A microscopic image showing several large, dark, spherical bacteria (Group A streptococci) arranged in a chain. The bacteria are connected by thin, pinkish-purple structures. The background is a light, pinkish-purple color with some smaller, faint spots.

Health Protection Surveillance Centre

**The Management of Invasive Group A
Streptococcal Infections in Ireland**

Invasive Group A streptococcus Sub-Committee 2006

The Management of Invasive Group A Streptococcal Infections in Ireland.

Invasive Group A Streptococcus Sub-Committee
Health Protection Surveillance Centre



Féidhmeannacht na Seirbhíse Sláinte
Health Service Executive



Table of Contents

Abbreviations	3
Background and Sub-Committee Membership	4
Foreword	5
Definitions	6
Summary of Recommendations	8
1. Introduction	12
2. Surveillance of invasive group A streptococcal infection	16
2.1 Background	16
2.2 Recommendations for a surveillance system	17
2.3 Typing	18
3. Diagnosis of invasive group A streptococcal infection	20
3.1 Clinical diagnosis	20
3.2 Radiological diagnosis	21
3.3 Laboratory diagnosis	21
4. Management of invasive group A streptococcal infection	26
4.1 Cases	26
4.2 Contacts	28
4.3 Infection Control Considerations	31
4.4 Outbreaks	32
Appendix 1 Consultations	35
Appendix 2 Proposed enhanced surveillance form	36
Appendix 3: 'At-risk' populations for invasive group A streptococcal infection	38
Appendix 4 Antibiotic dosing for children	39
Appendix 5 Patient Information Leaflet	40
Appendix 6 Pathogenesis - Bacterial virulence factors of group A streptococcus	41
Appendix 7 Communications with the media by the outbreak control team	42
Reference List	43

Abbreviations

AMLS	Academy of Medical Laboratory Science
BNFc	British National Formulary for Children
CDC	Centers for Disease Control and Prevention
CIDR	Computerised Infectious Disease Reporting
CLSI	Clinical and Laboratory Standards Institute
DoHC	Department of Health and Children
DPH	Director of Public Health
FSAI	Food Safety Authority of Ireland
GAS	Group A streptococcus - <i>S. pyogenes</i>
HCW	Healthcare worker
HPSC	Health Protection Surveillance Centre
HSE	Health Services Executive
ICNA	Infection Control Nurses Association
ICGP	Irish College of General Practitioners
iGAS	Invasive Group A streptococcal infection
IV	Intravenous
IVDU	Injecting drug user
MLST	Multilocus sequence typing
MOH	Medical Officer of Health
NF	Necrotising fasciitis
NAAT	Nucleic acid amplification techniques
OCT	Outbreak control team
PCR	Polymerase chain reaction
PFGE	Pulsed field gel electrophoresis
RADT	Rapid antigen detection tests
RCPI	Royal College of Physicians of Ireland
RCSI	Royal College of Surgeons in Ireland
SIGN	Scottish Intercollegiate Guidelines Network
STSS	Streptococcal toxic shock syndrome

Background and Sub-Committee Membership

In February 2005, the Scientific Advisory Committee of the Health Protection Surveillance Centre (HPSC) proposed that a sub-committee be established to produce national guidelines for the surveillance, diagnosis and management of invasive group A streptococcus infection (iGAS). This was in response to a recent cluster of iGAS in Health Services Executive (HSE) - Western Area.

Nominations were requested from the Royal College of Physicians of Ireland (RCPI), RCPI Faculty of Pathology, RCPI Faculty of Public Health Medicine, RCPI Faculty of Paediatrics, RCPI Institute of Obstetrics and Gynaecology, Royal College of Surgeons in Ireland (RCSI), Irish College of General Practitioners (ICGP), Infection Control Nurses Association (ICNA) and the Academy of Medical Laboratory Science (AMLS).

The following were the nominated members of the iGAS sub-committee:

Name	Nominating body
Dr Fidelma Fitzpatrick (Chair) (Joined October 2005)(FF)	HPSC
Dr Lelia Thornton (Chair - to October 2005)(LT)	HPSC
Dr Colm Bergin (CB)	RCPI
Ms Helen Barry (HB)	AMLS
Prof Mary Cafferkey (MC)	RCPI Institute of Obstetrics & Gynaecology
Ms Edith Daly (ED)	ICNA
Prof Hilary Humphreys (HH)	RCSI
Dr Susan Knowles (SK)	RCPI Faculty of Pathology
Dr Aine McNamara (AM)	HPSC
Dr Edina Moylett (EM)	RCPI Faculty of Paediatrics
Dr Diarmuid O'Donovan (DD)	RCPI Faculty of Public Health Medicine
Mr Ajay Oza (AO)	HPSC

The terms of reference of the iGAS sub-committee were as follows:

1. To review international best evidence and to make recommendations for the management of iGAS.
2. To make recommendations on the diagnostic requirements for iGAS.
3. To review existing surveillance data on iGAS and advise on the need for enhanced surveillance.

The sub-committee first met in May 2005. Members agreed the terms of reference as listed above. It was agreed that these guidelines should build on existing guidelines from other countries including the UK, US and Canada.¹⁻³ The sub-committee initially planned to grade the evidence available in the literature as outlined by the Scottish Intercollegiate Guidelines Network (SIGN).⁴ However, it became apparent that this would not be possible due to the heterogeneity of evidence available, the lack of good quality evidence available for SIGN recommendations, and other work commitments of sub-committee members, which precluded a more detailed literature review, which in any case had already been done by others as detailed above.

Three separate sub-groups were established to review the relevant literature and produce recommendations as follows:

- Surveillance sub-group
AM (Chair), ED, LT, AO.
- Diagnosis and Typing sub-group
SK (Chair), MC, HB, HH, AM, AO, FF (joined October 2005).
- Clinical management sub-group
DD (Chair), CB, ED, EM, LT, FF (joined October 2005).

A draft of this document was sent for consultation in February 2006 to a range of organisations. (Appendix 1)

Foreword

This document represents the expert opinion of the iGAS sub-committee, following a review of the scientific literature and a consultation exercise.

While we accept that some aspects of the recommendations may be difficult to implement initially due to a lack of facilities or insufficient personnel, we strongly believe that these guidelines represent best practice. Where there are difficulties, these should be highlighted locally and elsewhere so that measures are taken to ensure implementation, including the provision of appropriate resources and personnel.

Definitions

Invasive Group A streptococcal infection (iGAS) is a notifiable disease under the Infectious Diseases Regulations 1981. A medical practitioner and a clinical director of a diagnostic laboratory, on suspecting or identifying a case of iGAS, are obliged to send a written or electronic notification to a Medical Officer of Health.

1) Case Definition (Current as of 1st January 2004)

The case definition of iGAS comprises both clinical and laboratory criteria as outlined below:

- **Clinical criteria**

iGAS comprises an acute febrile illness that may be associated with streptococcal toxic shock syndrome (STSS). STSS is characterised by hypotension (fifth percentile of systolic blood pressure in children, or < 90 mmHg systolic pressure in adolescents and adults) and two or more of the following:

- Renal impairment (creatinine > twice upper limit of normal for age)
- Coagulopathy (platelets < 100,000 X 10⁶/l or evidence of disseminated intravascular coagulation)
- Liver dysfunction (ALT, AST or bilirubin > twice upper limit of normal for age)
- Acute respiratory distress syndrome (pulmonary infiltrates and hypoxaemia without cardiac failure or generalised oedema)
- Generalised erythematous rash that may desquamate
- Soft tissue necrosis (necrotising fasciitis (NF), myositis, gangrene)

- **Laboratory criteria**

(a) Isolation of Group A streptococcus (*S. pyogenes*) from a normally sterile site (e.g. blood, cerebrospinal fluid, pleural fluid, body cavity or tissue biopsy specimen)

(b) For probable case (STSS only): Isolation of group A streptococcus from a nonsterile site (e.g. throat, sputum, vagina).

Probable Case (STSS): A probable iGAS case is one that is clinically compatible and meets the probable laboratory criteria.

Confirmed case: A confirmed iGAS case is one that is laboratory confirmed.

(2) Contacts

Household contacts: All contacts living in the same household as a case of iGAS within the seven days prior to the case patient becoming ill.

Other Close Contacts: Persons who share sleeping arrangements
or
Persons who have had direct mucous membrane contact with the oral or nasal secretions of a case within seven days prior to case patient illness.

(3) Outbreak

Two or more epidemiologically linked iGAS cases
or
where the observed number of iGAS cases exceeds the expected number.

