Epidemiol. Infect. (1998), **121**, 515–521. Printed in the United Kingdom

A community outbreak of invasive and non-invasive group A beta-haemolytic streptococcal disease in a town in South Wales

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(*Accepted 29 May 1998*)

SUMMARY

An increase in the incidence of invasive and non-invasive infections caused by group A β-haemolytic streptococci (GAS) was noted in and around the town of Glynneath (population approx. 4000) in West Glamorgan, South Wales between 1 January and 30 June 1995. A total of 133 cases was ascertained with 127 (96%) occurring between 1 March and 30 June 1995. Six patients had invasive disease (one died) and all presented at the peak of the outbreak. There were 127 non-invasive cases of whom 7 were hospitalized. The outbreak was investigated to determine its extent and whether it was caused by a single M-serotype of GAS. Serotyping showed that 13 different M-serotypes were involved with the M1 serotype predominating. The overall incidence of GAS invasive disease in West Glamorgan (population 365000) increased sevenfold from a crude incidence of $0{\cdot}5/10^5$ per year in 1994 to $3{\cdot}5/10^5$ per year in 1995, but fell back to $0{\cdot}75/10^5$ per year in 1996. Eighty-two (80%) out of 102 individuals affected by GAS replied to a health questionnaire; sore throat was the commonest symptom reported (97%). Thirty-nine of these index cases identified at least one other member of their household who had experienced similar symptoms. The interval between the onset of illness in members of a single household was 0–83 days with a mean of 22 days. The mean duration of illness was 13·5 days and 61% of patients were treated with penicillin V for a mean duration of 9·3 days. Twenty-one per cent of GAS isolates were erythromycin-resistant and the M4 and M6 serotypes were especially resistant to erythromycin (87·5 and 100% resistance, respectively). Penicillin V failed to eradicate GAS from the throats of 25% of assessable patients. In this community, an outbreak of non-invasive disease caused by GAS was linked in time and place with an outbreak of serious invasive disease.

INTRODUCTION

The past few years have seen an increase in reports of severe disease caused by GAS including streptococcal toxic shock syndrome and necrotizing fasciitis [1–6]. Outbreaks of invasive GAS disease tend to occur over prolonged periods of time and may be caused by multiple serotypes [3, 6]. It is not clear whether an increase in severity of these infections is due to the introduction of new, more virulent organisms, or to changes in host susceptibility [7]. An enhanced understanding of the epidemiology of both invasive and non-invasive group A streptococcal disease would

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https://doi.org/10.1017/S095026889800168X Published online by Cambridge University Press

facilitate early diagnosis, treatment and prevention of serious infections caused by GAS. A study of a small community where a sudden increase in invasive group A streptococcal infection occurred concurrently with a community-wide upsurge of non-invasive GAS infections is reported.

METHODS

In March 1995, the Public Health Laboratory (PHL) in Swansea, noted a significant increase in the number of GAS culture-positive pharyngeal specimens received from family health practitioners in the town of Glynneath (population approx. 4000) in West Glamorgan (population 365000), South Wales. When contacted, the practitioners confirmed a recent increase in the numbers of patients presenting with symptoms of upper respiratory infection. The public health authorities were informed but it was not considered necessary to alert the general public.

Clinical, laboratory and demographic data on cases of invasive GAS arising from Glynneath between 1 January to 31 December 1997 were collated from the Swansea PHL database. A case of GAS disease was considered invasive if the isolate was obtained from normally sterile body fluids. Non-invasive GAS disease was defined as a symptomatic person from whom GAS was isolated from a non-sterile site.

