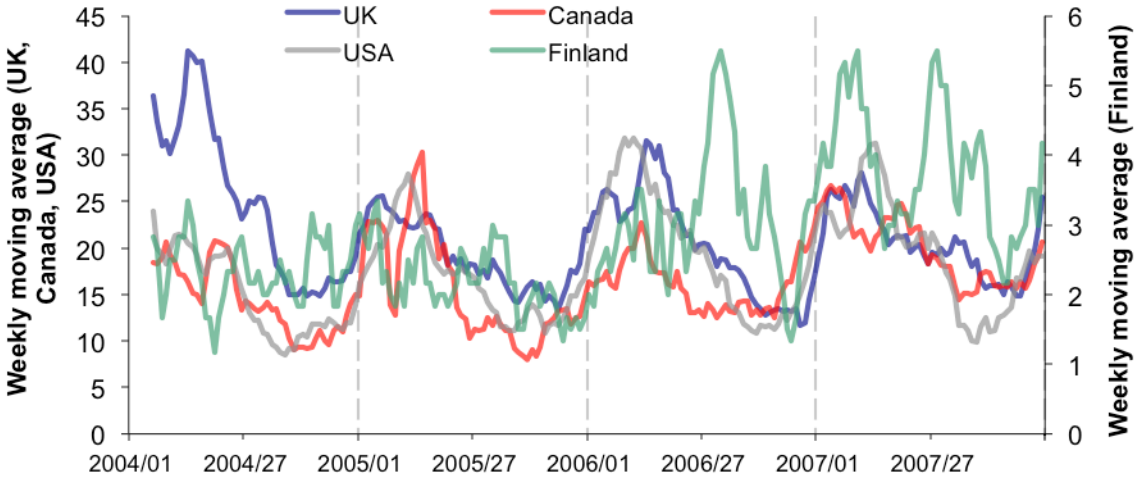

Figure 2: Seasonal patterns of invasive *S. pyogenes* infection by country (six-week moving averages) (Lamagni, et al., 2009b)

reflect differential access to healthcare or general living conditions—but could also encompass some genetic predisposing factors. Future studies will assist in identifying potential strategies to mitigate this risk.

Acute and chronic risk factors

While numerous observational studies have described the frequencies of potential risk or predisposing factors in patients with invasive *S. pyogenes* disease, rigorous assessment through analytical means has been rather more limited. Nonetheless, some commonalities are found across studies (Table 1). The relative importance of these factors may change over time as the prevalence of the acute or chronic predisposing factors changes in frequency, such as influenza activity (Zakikhany, et al., 2011). As a result, continuous monitoring or periodic reassessment is essential as a means to recognize secular trends.

A key epidemiological feature of invasive *S. pyogenes* disease is its occurrence in individuals with no identified risk factors or predisposing conditions, which occurs in around 20-30% of all invasive *S. pyogenes* cases (Lamagni, et al., 2008a; O'Loughlin, et al., 2007). This proportion is higher in children with invasive disease, with estimates of 50–80% of pediatric cases having no identified risk factors (Lamagni, et al., 2008b; O'Loughlin, et al., 2007).

Of cases with identified acute or chronic risk factors, skin lesions, including traumatic, surgical, or chronic, are the most common risk factors identified, as they provide a portal of entry for the *Streptococcus* bacterium. These are typically reported in 17-25% of all cases (Lamagni, et al., 2008a). Blunt trauma predisposing to necrotizing fasciitis has been reported in many cases (Lamb, Sriskandan, & Tan, 2015). Acute viral respiratory infections, and influenza in particular (Morens, Taubenberger, & Fauci, 2008), are recognized risk factors for invasive *S. pyogenes* infection, with secondary infections generally occurring within one week of influenza diagnosis (Zakikhany, et al., 2011). The relative importance of influenza as a risk factor for invasive *S. pyogenes* infection will therefore be highly dependent on the levels of circulating influenza and the populations affected.

Among children, recent varicella infection is a common risk factor that can be identified in 14%–16% of pediatric invasive *S. pyogenes* cases in the absence of universal varicella vaccination programs (Lamagni, et al., 2008b; Laupland, Davies, Low, Schwartz, Green, & McGeer, 2000; Patel, Binns, & Shulman, 2004). The invasive presentations among cases with chicken pox are varied, although they most commonly manifest as severe soft tissue infections, including necrotizing fasciitis. The interval between chicken pox onset and *S. pyogenes* infection is typically around 4–5 days after the onset of chicken pox, but can occur up to 12 days later (Laupland,

et al., 2000). Estimates during the two weeks after varicella onset suggest between a 40- and 60-fold elevation in the risk of invasive *S. pyogenes* infection during this period. While this excess risk may relate directly to inoculation of pox lesions with *S. pyogenes*, the varied range of focal and non-focal presentations suggests that additional factors, such as immunosuppression, play a role (Laupland, et al., 2000).