Summary of Recommendations

A: Surveillance of invasive group A streptococcal infection

Recommendation 1: Enhanced Surveillance of invasive group A streptococcal infection

- An enhanced surveillance system for iGAS should be introduced in Ireland
- An enhanced surveillance form (Appendix 2) providing information on clinical presentation, risk factors, modes of acquisition, outcomes and results of strain typing should be agreed
- Enhanced surveillance fields for iGAS should be added to the Computerised Infectious Disease Reporting system (CIDR) to allow for computerised reporting
- The case definition of iGAS should be reviewed. iGAS is the most severe form of GAS infection, when the bacterium infects a normally sterile site, typically manifested as STSS or NF
- All iGAS isolates should be referred to a reference laboratory for epidemiological typing. We recommend that an Irish Streptococcal Reference facility is established and appropriately funded. Pending establishment these isolates should be sent to an international reference laboratory

Recommendation 2: Typing of invasive group A streptococcal isolates

- A combination of phenotypic and molecular methods, should be used to
 - Type isolates recovered from invasive infections caused by *S. pyogenes* (group A streptococcus - GAS)
 - Investigate local clusters of invasive disease or other unusual group A streptococcal infections
- Isolates collected, as part of national surveillance should be compared with isolates from other countries, to determine evolutionary trends and the emergence of virulent strains. This could be done in conjunction with laboratories abroad and as part of an international network

B: Diagnosis of invasive group A streptococcal infection

Recommendation 3: Clinical diagnosis of invasive group A streptococcal infection

- Patients with iGAS are likely to benefit from prompt diagnosis and treatment
- Initial signs and symptoms may be non-specific. Clinicians should have a high index of suspicion especially in 'at-risk' patients (Appendix 3)
- High fever, chills, rigors, sweats, myalgia, localised pain, suggest septicaemia and invasive bacterial infection. However other causes including focal infection, auto-immune disease and malignancy are also possible
 - The most common initial symptoms of streptococcal toxic shock syndrome (STSS) are fever and severe pain, which is abrupt in onset and usually precedes tenderness or physical findings
 - Clinical findings of necrotising fasciitis (NF) are more prominent in the later stages and include pain and tenderness out of proportion to the appearance of the area, oedema, erythema, anaesthesia and bullae formation
- Empiric treatment chosen should be effective against GAS, in addition to other pathogens

Recommendation 4: Radiological diagnosis of invasive group A streptococcal infection

- Early surgical intervention should not be delayed by waiting for diagnostic imaging, as intra-operative findings will allow a definitive diagnosis and potentially curative debridement

Recommendation 5: Laboratory diagnosis of invasive group A streptococcal infection

- Cultures of blood and focal sites of infection should be taken in all cases of suspected iGAS, ideally before antibiotic therapy is commenced
- Throat, vaginal and anal swabs may indicate a portal of entry, although a positive result does not distinguish GAS infection from carriage
- Retrospective diagnosis using serological antibody tests should be considered, using acute and convalescent serum samples, in probable clinical cases of iGAS

Recommendation 6: Microbiological identification of group A streptococcus

- Gram stain is useful on specimens normally devoid of indigenous streptococcal flora such as a surgical aspirate or biopsy specimen
- Specimens should be cultured on Columbia blood agar plates, under both aerobic and anaerobic atmospheric conditions, for 18-24 hours at 35-37°C and negative plates rechecked at 48 hours. Plating onto selective media may be necessary for non-sterile site specimens. Gram-positive, catalase-negative, β -Haemolytic colonies should be grouped by Lancefield serology
- iGAS isolates should be confirmed to species level using validated methodology
- All streptococci from iGAS cases should be stored in such a manner as to enable further testing
- The consultant medical microbiologist (or if there is no microbiologist, another appropriate medical consultant involved in the patient's care) is to be informed immediately of all presumptive and confirmed group A isolates
- The Medical Officer of Health (MOH) is to be informed of confirmed iGAS isolates if the infection is likely to meet the case definition of iGAS

Recommendation 7: Antimicrobial sensitivity testing

- Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS) methodology should be used when performing antimicrobial susceptibility tests
- E-tests and validated plate incorporation methods may be used for MIC determination
- The iGAS isolate should be tested for susceptibility against a range of antibiotics including penicillin, vancomycin, erythromycin, and clindamycin. Other antibiotics may be appropriate such as gentamicin, chloramphenicol, tetracycline, linezolid and rifampicin. It is not necessary to test for susceptibility to cephalosporins

C: Management of invasive group A streptococcal infection

Recommendation 8: Management of cases

- iGAS cases should be managed in conjunction with the consultant medical microbiologist or infectious diseases physician
- Intravenous (IV) fluid resuscitation, haemodynamic stabilisation and appropriate intensive care (ICU) as clinically indicated
- Empiric therapy (Adults):

Suspected severe iGAS (eg. STSS, NF, myonecrosis):

IV benzyl penicillin 2.4 grams every 4 hours

Plus

IV clindamycin 600-900mg TDS

Plus

IV flucloxacillin 2g QDS

For other less severe cases (eg. Post-partum infection):

IV benzyl penicillin 1.2-2.4 grams every 4 - 6 hours

Plus/Minus

IV gentamicin standard dose 5mg/Kg once daily (to be adjusted based on renal function and body mass index)

(For paediatric doses refer to the British National Formulary for Children (BNFc), the Royal College of Paediatrics and Child Health "Medicines for Children" and/or Appendix 4)

When a mother develops peripartum iGAS infection, the infant should have a full diagnostic evaluation and a minimum of 10 days intravenous benzyl penicillin. Gentamicin may be added until blood cultures are sterile and the infant is clinically well. Clindamycin may also be added, if severe iGAS affecting the skin or soft tissues.

If severe iGAS is confirmed microbiologically:

IV benzyl penicillin 2.4g every 4 hours

plus a second agent: for example

IV clindamycin 600-900mg TDS

or

IV gentamicin standard dose 5mg/Kg once daily

(to be adjusted based on renal function and body mass index)

The choice of second agent varies with the clinical presentation and should be made in conjunction with the consultant medical microbiologist/infectious diseases physician.

(For paediatric doses refer to the British National Formulary for Children (BNFc), the Royal College of Paediatrics and Child Health "Medicines for Children" and/or Appendix 4)

- Prompt surgical intervention if NF is suspected
- Consider IV immunoglobulin for STSS or NF if associated with organ failure
- Isolate in a single room if iGAS confirmed until 24 hours on appropriate antimicrobial therapy. Consider isolation if iGAS is strongly suspected

Recommendation 9: Management of Contacts

- Chemoprophylaxis should be administered to:

- Close contacts if they have symptoms suggestive of localised GAS infection
- Mother and baby if either develops iGAS in the neonatal period (first 28 days of life)

- Where chemoprophylaxis is indicated:

- Oral penicillin V (250-500mgs QDS, appropriately adjusted for children - Appendix 4) for 10 days is the drug of first choice
- Azithromycin 12mg/kg/day in a single dose (maximum daily dose of 500mg/day) for five days, is a suitable choice for those who are allergic to penicillin
- In the unlikely event of an allergy to penicillin and azithromycin the local consultant microbiologist or infectious diseases physician should be contacted to discuss a suitable alternative. (eg. cephalosporin (if there is no history of anaphylaxis to penicillin) or clindamycin)

- Contacts with symptoms suggestive of iGAS should be immediately referred to the Emergency Department for assessment
- Other close contacts should receive a GAS information leaflet (Appendix 5) and be advised to seek immediate medical attention if they develop such symptoms
- A heightened index of suspicion for iGAS in close contacts should be maintained for 30 days after the diagnosis is made in the index patient

Recommendation 10: Infection Control Considerations

- Hand hygiene should be performed before and after all patient and equipment contact and after glove removal
- Gloves, apron and surgical mask should be worn for contact with the patient and equipment as appropriate
- Isolation in a single room with en-suite facilities is recommended for all patients who are known to have GAS infection until they have received 24 hours treatment with an appropriate antibiotic

Recommendation 11: Management of an outbreak of invasive group A streptococcal infection

- An outbreak control team (OCT) with multidisciplinary representation as appropriate from infection control, clinical microbiology, infectious diseases, public health medicine, nursing and management should be set up for both hospital and community iGAS outbreaks
- The decision to give chemoprophylaxis and to whom should be based on careful assessment of all the epidemiological information available
- The OCT will endeavour to keep the public and media as fully informed as possible without prejudicing the investigation and without compromising any statutory responsibilities, legal requirements or patient confidentiality

Chapter 1: Introduction

1.1 Background

Group A streptococcus (GAS - *Streptococcus pyogenes*) causes a range of diseases in humans including pharyngitis, soft tissue infection, scarlet fever, septicaemia, rheumatic fever and post streptococcal glomerulonephritis. Invasive Group A streptococcal infection (iGAS), which includes necrotising fasciitis (NF) and bacteraemia, carries a significant mortality especially when complicated by streptococcal toxic shock syndrome (STSS). The mechanisms underlying susceptibility and immunity to GAS infection are not well understood. In addition to the M protein, GAS possess several surface factors which play a role in pathogenesis. (Appendix 6)

Worldwide rates of iGAS increased from the 1980s to the 1990s but have been relatively stable over the past five years. The increase was associated with an increased prevalence of serotypes M-1 and M-3.⁵ In the US, the incidence of iGAS in 2003 was 3.8/100,000 population, 32.3% of which initially presented as cellulitis, 26.3% as primary bacteraemia, 6.4% STSS and 6.9% NF. Four (0.3%) cases occurred in patients with varicella. Death occurred in 14.7% of all invasive cases.⁶ A three-year European GAS surveillance programme (Strep-EURO) was launched on 1st September 2002 to develop a pan-European epidemiological perspective on severe GAS disease. Its main objective was to improve the knowledge of the epidemiology of GAS infections in Europe by measuring the burden, risk factors and microbiological characteristics of cases in participating countries.⁷ Over 50 members from 11 European countries participated in the project; Ireland was not a participant. (Section 2.1)

1.2 Legislation

iGAS is a notifiable disease under the Infectious Diseases Regulations 1981. Under Section 14 of these regulations, as amended by S.I. No. 707 of 2003, a medical practitioner and a clinical director of a diagnostic laboratory, on suspecting or identifying a case of the infection, are obliged to send a written or electronic notification to a medical officer of health.