Household survey

To further investigate the nature and dimensions of the outbreak in the community, a two-page self-administered questionnaire was prepared. A copy was sent to the households of 101 randomly selected cases of non-invasive GAS disease, and to that of the only known invasive case at the time. Households received questionnaires within 2 weeks of disease onset in the index case. A formal letter accompanied the questionnaire, explaining its purpose and assuring the potential respondent of confidentiality. Respondents were supplied with a list of symptoms and requested to indicate with a tick mark, those they had experienced. Other information sought included the name of nurseries, schools and colleges attended by the index case, the nature and duration of any antibiotic treatment received, and if another member of the household had experienced a similar illness. No enquiries were made pertaining to the consumption of non-steroidal anti-inflammatory drugs (NSAIDs). The questionnaire was completed on behalf of the index case where it was not possible for the individual to do so (e.g. in the case of a child). Bacteriological confirmation was sought for all secondary cases identified from the household survey. The information obtained from the questionnaires was analysed using the EPI-INFO 6 epidemiological software [8].

Laboratory methods

Group A streptococci were isolated on Columbia Agar (with 5% horse blood) medium. GAS were identified by colonial morphology and Lancefield carbohydrate grouping using a commercial kit (Prolex). Blood isolates were cultured using Bactec 460 and Bactec 9240 systems. Antimicrobial susceptibility testing was performed using a comparative disk diffusion method on 5% lysed blood agar.

A total of 122 GAS isolates were serotyped at the Streptococcus and Diphtheria Reference Unit in the Central Public Health Laboratory, Colindale, London. These included isolates from all but one of the invasive cases.

To assess the ability of penicillin V to eradicate throat carriage of GAS, 24 culture-positive patients had pharyngeal swabs taken after completing a 10–17 day course of penicillin V. Direct detection of antigen from throat swabs was not performed and no virological studies were carried out.

RESULTS

Over a period of 24 months (1 January 1994 to 31 December 1995), a total of 202 cases of GAS disease were ascertained by the PHL Swansea from residents of the Glynneath area. One hundred and thirty-three cases were reported between 1 January and 30 June 1995. Of these, 127 (96%) occurred in the second quarter of the year (1 March to 30 June 1995).

Six cases were invasive. There was one fatality (GAS pneumonia in a female, 64 years). Four had cellulitis (females 78, 53, 25; male 72 years) as the primary manifestation of GAS infection and one had primary peritonitis (female 13 years). All but one were identified by the case-definition employed. The exception was a 25-year-old female with GAS cellulitis of such severity as to justify her classification as an invasive case (blood cultures were not submitted).

The first invasive case occurred in February 1995. Within the next 5 weeks, another case had been

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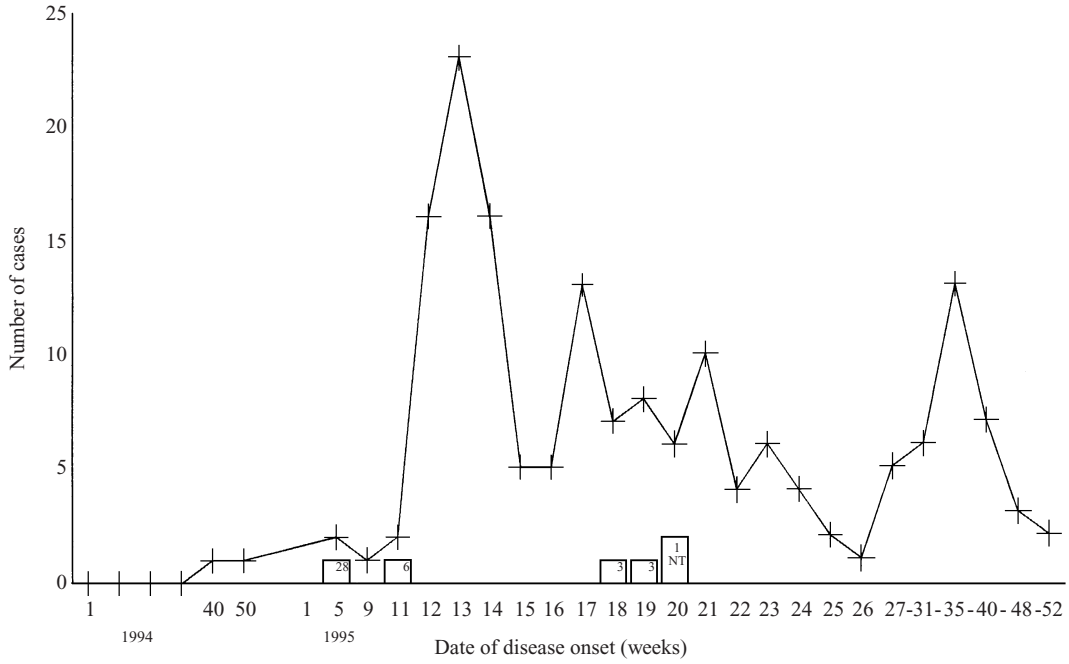