A number of co-morbidities have been associated with an excess risk of invasive *S. pyogenes* infection, of which heart disease, diabetes, and malignancy have more robust supporting evidence (Table 1). Controversy remains over the potential role of non-steroidal anti-inflammatory drugs in elevating the risk of invasive *S. pyogenes* disease. While several studies have reported an association with necrotizing fasciitis and streptococcal toxic shock syndrome, these may not reflect a causal relationship; other confounding factors may have an influence, such as delays in seeking and receiving appropriate treatment or self-medication of severe pain associated with necrotizing fasciitis. Further studies are needed to explore this potentially important factor (Factor, et al., 2005; Lamagni, et al., 2008b; Zerr, Alexander, Duchin, Koutsky, & Rubens, 1999).

Table 1: Documented risk and predisposing factors associated with invasive *S. pyogenes* infection

Demographic factors		
	Age (infants & elderly)	**Ethnicity** ~
	Male sex	**African American**
		Bedouin population
		Canadian Arctic aboriginal
		East African
		Jewish
		Native American
		Native Alaskan
		Indigenous Australian
		Pacific Islanders
Underlying conditions		
	Alcoholism	**Injecting drug use**
	Benign tumour	Liver disease
	Chronic respiratory conditions	**Malignancy**
	Chronic & traumatic skin lesions	Metabolic disorders
	Congenital abnormalities	**Non steroidal anti-inflammatory drug use**
	Diabetes	Neurological & psychological disorder
	Endocrine disorders	Obesity
	Epilepsy	**Pregnancy & childbirth**
	Gastrointestinal disorders	Prematurity
	Glaucoma	Renal diseases
	Heart disease	Rheumatoid arthritis & polymyalgia rheumatica
	Hypertension	**Smoking**
	Immunosuppression (non-HIV related)	**Steroid use**
		Trisomy
		Vascular disease

Table 1 continued from previous page.

Demographic factors		
Antecedent /concurrent infection		
	Epstein-Barr virus	Pneumonia
	Herpes zoster	Rotavirus
	HIV	Scabies
	Influenza	**Varicella (children)**
Living conditions & socioeconomic factors	**Co-habitation with a child High number of household members**	**Low number of rooms in household** Living in unhygienic conditions
	Hypothermia	**Malnutrition (children)**
Ecological factors		
Winter onset		

* bold font indicates excess risk demonstrated through analytical epidemiological studies comparing incidence to normative population data or control group
~ compared to populations of white European decent

Pregnancy and the puerperium

Many of the factors identified to confer an excess risk of invasive *S. pyogenes* infection also serve to elevate the risk of susceptibility to a number of infectious diseases. Two are more specific to *S. pyogenes* infection: varicella (as described above) and pregnancy and childbirth. The latter has long been recognized as a risk factor for severe sepsis, but has perhaps been under-considered in modern times. While the incidence of puerperal sepsis and associated mortality has dramatically fallen over the course of the last century (Figure 1), pregnancy and the puerperium remain periods of considerable risk.

Maternal invasive *S. pyogenes* infections are particularly associated with late pregnancy (beyond 30 weeks gestation) and four weeks post-delivery (Lamagni, et al., 2011; Yamada, et al., 2010). Although the number and relative proportion of invasive *S. pyogenes* infections associated with late pregnancy or recent childbirth is low, typically 2–4% of all invasive *S. pyogenes* infections, this represents a substantial elevation in risk during a relatively short period, and which is estimated at 20–100 fold higher than in age-sex matched controls (Deutscher, et al., 2011; Chuang, Van Beneden, Beall, & Schuchat, 2002; Lamagni, et al., 2008b; Lamagni, et al., 2011). Of note is the range of focal and non-focal clinical manifestations of *S. pyogenes* disease in these women, including pneumonia, septic arthritis, necrotizing fasciitis, and genital tract sepsis (Chuang, Van Beneden, Beall, & Schuchat, 2002; Lamagni, et al., 2011; Sriskandan, 2011). The source of these infections is poorly understood, but seminal work undertaken at Queen Charlotte's hospital in London during the 1930s suggested that the woman's genital tract is an uncommon source, with either her throat or that of a close contact (family member or healthcare staff) a more common source for the infection (Colebrook, 1935). This correlates with vaginal carriage studies that indicate very low *S. pyogenes* carriage rates (<1%) (Hassan, et al., 2011; Mead & Winn, 2000). The reasons for the excess risk during the puerperium are not well understood, but may relate to immunological changes during pregnancy, coupled with specific characteristics of the organism (Mason & Aronoff, 2012). (See the section on Trends in *emm* type prevalence and disease associations).

While other organisms play an important etiological role in maternal sepsis (Acosta, et al., 2014; Maternal, Newborn and Infant Clinical Outcome Review Programme, 2014), outcomes can be especially severe for *S. pyogenes* maternal sepsis, with case fatality rates of around 2% are reported for the USA and UK (Deutscher, et al., 2011; Lamagni, et al., 2009a). In developing countries, between 8 and 12% of all maternal deaths can be attributed to sepsis, and while the full role of *S. pyogenes* in this considerable global burden is not well

understood, it is likely to be significant (Khan, Wojdyla, Say, Gülmezoglu, & Van Look, 2006). Of note is the onward risk of invasive disease to neonates born to mothers who developed *S. pyogenes* infection (see Control and Prevention) and the poor outcomes for many of these infants (Hamilton, Stevens, & Bryant, 2013; Lamagni, Oliver, & Stuart, 2015; Mahieu, Holm, Goossens, & Van Acker, 1995; Miyairi, Berlingeri, Protic, & Belko, 2004).