1.3 Definitions

1.3.1 Case Definition of invasive group A streptococcal infection⁸

The case definition of iGAS comprises both clinical and laboratory criteria as outlined below:

1.3.1.i Clinical criteria

iGAS comprises an acute febrile illness that may be associated with STSS. STSS is characterised by hypotension (fifth percentile of systolic blood pressure in children, or < 90 mmHg systolic pressure in adolescents and adults) and two or more of the following:

- Renal impairment (creatinine > twice upper limit of normal for age)
- Coagulopathy (platelets < 100,000 X 10⁶/l or evidence of disseminated intravascular coagulation)
- Liver dysfunction (ALT, AST or bilirubin > twice upper limit of normal for age)
- Acute respiratory distress syndrome (pulmonary infiltrates and hypoxaemia without cardiac failure or generalised oedema)
- Generalised erythematous rash that may desquamate
- Soft tissue necrosis (NF, myositis, gangrene)

1.3.1.ii Laboratory criteria

- (a) Isolation of Group A streptococcus (*S. pyogenes*) from a normally sterile site (e.g. blood, cerebrospinal fluid, pleural fluid, body cavity or tissue biopsy specimen)
- (b) For probable case (STSS only): Isolation of Group A streptococcus from a nonsterile site (e.g. throat, sputum, vagina).

Probable case: A probable iGAS case is one that is clinically compatible (1.3.1.i) and meets the probable laboratory criteria (1.3.1.ii.b).

Confirmed case: A confirmed iGAS case is one that is laboratory confirmed.

1.3.2 Invasive group A streptococcal infection contacts

For the purpose of iGAS surveillance, relevant contacts of a case of iGAS would include household and other close contacts as defined below:

Household contacts

All contacts living in the same household as the iGAS case within the seven days prior to the case patient becoming ill.

Other close contacts

Other close contacts of an iGAS case include:

- Persons who share sleeping arrangements
- Persons who have had direct mucous membrane contact with the oral or nasal secretions of a case within seven days prior to case patient illness

1.4 Epidemiology of invasive group A streptococcal infection in Ireland

iGAS became a notifiable disease in 2004. Since then, 84 cases have been notified: 35 in 2004 and 49 in 2005. (Fig 1.1) The incidence rate per 100,000 inhabitants was 0.89 in 2004 and 1.25 in 2005.

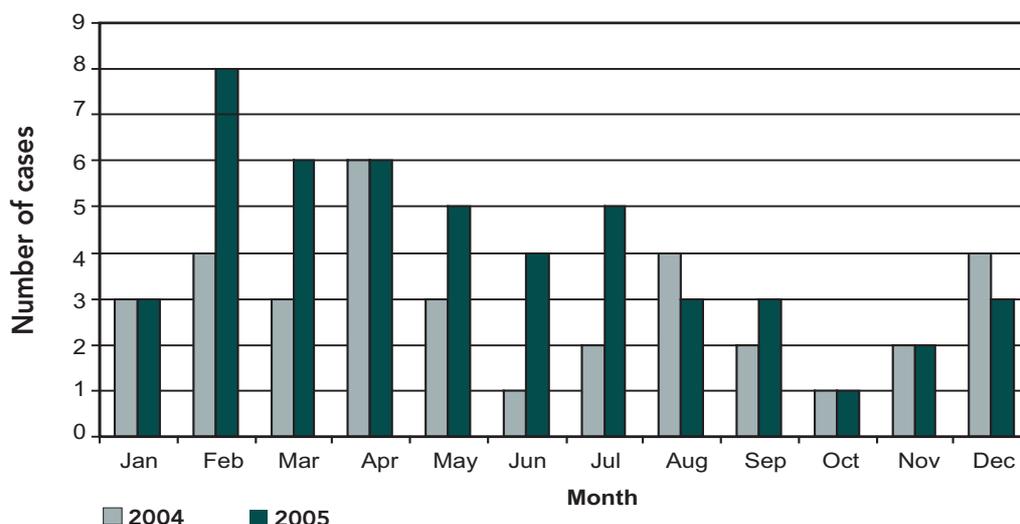


Fig 1.1 Notified cases of iGAS by month 2004 and 2005.
Source: HPSC & CIDR 2006.

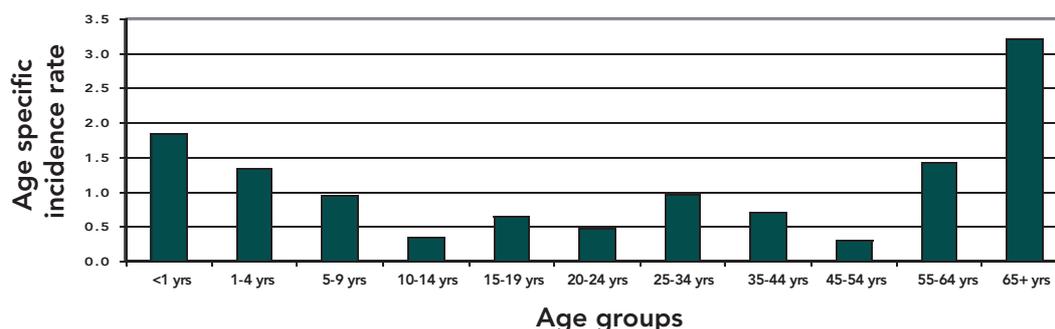


Figure 1.2 Age-specific incidence rate (per 100,000) of iGAS cases for 2004 and 2005 combined
Source: HPSC & CIDR 2006.

Age-specific incidence rate (per 100,000) of iGAS for the two years, 2004 and 2005, combined showed that all age groups were affected with a higher incidence among the elderly (33% of all infections occurred in the age-group 65 years or over) (Fig 1.2). Overall, slightly more males (53%) were affected than females. At present, in the absence of enhanced surveillance, there are no data on clinical presentation of or mortality associated with iGAS in Ireland.

There is concern that there has been an increase in the incidence of iGAS in Ireland.⁹ However, as surveillance was established for the first time two years ago, and data were not routinely collected prior to 2004, it is difficult to confirm this trend objectively. In early 2005, possible temporal and geographic clustering of cases of iGAS was noted in HSE-Western Area. (Fig 1.3) Typing data were available for 13 of the 17 isolates in the cluster. Serotype M-1 (six isolates), M-12 (two isolates), M-87 (two isolates) and one isolate each of M-3, M-5 and M-28 were reported. These particular types are frequently seen internationally, with M-1 and M-3 being the most common. These results indicate that the cases in the possible cluster were not caused by spread of a single strain of the pathogen and thus did not form a single outbreak of iGAS.

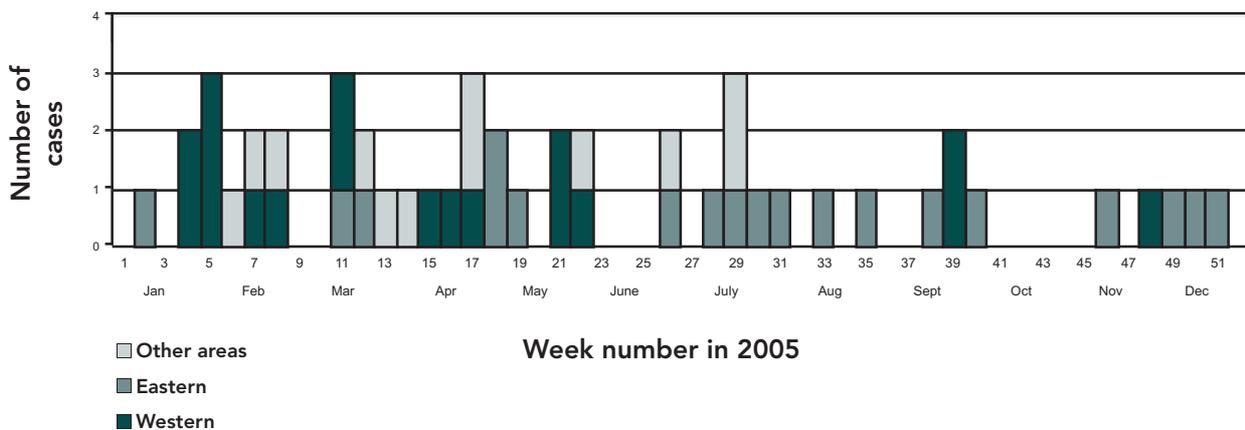


Figure 1.3 Epidemic curve for 2005. Number of cases occurring in the Eastern and Western HSE-Health Areas are highlighted Source: HPSC & CIDR 2006.

At present, cases and isolates of iGAS are notified to departments of public health by clinicians and laboratories. The recommended minimum dataset includes sex and age. Although an agreed enhanced surveillance system is not in place, some laboratories and departments of public health use a draft enhanced surveillance form to provide more detailed clinical and epidemiological information. (Appendix 2) This information is then reported to the Health Protection Surveillance Centre (HPSC).

1.5 Acquisition of group A streptococcus and invasive infection

Eighty-five percent of iGAS is thought to occur sporadically in the community, 10% in hospital patients, 4% in residents of long-term care facilities, and 1% occur after close contact with a GAS case.^{10;11} The portal of entry for GAS was unknown in almost 25% of the cases of severe invasive disease in one report.¹² Most commonly, infection begins at a site of minor local trauma.¹³ While infection may rarely occur secondary to GAS pharyngitis, respiratory viral infections such as influenza and the cutaneous lesions of varicella have provided portals of entry.^{13;14}

Up to 30% of the general population are asymptomatic carriers of GAS.¹⁵ Despite recent progress in improving our understanding of GAS virulence factors and genetic regulation,¹⁶ the relationship between GAS carriage, transmission and iGAS is poorly understood. Environmental factors associated with an increased risk of iGAS are household size and the presence of a child with a sore throat. These factors highlight the importance of person-to-person transmission of GAS.¹⁷ In addition, the duration of contact with the index case is thought to influence rates of carriage and infection.^{12;18} In one study, transmission of GAS occurred in 27% of contacts who had spent more than 24 hours per week with their respective index cases in contrast with 2% who had spent 12-23 hours per week with their respective index case.¹⁹ Two North American prospective studies designed to identify subsequent cases among household contacts (who were observed for a total of 66.5 million person-years) identified five confirmed cases of subsequent

iGAS, giving a relative risk of iGAS among close household contacts from 66 to 294/100,000 contacts.^{10;20} In addition to bacterial factors, (Appendix 6) host factors such as the presence of type-specific anti-streptococcal-antitoxin antibodies, the cytokine response, and the presence of underlying disease, may also influence the susceptibility to specific strains and the clinical presentation. The incidence of iGAS appears to be highest among young children and those greater than 65 years with the greatest mortality in the latter group. Additional 'at risk' populations are outlined in Appendix 3.