Fig. 1. Invasive and non-invasive GAS infections ascertained in Glynneath, Wales (January 1994–December 1995). BAR, Invasive infections-serotypes R28, M6, M3, M1, NT-Not typed; LINE, Non-Invasive infections.

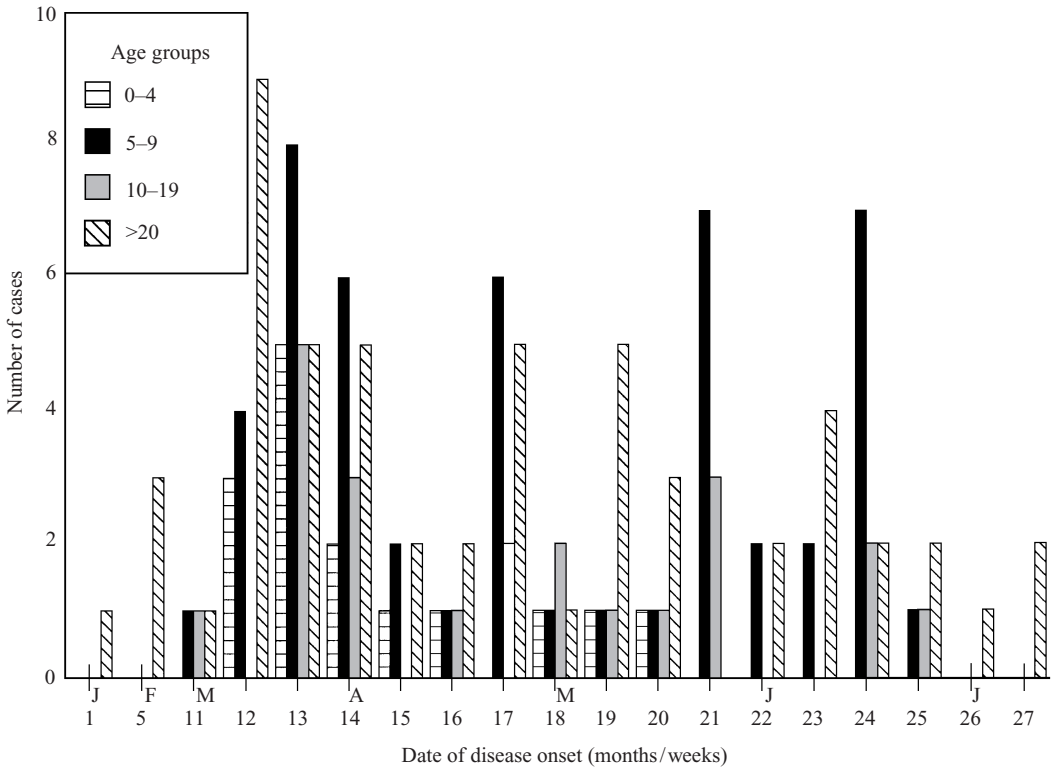

Fig. 2. Non-invasive cases of GAS infection by age and date of onset (Glynneath, Wales; January–July 1995).

reported. The occurrence of the second case was associated with a dramatic increase in the incidence of non-invasive disease. This is illustrated in Figure 1. An early peak was observed in adults over the age of 20 with subsequent peaks occurring in children aged 0–4 years, followed by children of school age (5–9 years) (Fig. 2). Although cases of GAS were identified among all age groups, there was a significant difference