Epidemiology of superficial disease

The main focus of epidemiologic research on *S. pyogenes* infections has been and still is invasive *S. pyogenes* disease, RHD, and toxin-mediated diseases. Our understanding of the epidemiology of less severe (but still extremely common) superficial infections is limited, despite the substantial burden presented by these diseases, especially streptococcal pharyngitis and tonsillitis. This can and does predispose sufferers to other more serious infections, such as scarlet fever and invasive *S. pyogenes* infections. Such superficial diseases still represent a significant burden on healthcare providers, and are also a constant reservoir for deep-seated infections.

Epidemiology of pharyngitis

According to the Royal College of Physicians, "Pharyngitis is one of the most common reasons for patients to consult with their general practitioner. Acute tonsillitis and pharyngitis account for over 800 consultations per 10,000 patients annually, in addition to the economic impact of days missed from school or work" (European Medical Alliance, 2015).

Pharyngitis is diagnosed in approximately 11 million people in the United States each year. Although most cases are viral, *S. pyogenes* is the cause in 15–30% of the pharyngitis cases in children and 5–20% in adults. Cases usually occur in late winter and early spring (Choby, 2009). In Australia, the incidence of acute sore throat among school-aged children with culture-positive *S. pyogenes* has been estimated at 13 per 100 person-years with one in four of all children with acute sore throat having serologically confirmed *S. pyogenes* pharyngitis (Danchin, et al., 2007). In addition, 43% of families with an index case of *S. pyogenes* pharyngitis have a secondary case. Again, late winter and early spring are peak *S. pyogenes* seasons (Danchin, et al., 2007). It is also estimated that 15% of school-age children in developed countries will develop a symptomatic case of *S. pyogenes* pharyngitis each year, whereas the incidence of *S. pyogenes* pharyngitis in less developed countries may be five to ten times that number (Carapetis, Steer, Mulholland, & Weber, 2005).

Epidemiology of scarlet fever

Disease incidence

While the incidence of scarlet fever has dramatically fallen over the last century, there has been a resurgence in interest in studying scarlet fever after recent reports of increased incidence and large-scale outbreaks. While scarlet fever is no longer generally the life-threatening condition that it once was (Figure 1), scarlet fever outbreaks can spread rapidly and cause considerable public alarm. Notification data provide a means of monitoring disease in some countries, along with primary care surveillance networks. Rates of infection in the UK have been around 4 per 100,000 population prior to recent events, which is similar to rates in Hong Kong (Guy, et al., 2014; Luk, et al., 2012).

An upsurge in scarlet fever was reported in Vietnam in 2009 with a 40% increase in disease incidence (ProMED-Mail, 2009). Two years later, this was followed by reports of remarkable increases in disease incidence in Hong Kong and mainland China between 2011 and 2012. (ProMED-Mail, 2009; ProMED-Mail, 2012; ProMED-Mail, 2011). Scarlet fever rates in Hong Kong reached 24/100,000 population in 2011, a nine-fold increase over recent years (Luk, et al., 2012). During 2014, the UK became the latest country to report on remarkable increases in scarlet fever, as it reached its highest rate of incidence since the 1960s. Elevations in disease incidence were reported across the entire UK, with rates reaching 49 per 100,000 in some parts of the country (Guy, et al., 2014).

Investigations in each country have failed to fully explain why these phenomena have occurred. As with all re-emerging infections, campaigns to re-educate clinicians on signs and symptoms to look out for are important, as well as optimal management of the disease. Continued vigilance will remain essential to monitor disease incidence in these countries and to assess changes in countries that have yet to be affected.

Risk factors

Scarlet fever incidence follows a similar seasonal pattern to invasive disease, with the highest incidence of cases and outbreaks occurring in the spring (Briko, et al., 2003; Guy, et al., 2014). Children under 10 years of age are primarily affected, although children and adults of all ages are susceptible to infection. Residential institutions for children are settings with particularly heightened transmission (Briko, et al., 2003).

Epidemiology of rheumatic fever, rheumatic heart disease, and other sequelae

Acute rheumatic fever is an inflammatory response to *S. pyogenes* infection that typically occurs two to three weeks after a throat infection. Worldwide, approximately 500,000 new cases occur annually, and at least 15 million people have chronic rheumatic heart disease (Carapetis, Steer, Mulholland, & Weber, 2005; Webb, Grant, & Harnden, 2015). Reviews of population based data have estimated that approximately 336,000 cases of acute rheumatic fever (ARF) occur yearly in children aged 5–14 years, Additionally, ARF was at one time the leading cause of death in children in some parts of the world (Bland, 1987). More than 471,000 cases of ARF occur in all age groups (Carapetis, Steer, Mulholland, & Weber, 2005). Populations that are affected by ARF and RHD are most frequently found in developing countries in impoverished settings that do not have adequate medical or health infrastructure. Data collection is not often possible in those countries and as a result, the incidence of RF and RHD is likely to be underestimated.