1.6 Transmission

- **Incubation period:** 1 - 3 days
- **Period of communicability:** 7 days before the onset of the iGAS until 24 hours after appropriate antibiotic treatment is commenced.¹
- **Treatment of infected persons with an appropriate antibiotic for 24 hours or longer generally eliminates their ability to spread the bacteria.**²¹

GAS is spread by:

- **Contact with secretions from the nose and throat of infected persons (direct, indirect or droplet). Direct contact with large droplets is the major mode of transmission.¹ Airborne spread has also been suggested²²**

or

- **Contact with infected wounds or skin lesions²¹**

The risk of spreading GAS is highest when a person is ill, for example with a GAS throat infection or with an infected wound. Asymptomatic carriers are considered less infectious.¹ For nosocomial transmission, the main reservoirs for GAS appear to be the pharynx, the skin, the rectum, and the female genital tract.²²⁻²⁴

1.7 Invasive group A streptococcal clinical syndromes

iGAS is usually diagnosed clinically by either isolation of GAS from a normally sterile site or from a nonsterile site in the presence of STSS. The course of severe iGAS is often rapid, requiring a prompt diagnosis and initiation of appropriate therapy including early surgical referral. It is essential to identify opportunities for prevention of this disease because of the severity of iGAS and the high case fatality rate. The clinical syndromes associated with iGAS are outlined in Chapter 3.

Chapter 2: Surveillance of invasive group A streptococcal infection

Recommendations:

- An enhanced surveillance system for iGAS should be introduced in Ireland
- An enhanced surveillance form (Appendix 2) providing information on clinical presentation, risk factors, modes of acquisition, outcomes and results of strain typing should be agreed
- Enhanced surveillance fields for iGAS should be added to the Computerised Infectious Disease Reporting system (CIDR) to allow for computerised reporting
- The case definition of iGAS should be reviewed. iGAS is the most severe form of GAS infection, when the bacterium infects a normally sterile site, typically manifested as STSS or NF
- All iGAS isolates should be referred to a reference laboratory for epidemiological typing. We recommend that an Irish Streptococcal Reference facility is established and appropriately funded. Pending establishment these isolates should be sent to an international reference laboratory

2.1 Background

Since the 1980s there has been an increase in the number of cases of severe iGAS worldwide. In particular, reports from the former Czechoslovakia and from the US described STSS, which was a previously unrecognised complication of GAS infection. Furthermore, in the UK in 1994, a cluster of NF cases was reported.²⁵ This prompted many countries to commence active surveillance of iGAS to track changes in the occurrence of the disease.

In the US, passive surveillance for iGAS and STSS has been in operation since 1995. Active, population-based surveillance is conducted in 10 states at the Centers for Disease Control and Prevention (CDC) Emerging Infections Programs Network, which is a collaboration between the CDC, state health departments, and universities. For each case of invasive disease in the surveillance population, a case report including demographic characteristics, clinical syndrome, and outcome of illness is completed and bacterial isolates are sent to the CDC and other reference laboratories for additional laboratory evaluation.⁶

In Canada, iGAS is a notifiable disease with surveillance undertaken in all provinces. In Ontario, the group A streptococcal study has been underway since 1992 providing information on epidemiological trends and pathogenesis of the disease. All sterile site isolates of GAS are reported to the study office by the identifying laboratory, and clinical information, epidemiologic data and isolates are collected and analyzed. Blood samples are collected on a subset of cases for studies of super antigens and the effect of IVIG on cytokine response.²⁶

Initial results from Strep-Euro (Section 1.1) show that over 5,000 cases of iGAS were identified in the first 18 months, which was more than had been anticipated.²⁷ Three thousand cases were from the UK (incidence of 3.8/100,000). Sweden, Denmark and Finland reported similar incidences but other countries had much lower rates. This might be due to the fact that the surveillance in northern Europe approached total coverage. The type distribution of iGAS also varied markedly with an increase of new invasive types seen (*emm* 77, 81, 82, 89). In the UK intravenous drug use was found to be a major risk factor for iGAS. Macrolide-lincosamide-streptogramin B (MLS_B) type resistance was noted in some countries (France, Italy) while tetracycline-resistance was encountered in almost all countries.

Current surveillance of iGAS in Ireland is outlined in Section 1.4. As discussed, an apparent cluster of cases was identified in HSE-Western Area in early 2005. As no laboratory in the Republic of Ireland currently performs serological classification or epidemiological typing of GAS, isolates were sent to the Public Health Laboratory in Colindale, UK for M-serotyping. We recommend that as in this case, all iGAS isolates are referred to a reference laboratory for epidemiological typing. We support referral of GAS

isolates to an expert facility and as such that an Irish Streptococcal Reference facility is established and appropriately funded.

2.2 Recommendations for a surveillance system

The purpose of a surveillance system for iGAS is to measure trends in the burden of iGAS, identify populations at increased risk and provide a basis for epidemiological studies.

The objectives of a surveillance system for iGAS are:

- To ensure early detection of clusters/outbreaks of iGAS so that effective control measures can be implemented
- To monitor trends in iGAS
- To allow for meaningful comparisons to be made over time between different regions and with other countries
- To assist in the evaluation of prevention and control measures
- To inform health care planning
- To support ongoing research into sources, transmission, risk factors, pathogenesis and control of iGAS

The system attributes necessary for the performance of this surveillance system include representativeness, acceptability, simplicity, timeliness, flexibility, sensitivity, positive predictive value and stability.²⁸ The current iGAS surveillance system does not achieve these objectives. Additional information is required, such as clinical presentation, risk factors, modes of acquisition, outcomes and details of strain typing. A national enhanced surveillance system would assist in bridging these gaps. An enhanced surveillance form has been produced by this group and is included in Appendix 2. This is based on the Strep-Euro enhanced surveillance form, which was designed by those EU countries participating in Strep-Euro.

We propose that for each case identified, details of the iGAS isolate would be provided by the laboratory, and clinical and epidemiological details would be supplied or confirmed by public health personnel investigating the case. The information would be coordinated by the Medical Officer of Health (MOH) at a Health Service Executive (HSE) - regional level. The completed form would then be sent to the HPSC. It is the responsibility of the HPSC to collate and analyse data at a national level. CIDR is the computerised electronic information system for surveillance of clinical and laboratory information on communicable diseases, outbreaks and antimicrobial resistance in Ireland. HPSC, the HSE - health areas, Food Safety Authority of Ireland (FSAI) and the Department of Health and Children (DoHC) were involved in the development of this shared national system. We recommend that enhanced surveillance fields for iGAS should be added to CIDR to allow for computerised reporting.

It is envisaged that an annual report of the surveillance of iGAS in Ireland would be produced by the HPSC and disseminated to public health departments and the clinical laboratories. Interim reports would also be available in Epi-Insight as required. By improving our understanding of the epidemiology of iGAS in Ireland we will be able to identify and quantify clusters of iGAS more accurately and recommend appropriate prevention and control guidance.

One of the issues that arose during the consultation period of this document was that the current case definition for probable cases of iGAS included only patients presenting with STSS. The concern was that a small number of iGAS cases (eg. post-varicella iGAS with NF and GAS cultured from wound swab) would be missed by this definition. In addition, there was concern that the definition of confirmed iGAS infection relied on laboratory criteria only rather than a combination of laboratory and clinical criteria. While changing the iGAS case definition is outside the scope of this group, we recommend that the case definition of iGAS is reviewed to consider these matters.

2.3 Typing

Recommendations:

- **A combination of phenotypic and molecular methods, should be used to**
 - **Type isolates recovered from invasive infections caused by *S. pyogenes* (group A streptococcus - GAS)**
 - **Investigate local clusters of invasive disease or other unusual GAS infections**
- **Isolates collected, as part of national surveillance should be compared with isolates from other countries, to determine evolutionary trends and the emergence of virulent strains. This could be done in conjunction with laboratories abroad and as part of an international network**

2.3.1 Background

Bacterial typing sub-divides bacteria of the same species into different types, to assist in halting an outbreak, contributing to our knowledge of the pattern of infection, or tracking the evolutionary progression of strains of that particular organism.²⁹ Before considering which typing method is appropriate, careful consideration should be given to the questions that are being posed and whether the results of typing will be reproducible in both a laboratory and clinical context.

Traditionally, bacteria were typed according to physical or phenotypic characteristics, e.g. susceptibility to lysis by phages as was commonly used up to recently for the typing of *Staphylococcus aureus*. More recently, phenotypic methods have been complemented or replaced by the use of a variety of molecular typing approaches.^{30;31} However, it is important to identify in advance, before deciding on a typing method, whether one is comparing a limited number of strains or conducting a major epidemiological survey of national or international isolates.³¹ For example, pulsed-field-gel electrophoresis (PFGE) has been used for over a decade to type a variety of bacteria, including *S. aureus*. Many authors continue to use interpretative criteria, developed in the mid-1990s for the comparison of isolates from a local outbreak,³² when using this technique to study large collections of isolates from different epidemiological circumstances or to trace the evolutionary development of a clone.