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Table 1. *Age stratification of GAS cases and population sizes** (*Glynneath, Wales; January 1995 – January 1996*)

Age group (years)	Population size (%)	Number of cases (%)	Age-group specific rate (%)
0–4	240 (6)	17 (9)	7·1
5–9	233 (6)	53 (29)	22·7
10–19	452 (12)	35 (19)	7·7
20–29	541 (14)	30 (16)	5·5
30–39	524 (13)	25 (14)	4·7
40–49	513 (13)	7 (4)	1·4
50–59	466 (12)	7 (4)	1·5
60–74	612 (16)	5 (3)	0·8
> 74	334 (9)	2 (1)	0·6
Total	3915 (100)	181 (100)	4·6

* Source: West Glamorgan County Council.

($P < 0{\cdot}0001$) in group specific attack rates (Table 1). The highest number of cases (53/183, 29%) was observed in the age group 5–9 years. A higher proportion of the cases was female (134/202, 66%). The sex-specific rates also differed significantly (females 6·8%, males 3·6%; CI for difference 1·8–4·6%, $P < 0{\cdot}05$).

Eighty-two (80%) out of 102 index cases/households completed and returned the health (household) questionnaire. There were no secondary cases in 43 households including that of the only invasive case involved in the household survey (female, 25 years). The other 39 households each identified at least one member (other than the index case) as having experienced symptoms similar to those of the index case. This gave a total of 58 possible cases of secondary GAS infection. Sixteen of these were bacteriologically confirmed. Thus, there was a total of 98 confirmed (82 index, 16 secondary) and 42 possible cases of GAS infection from 82 households.

Analysis of the questionnaires revealed that the commonest symptom experienced was sore throat (97%) followed by fever (79%). No gross haematuria was reported. There was no correlation between symptoms and the serotype of GAS isolated. Nearly one in four patients reported having a skin rash, but there was only one notification of scarlet fever. This was a child who had had an upper respiratory tract infection with GAS. Joint pain was reported significantly more frequently in boys than in girls ($P = 0{\cdot}006$). The duration of reported illness in the community was 2–120 days (mean 13·5 days). Antibiotics were prescribed for 75/82 (91%) of the patients, penicillin V being the most frequent (46/75; 61%) followed by erythromycin (9/75; 12%) and amoxycillin (2/75; 3%). Eighteen of 75 respondents (24%) did not specify the type of antibiotic taken. The mean duration of therapy for each course was 9·3 days.

Invasive GAS disease was caused by four different serotypes (Fig. 1). Serotype M6 was twice isolated from the same individual (female, 25 years) who was sampled on two separate occasions (2 weeks apart). The isolate from the one fatal case was not types.

In the community the M1 serotype was the most prevalent (52%, 61/117), followed by serotype M4 (14%, 16/117). Other serotypes found during the outbreak are listed in Table 2. The distribution of serotypes among members of seven households with two or more cases each showed that members were homogenous for a given serotype (M6 and M75 in each of 2, and M1 in 5 households). The interval between disease onset in primary and secondary cases varied among households from 0 to 83 days (mean 22 days).

Secondary cases of GAS disease occurred even in households where index cases reported taking a full 10-day course of antibiotics. Antibiotic susceptibilities of the GAS isolates are shown in Table 3. All isolates were susceptible to penicillin and cephalexin. Erythromycin resistance was observed in 21% of isolates with high frequencies among serotypes M6 and M4 (Table 4). Resistance to trimethoprim was also common (71%). In 6 of the 24 patients who received a 10–17 day course of penicillin V, GAS were still present even after treatment, giving an apparent eradication failure rate for penicillin V of 25%. In 5 of the 6, the GAS isolated was of the same serotype as the original isolate.