The highest incidence of RF and RHD reported globally is among Pacific populations, the New Zealand Maori (Jaine, Baker, & Venugopal, 2008). The majority of cases occur in low socioeconomic communities in the northern and central North Island and pockets around Wellington, the capital city (BPAC NZ, 2011) Maori children are about 20 times more likely to be hospitalized for rheumatic fever, and Pacific children are about 40 times more likely to be hospitalized for rheumatic fever than non-Maori/non-Pacific children—a result which has been attributed to *S. pyogenes* pharyngitis that goes untreated among Maori and Pacific people (Ministry of Health – Manatū Hauora, 2015). Rheumatic fever can be prevented by prompt diagnosis of an *S. pyogenes* throat infection and treatment with antibiotics. The New Zealand Ministry of Health's Rheumatic Fever Prevention Programme (RFPP) was established in 2011 to improve access to timely treatment for *S. pyogenes* throat infections among its at-risk communities; to increase awareness of rheumatic fever; and to reduce household crowding and therefore reduce the household transmission of *S. pyogenes* throat bacteria (Ministry of Health – Manatū Hauora, 2015).

A systematic review of ten population-studies was documented from 1967 to 1996 and described the mean global incidence of ARF at 19 per 100,000 (Tibazarwa, Volmink, & Mayosi, 2008). The highest reported annual incidence rate was 51 per 100,000, which came from a study conducted in India. The lowest incidence rates were found in America and Western Europe, while higher rates were found in Eastern Europe, Asia, Australasia, and the Middle East. Information from the Africa Region was unavailable although it is known that African nations have a high incidence of RHD (Carapetis, Steer, Mulholland, & Weber, 2005).

ARF occurs even within populations at high socioeconomic levels within industrialized countries (Veasy, Tani, & Hill, 1994). In the United States, the incidence of ARF is generally lower than that in developing countries, which reports an incidence that ranges from 2–14 per 100,000 (Bland, 1987; Carapetis, Steer, Mulholland, & Weber, 2005). The higher estimates are probably due to regional outbreaks documented in certain US regions, including Tennessee, Ohio, and Pennsylvania. These outbreaks have caused considerable concern: in particular, an

outbreak in Salt Lake City, Utah in the 1980s occurred where the incidence of ARF among children aged 3–17 years approached 12 per 100,000 (Veasy, Tani, & Hill, 1994).

The overall decline in ARF outbreaks is believed to be due to improvements in aspects of primary prevention, including access to healthcare and use of antibiotics. It has also been hypothesized that evolving differences in the streptococcal M protein type plays a major role in the number of diminishing cases (Shulman, Stollerman, Beall, Dale, & Tanz, 2006). However, it still remains unclear why the trend has moved away from rheumatogenic strains of *S. pyogenes* to those that do not commonly cause ARF; the answers may well be resolved with the advent and application of genomics.

Carriage and transmission of group A streptococci

While group A streptococci are known colonizers of the oropharynx, genital mucosa, rectum, and skin (especially at the site of lesions), rates of carriage in present-day populations are poorly understood. Studies examining carriage rates in healthy adults suggest low levels of carriage, typically less than 5% and 1% for throat and vaginal/rectal carriage respectively (Steer, Lamagni, Curtis, & Carapetis, 2012a). Estimates of pharyngeal *S. pyogenes* carriage in healthy children vary considerably from 2% up to17% (Marshall, et al., 2015; Gunnarsson, Holm, & Söderström, 1997; Martin, Green, Barbadora, & Wald, 2004).

Group A streptococci are transmitted through a number of modalities. Direct person-to-person transmission occurs through the inhalation of respiratory droplets or through skin contact. Transmission through environmental reservoirs has been strongly implicated in experimental or outbreak investigations, either through direct contact with contaminated objects and surfaces or through dust particles. Seminal investigations conducted in the late 1940s and 1950s in the context of high incidences of respiratory tract infection and rheumatic fever at the Warren Air Force base (Wyoming, USA) yielded a considerable body of knowledge on the transmission of *S. pyogenes*, and in particular, the influence of physical proximity on transmission rates. While transmission through consumption of food inoculated by food handlers colonized with *S. pyogenes* has become less common, it still occasionally occurs and does result in outbreaks (Kemble, et al., 2013).

Control and prevention

In the absence of licensed vaccines, modern day public health strategies for *S. pyogenes* disease focus on measures to minimize transmission and to provide protection for individuals who are at risk of invasive disease. Concern over the increasing incidence of invasive disease has led to the assessment of opportunities for controlling the spread of infection. As most cases of invasive disease occur sporadically rather than in identified clusters, opportunities for prevention through outbreak control are somewhat limited.