In recent years there have been many publications on typing GAS isolates using both phenotypic and molecular methods, and involving both small and large numbers of isolates. Many of these reports differ in terms of their applicability to national surveillance, or the techniques require specific research expertise. Some methods are relatively expensive when applied to large numbers of isolates.

2.3.2 Approaches to typing group A streptococcus

The M-protein is considered one of the major virulence determinants of GAS as it confers resistance to phagocytosis. Determining the different M serotypes, together with assessing the presence of opacity factor and T protein, have been the cornerstones of phenotypic typing methods for many years.^{33;34} However, M-typing is relatively specialised, requires standardised serology and may not be discriminatory enough when characterising new strains or tracking the spread of strains within a locality.

The *emm* gene of *S. pyogenes* encodes the M protein, the 5'-ends of which are highly heterogeneous.³⁵ Therefore isolates that are non-typable by serological methods can be genotyped by assessing *emm*.^{35;36} *Emm* typing has been applied in a number of local and international circumstances.³⁶⁻³⁸ Many of these studies were carried out in specialist laboratories using research methodologies. When applying a typing technique to answer simple questions about local spread, one needs to balance the sophistication of the typing method with the ease and expense of carrying it out. Vitali and colleagues describe a rapid method for typing GAS using polymerase chain reaction (PCR) to determine variations in the *emm* gene.³⁹ This simple protocol is claimed to correlate well with serotyping. In contrast, others have advocated the use of multilocus sequence typing (MLST) in preference to gel-based methods, as the sequence data is unambiguous, electronically portable and can be readily queried via the internet.⁴⁰ This probably represents a level of sophistication not required for characterising all national isolates or in tracing the origin and spread of isolates in a local outbreak.

2.3.3 Typing Group A streptococcus as part of national surveillance or in investigating outbreaks

There are many approaches to typing GAS isolates when attempting to compare national or local isolates. Furthermore, the aims and objectives of the various papers cited are quite different. A combination of typing methods has been used in the past to study local outbreaks. These include T- and M-typing, gas chromatography, PFGE, MLST, ribotyping and sequence analysis.⁴¹⁻⁴⁶ Some features of the commonly used typing techniques are outlined in Table 2.1 but approaches to typing are likely to evolve and change in the future as in other areas of molecular epidemiology.

We recommend that a combination of phenotypic and molecular methods should be used to

- Type isolates recovered from iGAS
- Investigate local clusters of iGAS or other unusual GAS infections

In addition, iGAS isolates collected as part of national surveillance should be compared with isolates from other countries, to determine evolutionary trends and the emergence of virulent strains. This could be done in conjunction with laboratories abroad and as part of an international network.

Table 2.1 Typing techniques used to characterise GAS isolates

Technique	Indications	Comment
M-, T- serotyping	<ul style="list-style-type: none"> • National isolates to determine circulating virulent strains 	<ul style="list-style-type: none"> • Specialised serology required • Not discriminatory but internationally recognised
PCR <i>emm</i> genotyping	<ul style="list-style-type: none"> • Local, national and international 	<ul style="list-style-type: none"> • Increasingly used collections • Well recognised genotypes • Gel-based
*PFGE/Ribotyping	<ul style="list-style-type: none"> • Local outbreaks or collections 	<ul style="list-style-type: none"> • Methodologies vary • Compliment other methods
+ MLST	<ul style="list-style-type: none"> • Diverse sources of isolates • Tracing the evolution of strains 	<ul style="list-style-type: none"> • Very discriminatory • Comparable on internet • Specialised technique

*Pulsed field gel electrophoresis

+ Multilocus sequence typing

Chapter 3: Diagnosis of invasive group A streptococcal infection

3.1 Clinical diagnosis

Recommendations:

- Patients with iGAS are likely to benefit from prompt diagnosis and treatment
- Initial signs and symptoms may be non-specific. Clinicians should have a high index of suspicion especially in 'at-risk' patients (Appendix 3)
- High fever, chills, rigors, sweats, myalgia, localised pain, suggest septicaemia and invasive bacterial infection. However other causes including focal infection, auto-immune disease and malignancy are also possible
 - The most common initial symptoms of streptococcal toxic shock syndrome (STSS) are fever and severe pain, which is abrupt in onset and usually precedes tenderness or physical findings
 - Clinical findings of necrotising fasciitis (NF) are more prominent in the later stages and include pain and tenderness out of proportion to the appearance of the area, oedema, erythema, anaesthesia and bullae formation
- Empiric treatment chosen should be effective against GAS, in addition to other pathogens.

Although initial signs and symptoms of iGAS are non-specific, physicians should have a high index of suspicion for this evolving syndrome most notably in 'at-risk' patients. (Appendix 3)

The clinical presentation of iGAS may include the following:

3.1.1 Streptococcal Toxic Shock Syndrome (STSS)

STSS is the most severe manifestation of iGAS, characterised by hypotensive shock and multi-organ failure. STSS may be seen in patients with or without NF. The most common initial symptoms are fever (although hypothermia may be present in patients with shock) and severe pain, which is abrupt in onset. These symptoms usually precede tenderness or physical findings. 20% have an influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhoea.¹³ The majority have clinical signs of soft tissue infection, such as localized swelling and erythema, which in 70% progress to NF or myositis and requires surgical debridement. Patients without soft tissue findings, may present with endophthalmitis, myositis, myocarditis, peritonitis, and overwhelming sepsis. Approximately 50% have normal blood pressure (systolic pressure >110 mm Hg) on admission but develop hypotension within the subsequent 4 hours.¹³

3.1.2 Necrotising fasciitis (NF)

NF is a deep-seated infection of subcutaneous tissue that results in the rapidly progressive destruction of fat and fascia but may spare skin and muscle. Clinical findings are more prominent in the later stages and include pain and tenderness out of proportion to the appearance of the area, oedema, erythema, anaesthesia and bullae formation. There are marked systemic symptoms, with early onset of shock and organ failure.

3.1.3 Other invasive disease

Bacteraemia with no identified focus

Cellulitis

Manifested as an infection of the lower dermis and subcutaneous soft tissue, characterised by blanching erythema, and oedema accompanied by pain and tenderness. There may be associated blister formation, lymphangitis, regional lymphadenopathy and systemic features such as fever and leucocytosis.

Myonecrosis

Usually occurs in association with NF as an expansion of the destructive process, but can be isolated, resulting from haematogenous seeding to muscle. Early signs include severe pain, swelling and erythema, though muscle compartment syndromes may develop rapidly.^{13,47-49} Aggressive surgical debridement is extremely important for establishing a diagnosis and removing devitalized tissue.

Focal iGAS

Meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, septic arthritis and surgical wound infections.

As outlined in Section 2.2, the current case definition of probable iGAS only includes patients presenting with STSS. A small number of iGAS cases that are consistent with invasive disease without STSS or GAS isolated from sterile-sites, may be missed by this definition. We have therefore recommended that the case definition is reviewed to consider these matters.

3.2 Radiological diagnosis

Recommendation:

- **Early surgical intervention should not be delayed by waiting for diagnostic imaging, as intra-operative findings will allow a definitive diagnosis and potentially curative debridement**

Diagnostic imaging may be useful to locate the site and depth of infection, although not always possible if iGAS is progressing rapidly. GAS NF and myonecrosis are not associated with iGAS in the soft tissues.⁵⁰

3.3 Laboratory diagnosis

3.3.1 Taxonomy and characteristics

S. pyogenes is the pathogen associated with iGAS infections. *S. pyogenes* is a Gram-positive, catalase-negative, non-motile, non-spore forming, facultatively anaerobic bacterium forming spherical or ovoid cells less than 2µm in diameter and occurring in chains. On culture, it is β-haemolytic on blood agar plates, and belongs to Lancefield serological group A. GAS are nutritionally fastidious. Certain strains of two other β-haemolytic streptococci, *S. dysgalactiae* subspecies *equisimilis* and *S. anginosus* are also Lancefield group A, although they are uncommonly isolated in clinical microbiology laboratories.⁵¹ Morphologically these colony types are smaller than *S. pyogenes*.

3.3.2 Safety considerations

Specimens from iGAS and subsequent laboratory material (agar plates, used diagnostic kits etc) are hazardous to health and should be handled in accordance with local safety guidance.

Transport of specimens and isolates must be in compliance with international agreements on the carriage of dangerous goods.⁵² Specimens and isolates must be stored and transported to ensure viability of the organism for as long as is required. Segregation, packaging, storage and disposal of waste must be in accordance with the guidelines issued by the DoHC in 2004.⁵³ The specimens should be processed in a clinical microbiology laboratory at Containment Level 2, in accordance with the Safety, Health and Welfare at Work (Biological Agents) Regulations 1998⁵⁴ and with local standard operating procedures under supervision of suitably qualified staff. All reagents and procedures should be evaluated and validated before use. The manufacturer's instructions must be followed if any commercially available kits are used.

3.3.3 Laboratory diagnosis

Recommendations:

- Cultures of blood and focal sites of infection should be taken in all cases of suspected iGAS, ideally before antibiotic therapy is commenced
- Throat, vaginal and anal swabs may indicate a portal of entry, although a positive result does not distinguish GAS infection from carriage
- Retrospective diagnosis using serological antibody tests should be considered, using acute and convalescent serum samples, in probable clinical cases of iGAS

As iGAS may result in a number of pathological conditions, the laboratory may expect specimens from both normally sterile sites (e.g. blood, cerebrospinal fluid, pleural fluid, biopsy specimens) or from non-sterile sites (e.g. throat, sputum, vagina). Ideally, specimens should be taken before antibiotic therapy is commenced.