DISCUSSION

Population-based studies provide valuable information about transmissible diseases and allow the ascertainment of data vital to the understanding of disease processes and transmission. An outbreak is defined as the occurrence of two or more cases of an illness associated in time and place [9].

The incidence of invasive GAS disease varies in different regions, countries and time periods. In a recent study from Ontario, Canada it was reported to be 1·5 cases/10^5 per year while in Denmark the incidence in children under 15 years of age was 1·8/10^5 per year and 4·7/10^5 per year in adults over

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Table 2. *Distribution of GAS serotypes by site of isolation* (*Glynneath, Wales, 1995*)

	Frequency per site							
Serotype	Throat	Ear	Wound	Vagina	Blood	PF*	Conjunctiva	Total
M1	57	4	1	0	1	1	0	64
M4	14	0		0	0	0	1	15
M22	8	0	0	1		0	0	9
R28	6	0	0	0	1	0	0	7
M3	4	0	0		1	0	0	7
M6	3	2	2	2	0	0	0	7
M11	3	0	0	0	0	0	0	3
M58	3	0	0	0	0	0	0	3
M25	2	0	0	0	0	0	0	2
M12	2	0	0	0	0	0	0	2
M9	1	0	0	0	0	0	0	1
M77	1	0	0	0	0	0	0	1
PT4245	1	0	0	0	0	0	0	1
Total (13)	105	6	3	3	3	1	1	122

* PF, peritoneal fluid.

Table 3. *Antimicrobial susceptibility patterns of GAS isolates tested* (*Glynneath, Wales, 1995*)

Antimicrobial agent	Number of isolates	Number susceptible (%)
Penicillin V	135	135 (100)
Cephalexin	135	135 (100)
Erythromycin	135	106 (78)
Trimethoprim	126	33 (26)
Ciprofloxacin	62	62 (100)

Table 4. *Erythromycin resistance of GAS isolates by serotype* (*Glynneath, Wales, 1995*)

Serotype	Number of isolates tested	Number resistant (%)
M4	16	14 (87)
M6	7	7 (100)
M11	3	1 (33)
R28	7	2 (28)
Untyped	13	5 (38)

60 years of age [10, 11]. In Sweden the incidence was also $1{\cdot}8/10^5$ per year while in the USA considerable variations existed between different ethnic groups with some populations of Native Americans having an average incidence of invasive GAS disease of $13{\cdot}3/10^5$ per year [12, 13]. Intravenous drug users have been identified as having a higher proportion of invasive GAS disease [14].

Six cases of invasive GAS disease occurred in the region of Glynneath all within a period of less than 3 months, with one fatality. There were no cases of invasive GAS disease recorded from that area in the previous 2 years (1993–4). Similarly, invasive GAS disease was not reported from Glynneath in 1996 and 1997. The total incidence of invasive GAS disease in this population increased from no cases in 1994 to an estimated $40/10^5$ per year in 1995. The incidence for the whole county of West Glamorgan also increased sixfold from $0{\cdot}5/10^5$ per year in 1994 to $3{\cdot}25/10^5$ per year in 1995 largely as a result of this outbreak. In 1996 the incidence fell back to $0{\cdot}75/10^5$ per year.

This outbreak of invasive GAS disease coincided with a notable increase in upper respiratory tract disease in the same town in what appeared to be a concomitant community outbreak of non-invasive GAS disease. This provided an opportunity to study the relationship between the two events, to establish if a common serotype of GAS was responsible for both events and to determine the nature and severity of the symptoms experienced by the population in question. There were at least 13 different serotypes circulating in the community with the M1 serotype most prevalent. Two of the six invasive cases were also caused by the M1 serotype. Whether this was due to enhanced pathogenicity of the M1 serotype or whether it merely reflected its increased prevalence in the community was uncertain. However, the M1 serotype has been linked to invasive disease more commonly than other

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serotypes and studies have shown that as the prevalence of the M1 serotype increases in a community so does the incidence of invasive disease [10, 15, 16]. Unfortunately data were lacking on the prevalence of GAS serotypes in West Glamorgan prior to this outbreak. Alternatively, GAS outbreaks have previously been reported to be caused by multiple serotypes as was noted in this outbreak [1, 3]. Although there is no clear explanation for it, the antigenic determinants of serotype may be independent of other agent-related determinants of virulence. Host factors may also be responsible for determining clinical expression [7].