Secondary household risk

As largely community-acquired infections, with around 1 in 10 linked to healthcare interventions, the initial focus of public health guideline developments has been to assess clustering patterns of invasive *S. pyogenes* disease within households to evaluate the overall risk of secondary transmission. Given the relatively low frequency of primary cases, such assessments require a large study population. To date, these have been undertaken by Canada, USA, Australia, and the UK. Very small numbers of household pairs have been identified through these systematic assessments, with many of these "secondary" cases being co-primary cases, by virtue of simultaneous presentation with the index case. For these pairs of cases, there's no opportunity for intervention to reduce the risk of invasive *S. pyogenes* disease or mitigate its impact (Lamagni, Oliver, & Stuart, 2015). Intervals between index and secondary cases have varied, but generally fall within a month of the onset of the index cases. While the numbers of such clusters are small, this represents a substantial risk of disease in household contacts that is variously estimated from 800 to over 5000 cases per 100,000 person-years (Table 2) (Lamagni, Oliver, & Stuart, 2015). This clearly represents a significant elevation in risk over background incidence, although further

studies are needed to add precision to these estimates. Different strategies for managing this elevated risk have been adopted by different countries and include antibiotic prophylaxis to all close contacts or in individuals at substantially greater risk (Steer, Lamagni, Curtis, & Carapetis, 2012a). Given the rapid onset of invasive *S. pyogenes* infection, advising close contacts on the need to seek medical attention if they develop the signs and symptoms of invasive *S. pyogenes* infection is an essential component of an overall risk management approach.

Table 2: International population-wide assessments of risk of invasive *S. pyogenes* infection in household contacts of index cases (Lamagni, Oliver, & Stuart, 2015)

Location	Year(s)	Background incidence	Cases in contacts	Attack rate in contacts		Rate Ratio
		rate/100,000 person-yrs	no.	rate/100,000 person-yrs	(95% CI)	
Ontario, Canada	1992-93	2.4	4	3581	(976 - 9168)	1492
USA	1997-99	3.5	1	804	(20 - 4480)	229
UK	2003	3.5	5	2579	(837 - 6018)	731
Victoria, Australia	2002-04	2.7	3	5468	(1128 - 15979)	2011
All countries	-	-	13	2681	(1428 - 4585)	-

Outbreak management

While the focus of public health guidelines has been on the management of outbreaks of invasive disease, many of the same principles apply to the control of less severe outbreaks, such as scarlet fever. Prevention measures can include:

- environmental decontamination and improved hygiene
- communication of elevated risk
- exclusion from workplace or school
- antibiotic prophylaxis and treatment

Epidemiological investigation of outbreaks is essential as a means to identify or exclude transmission routes, and therefore, to target prevention measures. Bacteriological screening of potentially exposed individuals can provide evidence of ongoing transmission within a given setting or target population, or a potential point source of transmission to others. Negative results should be cautiously interpreted, given that screening will miss colonized individuals by virtue of poor sampling technique, failure in processing and testing of specimens, or, at a more fundamental level, colonization at non-swabbed body sites. While rectal/vaginal carriage of *S. pyogenes* in healthcare staff has been implicated in several outbreaks, investigators may be reluctant to suggest swabbing such intimate sites in the absence of compelling epidemiological evidence. As a result, epidemiologic data identifying common links between cases and potential sources remains a key part of any investigation.

The role of the environment in facilitating the spread of *S. pyogenes* is potentially under-recognized, despite well-documented accounts that suggest a key environmental role in facilitating disease transmission. *S. pyogenes* are shed in the immediate environment of infected, untreated individuals in large numbers with viable bacteria cultivated from clothing and bedding belonging to the infected person, as well as in accumulated dust. Similarly, food can become inoculated and may facilitate the spread of infection to numerous recipients of foods prepared by infected kitchen staff (Kemble, et al., 2013). Therefore, identifying and decontaminating the environment is a fundamental component of outbreak management strategy.

Antibiotic treatment is recognized as an effective means to reduce transmission of the organism particularly for respiratory and cutaneous infections (Steer, Lamagni, Curtis, & Carapetis, 2012a). Studies assessing the effectiveness of antibiotics at decolonizing infected individuals have found that the majority of individuals no longer have viable *S. pyogenes* in their throat 24 hours after starting therapy. Therefore, this forms the minimum

exclusion period for colonized or infected individuals to prevent onward transmission, albeit with the recognition that a certain number of individuals may become recolonized through contact with non-treated carriers.

Outbreak settings

Few countries have systematic surveillance systems that provide comprehensive data on outbreaks of all types of *S. pyogenes* infection, which precludes our ability to make a meaningful assessment of the burden and characteristics of these events. Outbreaks of scarlet fever and pharyngitis continue to occur and are primarily reported in schools and preschool settings. Secondary prevention measures in these situations include reinforcement of hand hygiene and ensuring exclusion from school/nursery for a minimum of 24 hours after the initiation of antibiotics. Co-circulation of varicella represents a significant threat, and as such, varicella vaccination in groups that are likely to be susceptible (such as pre-schoolers) may also be considered in populations without universal varicella immunization programs.