3.3.3.i Blood culture

Blood cultures, preferably two sets, should be taken on all patients suspected of having iGAS. Whilst GAS bacteraemia is rarely associated with pharyngitis, bacteraemia is frequently present in patients with STSS (over 50% of patients)⁵⁵ and NF.^{56,57}

3.3.3.ii Tissue

Both surgical aspiration of infected skin/soft tissue and tissue biopsy are appropriate tissue specimens. However, culture results depend on the extent of GAS tissue involvement. Whilst controversy exists as to whether the leading edge or the midpoint of inflammation is best to aspirate or biopsy,⁵⁸⁻⁶² bacteriological results from fine-needle aspiration have been shown to be relevant in greater than 50% of patients with iGAS presenting as NF.⁶³ In contrast, GAS may be difficult to isolate from patients with cellulitis and the value of fine-needle aspiration in cellulitis is significantly less than those with NF.^{63,64}

3.3.3.iii Culture of other sites

A positive throat culture for GAS does not distinguish a carrier from a patient with iGAS and concomitant pharyngeal carriage. Vaginal and anal carriage may indicate a portal of entry, but likewise do not distinguish infection from asymptomatic colonisation. However, a combination of culture from non-sterile sites and serology may help diagnose iGAS, as carriers of GAS do not experience a convalescent rise in streptococcal antibody titre.⁶⁵

3.3.3.iv Rapid diagnostic tests

Diagnostic tests are available for the rapid detection of GAS both at point of care and in the diagnostic laboratory. A large range of rapid antigen detection tests (RADT) are available for GAS detection from throat swabs in the point-of-care setting.⁶⁶ These tests allow detection of the group A carbohydrate antigen directly from throat swabs by using enzyme immunoassay or optical immunoassay. Most RADT are reported to be highly specific.⁵⁵ However, sensitivity is lower than that of culture. The American Academy of Paediatrics (2006) recommends that a negative RADT be confirmed with a throat culture.⁵⁵ These methods are recommended for use at point of care for the diagnosis of GAS pharyngitis once the procedures are sufficiently well evaluated and validated locally, and all negative test results are confirmed using culture.

Rapid diagnosis of iGAS may also be made in the diagnostic laboratory using nucleic acid amplification techniques (NAAT).⁶⁷ Molecular methods include a chemiluminescent single stranded DNA probe that detects specific rRNA sequences unique to GAS and as a real time PCR method. In a study of tissue biopsy specimens from patients with NF, PCR for detection of streptococcal pyrogenic exotoxin B (*speB*) gene displayed concordant results with culture in ten patients from whom GAS was isolated and eleven patients who were culture negative or lacked serologic evidence of infection.⁶⁸ NAAT may be useful for confirming iGAS infections when cultures are negative,⁶⁹ although its role in routine diagnosis has not been demonstrated to date. Diagnosis using culture confers additional benefits over NAAT methods, including antimicrobial susceptibility testing and phenotypic typing methods. NAAT have also been used to detect GAS from throat swabs, although similar to culture techniques, a positive result does not distinguish true infection from carriage.

3.3.3.v Serology

Serology has little role in the acute diagnosis of iGAS. However, it may be helpful in establishing a retrospective diagnosis or in epidemiological studies. A rising titre from acute to convalescent specimens is a more accurate reflection of a previous GAS infection than a single high titre. Many factors influence GAS immune response and there is no absolute upper limit of normal. These factors include patient age (titres are maximal between ages 6-12 years), indigenous population, site of infection, season, prompt antibiotic treatment and corticosteroid administration.⁷⁰⁻⁷³ Performing more than one streptococcal antibody test will increase the chance of confirming a true previous GAS infection as the dynamics of the various streptococcal antibody responses differ from each other, and the maximal response is dependent on the time duration since the infection.⁷⁰ Antibodies are produced against various antigens including anti-streptolysin O, anti-DNAase B, anti-streptokinase, anti-streptococcal hyaluronidase and anti-NADase. The latter three tests are not commonly used for determination of previous GAS infection, as they are technically difficult and often only available in reference or research laboratories. Storing an early serum sample for later assay, with additional samples collected 1, 2, and 3 weeks later is suggested.⁷⁴

3.3.3.vi Additional investigations

Additional laboratory investigations may assist in the early differentiation of GAS NF from cellulitis. Initial C-reactive protein and creatine kinase levels are higher in patients with NF than those with cellulitis.⁷⁵ In the later stages of NF or STSS, biochemical features of disseminated intravascular coagulation or multi-organ failures may develop.⁵⁶

3.3.4. Microbiological identification of group A streptococcus

Recommendations:

- Gram stain is useful on specimens normally devoid of indigenous streptococcal flora such as a surgical aspirate or biopsy specimen
- Specimens should be cultured on Columbia blood agar plates, under both aerobic and anaerobic atmospheric conditions, for 18-24 hours at 35-37°C and negative plates rechecked at 48 hours. Plating onto selective media may be necessary for non-sterile site specimens. Gram-positive, catalase-negative, β-Haemolytic colonies should be grouped by Lancefield serology
- iGAS isolates should be confirmed to species level using validated methodology
- All streptococci from iGAS cases should be stored in such a manner as to enable further testing
- The consultant medical microbiologist (or if there is no microbiologist, another appropriate medical consultant involved in the patient's care) is to be informed immediately of all presumptive and confirmed group A isolates
- The Medical Officer of Health (MOH) is to be informed of confirmed iGAS isolates if the infection is likely to meet the case definition of iGAS

3.3.4.i Laboratory identification of group A streptococcus

Procedures for identification of microorganisms change frequently and it is important to refer to current textbooks, published articles, guidelines and bulletins.

Direct detection of streptococci via Gram stain is useful on those specimens normally devoid of indigenous streptococcal flora such as blood culture or aspirate. In GAS NF, the Gram stain of a surgical aspirate or biopsy specimen is often positive for Gram positive cocci in chains with few if any pus cells.⁵⁶

GAS may be grown on Columbia blood agar plates supplemented with horse blood, preferably under both aerobic and anaerobic atmospheric conditions, for 18-24 hours at 35-37°C and negative plates rechecked at 48 hours.⁷⁶ Haemolytic patterns may vary depending on the source of animal blood or type of basal medium used in blood agars. Sheep's blood is recommended for the culture of throat swabs.⁷⁷ Sheep's blood contains nicotinamide adenine dinucleotidase which hydrolyses the nicotinamide adenine

dinucleotide content to prevent the growth of *Haemophilus haemolyticus*, which may be confused with GAS. Plating on to selective media may be necessary for non-sterile site specimens. Streptococcus selective media include Columbia blood agar supplemented with 5% defibrinated horse blood and colistin and nalidixic acid⁷⁸ or Columbia blood agar supplemented with 5% defibrinated horse blood and colistin and oxolinic acid.⁷⁹

GAS colonies are about 0.5mm, domed, with entire edge and show complete break-up of the red blood cells surrounding the colony on the growth medium (β -haemolysis). Sub-surface haemolysis may be induced by stabbing the specimen through the agar and this is due in part to the oxygen labile streptolysin O.⁸⁰ β -Haemolytic streptococci should be grouped by Lancefield serology. Older antigen extraction and precipitation testing methods have been superseded by commercially available rapid antigen extraction and agglutination techniques for the Lancefield's grouping of β -haemolytic streptococci. A pure culture of the isolate should be stored to ensure viability if further testing is required. Further confirmation of the organism to species level using biochemical or other tests is optional, though advised.

3.3.4.ii. Reporting of positive results

Laboratory staff should inform the consultant medical microbiologist (or if there is no microbiologist, appropriate clinical staff) of presumptive and confirmed isolates of GAS. The consultant medical microbiologist should also be informed of additional test results as soon as the results become available. The clinician and infection control nurse should be informed in accordance with local reporting practices. The MOH should be informed of confirmed isolates of GAS if the infection is likely to meet the case definition of iGAS.⁸ The MOH should be informed of additional test results as soon as the results become available.

All iGAS isolates should be referred to a reference laboratory for epidemiological typing. (Section 2.3) Pending funding of a streptococcal reference facility in Ireland, isolates should be sent to an international reference laboratory.

3.3.5 Antimicrobial sensitivity testing

Recommendations:

- **Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS) methodology should be used when performing antimicrobial susceptibility tests**
- **E-tests and validated plate incorporation methods may be used for MIC determination**
- **The iGAS isolate should be tested for susceptibility against a range of antibiotics including penicillin, vancomycin, erythromycin, and clindamycin. Other antibiotics may be appropriate such as gentamicin, chloramphenicol, tetracycline, linezolid and rifampicin. It is not necessary to test for susceptibility to cephalosporins**

3.3.5.i Methodology

GAS susceptibility testing is usually performed by disc diffusion methods. A standard method should be used when performing susceptibility tests by disc diffusion. The recommended method is the Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS) methodology. Isolates should be plated onto Mueller-Hinton agar containing 5% sheep's blood and incubated at 35°C-37°C in 5% CO₂ for 20 - 24 hours.⁸¹ E-tests and validated plate incorporation methods may be used for MIC determination.⁸² For detailed methodology it is recommended to consult the most recent CLSI guidance.⁸¹

3.3.5.ii Choice of antibiotics for testing

The iGAS isolate should be tested for susceptibility against a wide range of antibiotics including agents that may be used in treatment and chemoprophylaxis. In the context of possible linked cases or an outbreak, the susceptibility profile may be useful epidemiologically.

The range of antibiotics tested may include the following:

- penicillin
- erythromycin
- clindamycin
- vancomycin

In addition, the following antibiotics may be included when appropriate (eg, a patient with penicillin hypersensitivity infected with an erythromycin-resistant strain, or for epidemiological typing); rifampicin ; chloramphenicol; tetracycline; linezolid; gentamicin.