Although the numbers available for study were low, the GAS serotypes within households remained surprisingly constant with nearly all affected members in a household having the same serotype. This feature has previously been reported [19, 20]. We were not able to demonstrate institutional transmission of single serotypes of GAS even though it has been shown to occur [21]. In line with previous observations [19, 20, 22, 23], over 83% of episodes of persistent carriage/relapse in this study were caused by the same serotype causing the initial infection. Since household members were homogenous for GAS serotype, it is plausible that household reinfection was responsible for the relapses and persistent carriage observed.

The persistence of GAS in the throats of treated household members may also be due to a reduction in efficacy of penicillin V. Previous studies have yielded conflicting results regarding the efficacy of this antibiotic in eradicating GAS from the throat [19, 20, 22, 23]. Short courses of cefuroxime-axetil or cefixime have been reported to give better results than either penicillin V or rifampicin [20, 22]. Further, with pre and post treatment, GAS isolates of not only the same serotype but also the same restriction endonuclease pattern have been reported [19]. Penicillin V failure (as opposed to reinfection) is another plausible explanation for GAS persistence.

The considerable resistance of GAS isolates in the present study to trimethoprim and erythromycin (Table 3) is a further cause for concern. Erythromycin treatment failure was highlighted in the case of a 25-year-old female who developed severe cellulitis of her arm after removal of a contraceptive implant. Being allergic to penicillin, she was treated empirically with erythromycin. The infecting GAS strain (serotype M6) was resistant to this antibiotic. Her uncontrolled cellulitis required surgical debridement and prolonged hospitalization. Culture from the debridement (12 days after the initial therapy) once again yielded GAS of the same serotype.

The prevalence of erythromycin-resistant GAS appears to be on the increase globally, with countries such as Finland reporting figures of up to 44% in some areas [17, 18]. It is therefore important that the use of macrolides as an alternative to penicillins should not be automatic, but based rather on local antimicrobial susceptibility patterns.

Although the index case was treated with antibiotics in almost all (91%, 78/82) of the households studied, in almost half (47%, 39/82) of these households, this measure appears not to have been effective in preventing the spread of the infection to other members. Admittedly, only 16 of the 58 secondary cases identified were culture confirmed. In addition, the limitations of the study size, and its duration must be conceded. Other factors not ascertained in this study such as poor compliance and incomplete courses of treatment, may have influenced the effectiveness of antibiotics in reducing the household spread of GAS infection.

In light of these observations, whether prophylaxis directed at household contacts of cases, or to the general population of Glynneath would have had an appreciable impact on this outbreak is debatable. The cost-effectiveness of such an intervention would have depended on early detection of the outbreak, as well as the characteristics and complexity of the affected population. In addition, modalities for achieving adequate coverage would have needed to be addressed. A more feasible strategy might be selective rather than mass prophylaxis, targeting specific at-risk groups. In this study, there was a high attack rate of GAS infection among children of school age. A possible target group therefore, could have comprised all household contacts of confirmed GAS cases within this group. Whether priority should be given to contacts of invasive cases remains controversial [21]. We were unable to demonstrate an increased risk among household contacts of invasive cases. On the contrary, there were no secondary cases in the household of the only invasive case [1/82] included in the household survey. There is a need for larger, controlled studies on this subject.

In this outbreak it was found that invasive disease due to GAS occurred concurrently with an increase in non-invasive disease, mostly upper respiratory tract infections, in the community. Family health practitioners should be encouraged to send swabs for bacteriological analyses whenever there is an increase

in upper respiratory tract infections in a community, especially if a greater incidence of cellulitis is noted.

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