Outbreaks of invasive *S. pyogenes* infection are uncommon, but do regularly occur primarily in hospital settings and facilities that offer long-term institutional care (Cummins, Millership, Lamagni, & Foster, 2012; Daneman, et al., 2007; Jordan, Richards, Burton, Thigpen, & Van Beneden, 2007). The institutionalized nature of the care provided in these environments translates to the potential for many residents and patients to develop infections through contact with colonized staff. When coupled with the inherent vulnerability of these populations, rapid investigation of *S. pyogenes* infections acquired in these settings is essential as a means to identify the source and instigate effective control measures. Colonized staff, whether symptomatic or asymptomatic, as well as potential environmental reservoirs that are epidemiologically linked to cases, should both be identified as part of outbreak investigations. Screening of staff, residents, and the environment can assist in understanding patterns of transmission and identify targets for prevention measures, including stepped-up decontamination and antibiotic prophylaxis to clear carriage in staff and residents. Invasive disease outbreaks affecting children are rare, but have been noted, particularly in cases where *S. pyogenes* and chicken pox have co-circulated in nursery or school settings.

Microbiologic surveillance

An important part of epidemiologic surveillance for *S. pyogenes* disease has been the characterisation of bacterial isolates. The pivotal work of Rebecca Lancefield led to the development of the classic serologic typing scheme based on the M protein, with more than 120 M proteins validated to date (Facklam, et al., 1999). Advances in the molecular field saw the emergence of the *emm* typing scheme based on the *emm* gene that encodes M protein. More than 234 *emm* types are recognized, with >1200 distinct allelic forms of the *emm* type-specific regions of *emm* genes, which are known as the *emm* subtypes (Beall, et al., 2000). Virtually all epidemiologic studies define *S. pyogenes* isolates according to their *emm* type, and therefore, the *emm* type provides the primary basis for understanding the epidemiology, biology, and genetic structure of the species. *Emm* typing has served the streptococcal scientific community for several decades and is still relevant to tracking outbreaks and surveillance. However, the differences in *emm* type diversity and disease associations have created challenges when extracting and analyzing data from developed countries to reach conclusions about developing countries. Comparative *emm* typing studies to determine prevalence in different regions and countries is made more complex by the different methods used. Some studies represent single time point surveillance, while others analyze isolates collected over time (Shulman, et al., 2009). Isolates from outbreaks and epidemics are also likely to differ from non-related sporadic isolates within the same location (McMillan, Sanderson-Smith, Smeesters, & Sriprakash, 2013). In both its serologic and nucleotide-based based "formats," *emm* typing has been used extensively to examine both geographic strains distribution and disease association. Large scale studies have been undertaken that have used *emm* sequence typing, particularly in the USA, Canada, and Europe (Lamagni, Efstratiou, Vuopio-Varkila, Jasir, & Schalén, 2005; O'Loughlin, et al., 2007; Luca-Harari, et al., 2009; Imöhl,

Reinert, Ocklenburg, & van der Linden, 2010; Friães, Lopes, Melo-Cristino, & Ramirez, 2013; Tamayo, Montes, García-Arenzana, & Pérez-Trallero, 2014).

There are also two other serologic typing schemes that have an important role in the understanding of the molecular epidemiology and genetic organization of the species, based on the serum opacity factor (SOF) and T protein. The original SOF typing scheme was serologic, where SOF type specific antiserum neutralized the enzymatic activity. The *sof* sequence types have been defined by Beall and colleagues (Beall, et al., 2000). Despite the close physical distance between *sof* and *emm* on the chromosome, several *emm* types are found in association with >1 *sof* type, and vice versa, which is indicative of horizontal genetic transfer of *emm* or *sof* to new genetic backgrounds (Efstratiou, 2000; Beall, et al., 2000). The T protein serologic typing scheme is based upon the trypsin-resistant T antigens that have been described as surface pili, which mediate adherence and promote biofilm formation (Manetti, et al., 2007).

A new cluster typing system based on *S. pyogenes emm* types was recently developed that uses the portion of the *emm* genes that encode the entire surface-exposed region of M proteins, for >1000 *emm* genes that correspond to 175 *emm* types. The 175 *emm* types can be grouped into two clades, two sub-clades, and 48 *emm* clusters, 16 of which encompass 82% of the *emm* types. The *emm* clusters represent functionally distinct groups of M proteins, as shown by the characterization of the host binding protein binding of 24 representative *emm* types. For the first time, the classification enabled a model where functionality attributes could potentially be ascribed to proteins from the same *emm* cluster. This novel complementary tool to *emm* typing should add meaningful information and could be widely used for *S. pyogenes* molecular epidemiology. This classification system will be hosted on the website from the streptococcal reference laboratory at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia (National Center for Immunization and Respiratory Diseases, 2012). The new typing system does not replace *emm* typing, but adds meaningful information to the current, broadly used typing scheme. A recent study that used the "cluster typing system" to assess the disease burden in New Caledonian, Australia, and Fiji identified a common point between the *emm* types present in these countries, whereas very few similarities could be found among the *emm* types, as only a limited number of *emm* clusters were responsible for most of the disease burden. Therefore, this study confirmed the high burden and supported the added value of the *emm*-cluster typing system to analyze the epidemiology and to contribute to global vaccine development efforts by informing vaccine formulation (Baroux, et al., 2014).

Trends in *emm* type prevalence and disease associations

Given the diversity of the structure and function of M protein, it is not surprising that *S. pyogenes* of certain M/*emm* types (and in particular, M1 and M3), are strongly associated with invasive infections. This is true for countries within Europe and the USA, in contrast to other regions of the world where types differ quite significantly.