Penicillin susceptible streptococcal isolates can be considered susceptible to ampicillin, cephalosporins, imipenen and meropenem and need not be tested against these agents.⁸¹

Worldwide GAS strains remain highly susceptible to penicillin and to date there are no reports of resistance.⁸³ Although the CLSI guidance recommends that routine penicillin testing of GAS isolates is not necessary,⁸¹ it appears prudent to test penicillin susceptibility to monitor for the emergence of resistance; similarly for vancomycin. Susceptibility and resistance to clarithromycin and azithromycin can be predicted by testing erythromycin.⁸¹ Although incomplete, 53 of 1,282 (4%) iGAS isolates in the UK enhanced surveillance of iGAS in 2003 were erythromycin resistant,⁸⁴ hence sensitivity is likely, but cannot be assumed. If azithromycin is to be used for chemoprophylaxis, susceptibility to erythromycin in the index case isolate should be confirmed before use. Chloramphenicol and tetracycline susceptibility may be useful epidemiological markers. Rifampicin susceptibility must be monitored, particularly in light of the emergence of rifampicin resistant strains.⁸⁵

Chapter 4: Management of invasive group A streptococcal infection

4.1 Management of cases

Recommendations:

- iGAS cases should be managed in conjunction with the consultant medical microbiologist or infectious diseases physician
- Intravenous (IV) fluid resuscitation, and haemodynamic stabilisation and appropriate ICU care as clinically indicated
- Empiric therapy (Adults):

Suspected severe iGAS (eg. STSS, NF, myonecrosis):

IV benzyl penicillin 2.4 grams every 4 hours
Plus
 IV clindamycin 600-900mg TDS
Plus
 IV flucloxacillin 2g QDS

For other less severe cases (eg. Post partum infection:)

IV benzyl penicillin 1.2-2.4 grams every 4 - 6 hours
Plus/Minus
 IV gentamicin standard dose 5mg/Kg once daily (to be adjusted based on renal function and body mass index)

(For paediatric doses refer to the British National Formulary for Children (BNFc), the Royal College of Paediatrics and Child Health "Medicines for Children" and/or Appendix 4)

When a mother develops peripartum iGAS infection, the infant should have a full diagnostic evaluation and a minimum of 10 days intravenous benzyl penicillin. Gentamicin may be added until blood cultures are sterile and the infant is clinically well. Clindamycin may also be added, if severe iGAS affecting the skin or soft tissues.

If severe iGAS is confirmed microbiologically:

IV benzyl penicillin 2.4g every 4 hours
plus a second agent: for example
 IV clindamycin 600-900mg TDS
or
 IV gentamicin standard dose 5mg/Kg once daily
 (to be adjusted based on renal function and body mass index)

The choice of second agent varies with the clinical presentation and should be made in conjunction with the consultant medical microbiologist/infectious diseases physician.

(For paediatric doses refer to the British National Formulary for Children (BNFc), the Royal College of Paediatrics and Child Health "Medicines for Children" and/or Appendix 4)

- **Prompt surgical intervention if NF is suspected**
- **Consider IV immunoglobulin for STSS or NF if associated with organ failure**
- **Isolate in a single room if iGAS confirmed until 24 hours on appropriate antimicrobial therapy. Consider isolation if iGAS is strongly suspected**

4.1.1 Fluid resuscitation and haemodynamic stabilisation

Management of iGAS includes prompt initiation of fluid resuscitation volume expansion and appropriate ICU care as clinically indicated.^{86,87} STSS may be associated with massive capillary leak necessitating considerable fluid replacement. All iGAS cases should be managed in conjunction with the consultant medical microbiologist or infectious diseases physician. All cases of severe iGAS should be managed in an ICU setting with expert input from individuals with specialist training in intensive care.

4.1.2 Prompt initiation of appropriate antimicrobial therapy

Intravenous (IV) antibiotic therapy should be commenced promptly, providing coverage for both GAS and *S. aureus* until the results of bacteriologic studies are available. Recommended initial empiric antibiotic therapy should include a β -lactamase-resistant anti-staphylococcal drug (e.g. flucloxacillin), benzyl penicillin and a protein synthesis-inhibiting drug such as clindamycin.

Once GAS is identified, the combination of high-dose IV benzyl penicillin and a second agent if severe infection, such as clindamycin/gentamicin is recommended. The choice of second agent varies with the clinical presentation and should be made in conjunction with the consultant medical microbiologist/infectious disease physician. Clindamycin is more effective than penicillin for treating well-established GAS infection in animal models. This is because the antimicrobial activity of clindamycin is not affected by inoculum size, has a long post-antimicrobial effect, and acts on bacteria by inhibiting protein synthesis.⁸⁸⁻⁹⁰ Inhibition of protein synthesis results in suppression of synthesis of bacterial toxins. Penicillin-binding proteins are not expressed during the stationary-phase growth of GAS, and thus penicillin is ineffective in severe deep infections where large numbers of bacteria are present.⁹¹

If a mother develops peripartum iGAS, the baby should undergo a full diagnostic evaluation with a minimum 10 days IV antibiotic therapy (benzyl penicillin). Gentamicin may be considered until blood cultures are sterile and the baby is clinically well. Clindamycin may also be added, if severe iGAS affecting the skin or soft tissues. A full diagnostic evaluation includes a full blood count and differential, blood culture, chest radiograph if respiratory symptoms are present and lumbar puncture, if feasible, if signs of sepsis. A positive blood culture should prompt a lumbar puncture.

The exact dose and duration of treatment is based upon the severity of illness and clinical improvement. For severe iGAS, IV antimicrobial therapy should be continued until the patient is afebrile, hemodynamically stable and negative blood culture results have been documented. The total duration of antibiotic therapy should be based on the duration established for infection of the underlying focus.

4.1.3 Prompt surgical intervention

When NF is suspected an urgent surgical opinion should be sought.⁹² Patients usually require at least one surgical exploration for drainage and debridement of affected necrotic tissue. At surgery, material should be obtained for immediate Gram stain and histopathological examination to confirm the diagnosis. (Section 3.3.3.ii) Fasciotomy may be indicated particularly in the setting of a compartment syndrome. More severe cases may require extensive debridement or amputation to arrest progress of the disease process.

4.1.4 Intravenous immune globulin (IVIG)

Data from a few case reports and one controlled trial suggest that adjunctive treatment with IVIG may have added benefit when given in addition to appropriate antimicrobial therapy for GAS TSS or NF.⁹³⁻⁹⁵ However in a murine model of GAS NF, IVIG provided no additional benefit to standard antimicrobial therapy.⁹⁶ The mechanism of action of IVIG is unclear but is postulated to result in suppression of the inflammatory response most notably via tumour necrosis factor-alpha as well as neutralisation of circulating bacterial toxins. Various regimens of IVIG, including 150 to 400 mg/kg per day for five days or a single dose of 1-2 g/kg, have been used, but the optimal regimen is unknown.

4.1.5 Isolation

Isolation in a single room with en-suite facilities is recommended for all patients who are known to have laboratory confirmed iGAS until 24 hours after they have received treatment with an appropriate antibiotic.⁹⁷ Isolation should be considered for patients in whom iGAS is strongly suspected.

4.2 Management of Contacts

Recommendations:

Chemoprophylaxis should be administered to:

- Close contacts if they have symptoms suggestive of localised GAS infection
- Mother and baby if either develops iGAS in the neonatal period (first 28 days of life)

Where chemoprophylaxis is indicated:

- Oral penicillin V (250-500mgs QDS, appropriately adjusted for children – Appendix 4) for 10 days is the drug of first choice
- Azithromycin 12mg/kg/day in a single dose (maximum daily dose of 500mg/day) for five days, is a suitable choice for those who are allergic to penicillin
- In the unlikely event of an allergy to penicillin and azithromycin the local consultant microbiologist or infectious diseases physician should be contacted to discuss a suitable alternative
- Contacts with symptoms suggestive of iGAS should be immediately referred to the Emergency Department for assessment
- Other close contacts should receive a GAS information leaflet (Appendix 5) and be advised to seek immediate medical attention if they develop such symptoms
- A heightened index of suspicion for iGAS in close contacts should be maintained for 30 days after the diagnosis is made in the index patient

4.2.1 Aim of antimicrobial chemoprophylaxis

Chemoprophylaxis aims to reduce the risk of iGAS by eradicating carriage of GAS in those contacts at highest risk. It may act in two ways:

- Eradicating carriage from established carriers who pose a risk of infection to others
- Eradicating carriage in those who have newly acquired the invasive strain and who may themselves be at risk

4.2.2. Effectiveness of antibiotic chemoprophylaxis

Although the risk of subsequent iGAS among household contacts is higher than the risk among the general population, subsequent iGAS among household contacts is rare. No controlled clinical trials have evaluated the effectiveness of chemoprophylaxis in preventing iGAS among household contacts of an iGAS case. Several trials have shown the effectiveness of antimicrobial agents in the eradication of GAS from the upper respiratory tract. These studies form the basis of UK, US and Canadian guidelines for antimicrobial regimens for the management of contacts of cases of iGAS although the efficacy is unknown.^{2,10,98} Estimates of the risk of subsequent iGAS are uncertain because of the small number of documented cases in household contacts. Consequently, public health policies on the management of iGAS contacts vary between countries.