There have been many large scale *emm*-typing surveillance studies undertaken over the last decade in almost all global regions, and it has become clear that the epidemiology of *S. pyogenes* differs between developing and developed regions of the world. Systematic reviews have documented the global epidemiology of these diseases (Smeesters, Mardulyn, Vergison, Leplae, & Van Melderen, 2008; Steer, et al., 2009a), and have highlighted that in developing countries, the *emm* type not only differs, but is much more diverse in comparison to the *emm* type found in developed countries. This has been observed in India, Fiji, Ethiopia, and Brazil (Abdissa, et al., 2006; Dey, et al., 2005; Smeesters, et al., 2006; Smeesters, Mardulyn, Vergison, Leplae, & Van Melderen, 2008; Smeesters, Dramaix, & Van Melderen, 2010; Steer, et al., 2009a). These studies have also showed that single-type dominance did not exist. The systematic review of the global *emm* type distribution undertaken by Steer and colleagues (Steer, et al., 2009a) revealed distinct differences in the *emm* type distribution and diversity of types between global regions and particularly in the molecular epidemiology in Africa and the Pacific (Figure 3). This could be due to the different clinical presentations prevalent within these regions: for example, there are differing

presentations of skin infections, impetigo, RF, and RHD, with large numbers of circulating strains. The review further emphasized the important need for further molecular epidemiologic data from regions where the disease burden is greatest.

Certain *emm* types regularly feature among the prevalent types that cause invasive disease; in particular, types 1, 3, 12, 28, and 89 are seen most frequently (Steer, et al., 2012b; O'Loughlin, et al., 2007). The most common *emm* type recovered in association with *S. pyogenes* invasive disease in developed countries globally is *emm*1. This *emm* type ranks very high in pharyngitis (National Center for Immunization and Respiratory Diseases, 2012; Shulman, et al., 2009; Steer, et al., 2009a). Studies on *emm*1 isolates that spread globally in the 1980s and early 1990s had two prophages that were absent from strains isolated prior to those periods (Cleary, LaPenta, Vessela, Lam, & Cue, 1998). Over the last few years, the evolution of *emm*1 isolates has been intensively studied through genome sequencing and other methods (Aziz & Kotb, 2008; Nasser, et al., 2014).

The prevalence of certain types in invasive or non-invasive infections is a reflection of the circulating types of *S. pyogenes* in the general population at a given time. The diversity of types in developing countries such as Ethiopia, India, Fiji, and Brazil is larger, and the type distributions differ significantly to those reported from Europe or the USA (Abdissa, et al., 2006; Sagar, Kumar, Ganguly, & Chakraborti, 2008; Steer, et al., 2008). Significant differences between genders regarding their infection with particular types have also been documented. For example, in a Pan-European study of type distributions, *emm*28 and *emm*87 were prevalent in females (Luca-Harari, et al., 2009). The role of *emm*28 isolates in puerperal fever is well recognized (Areschoug, Carlsson, Stålhammar-Carlemalm, & Lindahl, 2004; Mihaila-Amrouche, Bouvet, & Loubinoux, 2004). In contrast, *emm*83, *emm*81, and *emm*43 were associated with intravenous drug use and were preferentially found among males (Luca-Harari, et al., 2009).

Molecular epidemiology

In a relatively short period, studies of the molecular epidemiology of *S. pyogenes* have progressed from the study of single genes to population-based genomic comparisons, which significantly highlight the dynamic nature of the organism (McMillan, Sanderson-Smith, Smeesters, & Sriprakash, 2013). Epidemiologic investigations have repeatedly found non-random *S. pyogenes* serotype and disease type associations (Musser & Shelburne, 2009). Thus, molecular pathogenomic approaches have been applied to *S. pyogenes* for over a decade now and studies have revealed new information on molecular epidemiology and pathogenesis, particularly with regards to clone emergence and strain genotype/disease phenotype relationships (Musser & Shelburne, 2009).

It is well known that strains of the same serotype/*emm* type and MLST type can differ extensively in their pathogenomic/virulence gene content. Recent studies on the molecular anatomy of strain genotype with patient phenotype associations at the nucleotide level in M/*emm*3 have clearly identified unique and novel differences by using whole-genome sequence (WGS) approaches (Beres, et al., 2006; Al-Shahib, et al., 2014).

A large-scale analysis of 3,615 genome sequences, combined with virulence studies, was recently published by Nasser and colleagues (Nasser, et al., 2014). The study eloquently delineated the nature and timing of molecular events that contributed to an ongoing "global epidemic" caused by *S. pyogenes* M-type 1. The analysis of population-based sporadic strains from seven countries identified strong patterns of temporal population structure. The study concluded that "the molecular evolutionary events transpiring in just one bacterial cell ultimately produced many millions of human infections worldwide." Results from other well-documented studies (Athey, et al., 2014) that used WGS approaches in epidemiologic situations also highlight the important fact that high quality, well-curated databases are crucial to fully take advantage of the data generated by WGSs.

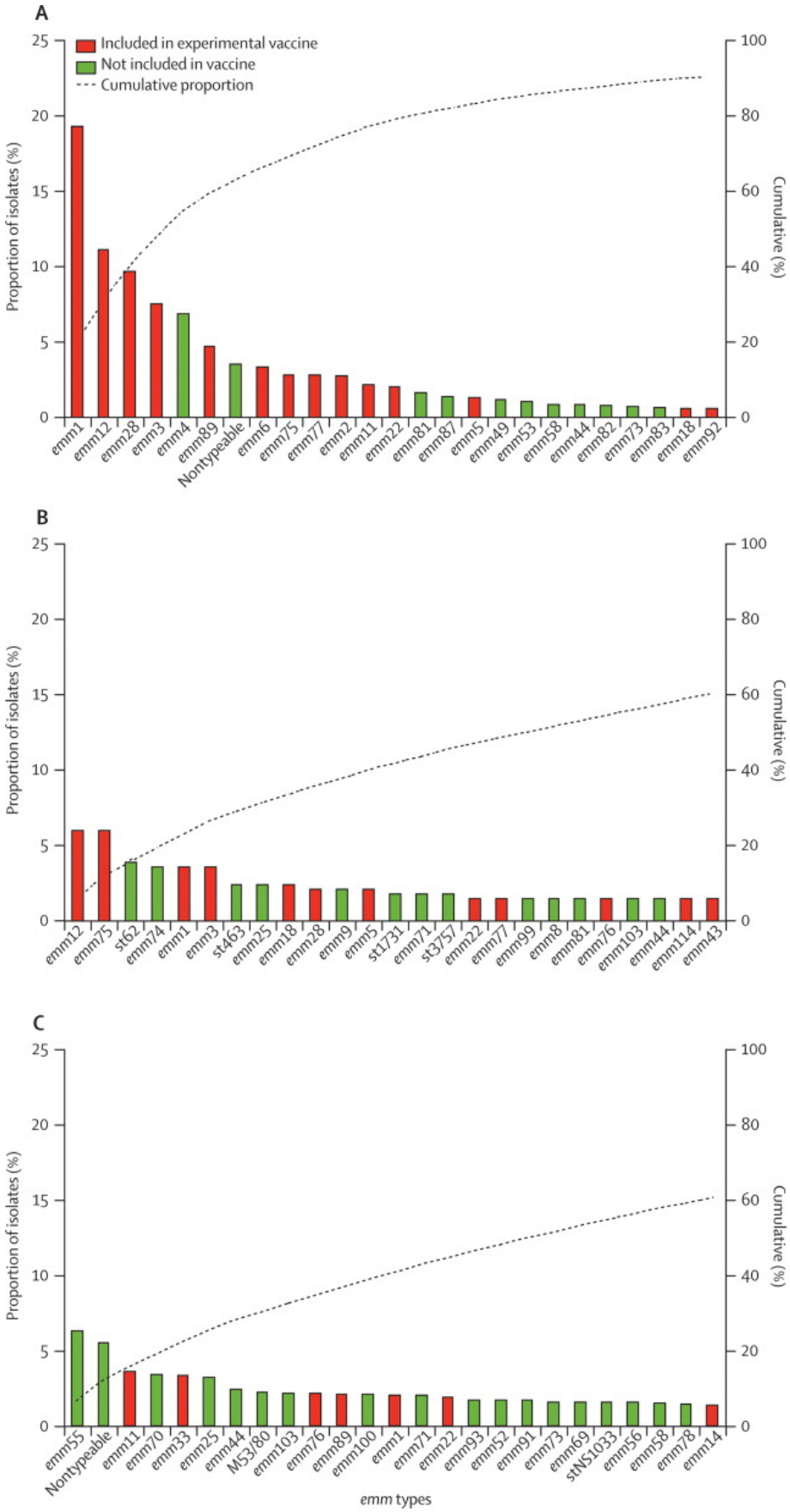

Figure 3: The 25 most common *emm* types as proportions of all isolates in high-income countries (A), Africa (B), and the Pacific region (C) In Africa, *emm* 112 and in the Pacific region *emm* 74 were equal to 25th, but are not included (Steer, Law, Matatolu, Beall, & Carapetis, 2009b)

Conclusions

Studies that expand *emm* typing surveillance to population genomics are providing new insights into not only the epidemiology, but also the pathogenesis and biology of the organism. Recent advances in molecular microbial characterization by whole-genome analysis are opening up tremendous new opportunities for a better understanding of the pathogenicity, evolution, and spread of *S. pyogenes* and the epidemiology of the diseases they cause. WGS holds the promise of improving the resolution and predictive value of typing, as applied to disease surveillance and outbreak investigations. However, there is a need to provide backward compatibility with currently used typing schemes that are well validated, to facilitate comparison and enhanced understanding of epidemiologic trends, in addition to gathering further epidemiologic data from regions where the burden of *S. pyogenes* disease is greatest.

The resurgence of *S. pyogenes* as a cause of serious human infections in the USA, Europe, and elsewhere has been thoroughly documented over the last few decades and has heightened public awareness about this organism, but only in recent years. An overall resurgence of disease, coupled with the lack of a licensed *S. pyogenes* vaccine and ongoing concern about the acquisition of penicillin resistance, remains a major concern and highlights the importance of strengthening global surveillance of this pathogen.

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