4.2.3 Recommended regimens

The following recommendations are based on current UK guidance.²

- Oral penicillin V (250-500mgs QID for ten days) is the drug of first choice where chemoprophylaxis is indicated (appropriately adjusted for children - Appendix 4)
- Azithromycin (12mgs/kg/day for 5 days) is a suitable choice for those who are allergic to penicillin

In the unlikely event of an allergy to penicillin and azithromycin, the local Consultant Microbiologist / Infectious Diseases Physician should be contacted to discuss a suitable alternative (eg. a cephalosporin (if there is no history of anaphylaxis to penicillin) or clindamycin)

4.2.4 Chemoprophylaxis following a single case of iGAS

It is recommended that chemoprophylaxis be administered to:

- Close contacts if they have symptoms suggestive of localised GAS infection (i.e. sore throat, fever, and skin infection)
- Mother and baby if either develops iGAS disease in the neonatal period (first 28 days of life)

If contacts have symptoms suggestive of iGAS (e.g. high fever, severe muscle aches, or localised muscle tenderness), then they should be immediately referred to the Emergency Department for assessment. A GAS information leaflet outlining the signs and symptoms of iGAS should be provided to all contacts. (Appendix 5) A heightened index of suspicion for iGAS in close contacts should be maintained for 30 days after the diagnosis is made in the index patient.

4.2.5 Management of Contacts in Specific Groups

4.2.5.i Injecting drug users

When iGAS occurs in injecting drug users (IVDUs), local drug services should be informed by the MOH about the clinical manifestations of GAS infection (sore throat, fever, skin infection, and/or localised muscle tenderness). This information should be disseminated among IVDU's, who should be advised to seek medical attention if they develop such symptoms or if they develop unusual skin lesions. General practitioners (GPs) and Emergency Departments should be alerted by the MOH to the occurrence of outbreaks of iGAS among IVDU's.

4.2.5.ii Nursing Homes

Following a single nursing home case, nursing homes should review infection control measures and maintain a heightened index of suspicion for 30 days after the diagnosis is made in the index patient. Close contacts among residents (sharing same room or side ward) and staff should only receive chemoprophylaxis if they have symptoms suggestive of localised GAS infection (i.e. sore throat, fever, skin infection) and the more likely diagnosis of a viral upper respiratory tract infection has been excluded. If close contacts have symptoms suggestive of invasive disease (e.g. high fever, severe muscle aches), localised muscle tenderness, they should be immediately referred to the Emergency Department for urgent assessment.

4.2.5.iii Nosocomial Infection

4.2.5.iii.a Contacts of postpartum or postsurgical infection

Obstetric iGAS Case - Definition:

- Isolation of GAS from either a sterile site, in association with a clinical postpartum infection (e.g. endometritis) or a surgical site infection, during the peripartum and postpartum period.³ The postpartum period includes all inpatient days and the first seven days after discharge.
- Infection is often community-acquired, but may be transmitted person to person or via a colonised or infected healthcare worker (HCW).

Surgical Site iGAS case - Definition:

- Isolation of GAS from a sterile site or a surgical site in a postsurgical patient, for whom the indication for surgery was not a pre-existing GAS infection, during the hospital stay or the first seven days after discharge.³
- Because of the short incubation period of GAS infections, cases that occur greater than seven days after discharge are more likely to be of community origin.³

The appropriate investigation of a single case of iGAS in a hospitalized patient is not well established, as many cases are community-acquired. In certain circumstances, a single obstetric or post-surgical case may warrant a limited epidemiological investigation by the Infection Control team. This investigation should be done in conjunction with the relevant clinical team to assess the potential for secondary cases. A limited epidemiological investigation includes:

1. Review of community risk factors for the case (contact with pharyngitis, cellulitis, invasive disease, contact with children).
2. Heightened surveillance for obstetric and surgical site GAS infections for the next 30 days.

If it is considered that the iGAS case was truly hospital-acquired and there are no community risk factors identifiable the following actions may be considered;

- Survey of staff involved in delivery/operation/examination of case - such as by questionnaire regarding recent illness consistent with GAS and throat/skin lesions swabs, if there are no community risk factors identifiable
- Swabbing close patient contacts of case (throat, skin lesions), all cases of endometritis and infants at discharge (throat, skin lesions, umbilicus)

4.2.5.iii.b Contacts of other nosocomial invasive group A streptococcal infection

The risks of on-going transmission of other nosocomial infections are less well described than postsurgical or obstetric infections. Infection after long-term carriage of GAS is probably rare. When nosocomial iGAS occurs, other than surgical site or obstetric infection, the organism may have been imported. Therefore the investigation should include investigation of the likelihood that visitors or another patient introduced the strain and a survey of staff with direct contact with the patient.

4.2.5.iv Healthcare Workers

Antimicrobial prophylaxis is not indicated for most HCWs who have been in contact with an infected patient.¹ If personal protective equipment (i.e. surgical mask and eye protection or face shield) has been worn, there is no exposure. In addition, if secretions from the nose, mouth or wound of the infected case did not contact a person's mucus membranes or non-intact skin that person was not exposed and does not need preventive antibiotics.¹ If exposure as defined above has occurred, the use of chemoprophylaxis is controversial. However, the Occupational Health Physician may consider chemoprophylaxis on a case-by-case basis.

4.3 Infection Control Considerations

Recommendations:

- Hand hygiene should be performed before and after all patient and equipment contact and after glove removal
- Gloves, apron and surgical mask should be worn for contact with the patient and equipment as appropriate
- Isolation in a single room with en-suite facilities is recommended for all patients who are known to have GAS infection until they have received 24 hours treatment with an appropriate antibiotic

4.3.1 Prevention of cross-infection

The prevention and control of iGAS may be best achieved by the use of standard and transmission based (contact and droplet) precautions.^{97,98}

4.3.1.i Standard precautions

Standard Precautions should be used when handling

- Blood or body fluids,
- Non-intact skin and mucous membranes.

4.3.1.ii Transmission-based Precautions

These include contact and droplet precautions.

Contact Precautions are designed to reduce the risk of transmitting GAS by direct or indirect contact. Gloves and aprons/disposable gown should be worn.^{97,98}

- Direct contact transmission: involves a direct body contact, surface to surface contact and physical transfer of microorganism between a susceptible host and an infected or colonised person. Direct spread may also take place on the hands of the HCW^{2;3;22;97;98}
- Indirect contact transmission involves contact of a susceptible host with a contaminated object or piece of equipment⁹⁸

Droplet precautions Droplets are generated from the source person primarily during coughing, sneezing, talking and during procedures such as suctioning and bronchoscopy. A surgical mask should be worn with eye protection or face shield for procedures where respiratory secretions or contact with the mucous membranes may take place, or if within 1 metre (3 feet) of the patient^{97,98}

4.3.2 Isolation of patients with invasive group A streptococcal infection

Isolation in a single room with en-suite facilities is recommended for all patients who are known to have iGAS infection until they have received 24 hours treatment with an appropriate antibiotic.⁹⁷

While we recommend that all patients with iGAS require isolation, we recognise that many institutions have limited isolation facilities. Therefore in these institutions, the group of iGAS patients who should take priority include

- Patients in maternity units with infections where GAS has been isolated
- Patients with profusely discharging wounds
- Abscess or draining wound that cannot be covered
- Patients with extensive skin sepsis
- Patients with extensive burns

Infected neonates should also be placed in isolation as soon as infection is suspected. The mother should receive chemoprophylaxis and it is not necessary to separate mother and baby. Breastfeeding is usually not contraindicated.

4.3.3 Isolation Precautions

The patient and visitors/carer/parent should be educated regarding the range of and need for precautions.⁹⁸ The following should be observed for all HCWs caring for patients with iGAS:

4.3.3.i Personal protection

- All cuts and skin lesions should be covered with a waterproof dressing
- Gloves and apron should be worn for contact with the patient and equipment, where a patient has burns or extensive wounds, a disposable gown may be worn
- Facial protection (surgical mask) is required if within 1 meter (3 feet) of the patient or when dressing extensive wounds and within the first 24 hours of appropriate antimicrobial treatment
- As per standard precautions, facial protection (surgical mask) is required when splashing with blood or body fluids is anticipated

4.3.3.ii Hand hygiene

- Antiseptic hand-hygiene or hand decontamination with an alcohol hand-gel should be performed before and after all contact with the patient and equipment

4.3.3.iii Isolation Room

- Limit movement of staff and transport of patient from the isolated area
- Keep all charts outside the room
- Stock room with essential equipment only
- Limit the number of visitors

4.3.3.iv Cleaning of the environment and equipment

- The isolation room should be cleaned daily using designated cleaning equipment and an appropriate disinfectant as per hospital protocol
- Decontaminate baby-feeding equipment individually: wash with detergent and hot water, rinse well and autoclave or liquid disinfect as appropriate and as per manufacturer's guidelines
- Wash all equipment, environmental surfaces and toys daily with detergent and hot water; disinfect as appropriate after cleaning (usually with 1,000 p.p.m. hypochlorite)
- Decontaminate bedpans/commode pans in bedpan washer

4.3.3.v Waste Management

- Handle all used linen as infected linen
- Dispose of all healthcare risk waste as according to the DoHC guidelines⁵³

4.4 Management of an outbreak of invasive group A streptococcal infection

Recommendations:

- An outbreak control team (OCT) with multidisciplinary representation as appropriate from infection control, clinical microbiology, infectious diseases, public health medicine, nursing and management should be set up for both hospital and community iGAS outbreaks
- The decision to give chemoprophylaxis and to whom should be based on careful assessment of all the epidemiological information available
- The OCT will endeavour to keep the public and media as fully informed as possible without prejudicing the investigation and without compromising any statutory responsibilities, legal requirements or patient confidentiality

4.4.1 Definition of an Outbreak

A tool that may prove useful in establishing the existence of a community outbreak is the CDC interactive calculator.⁹⁹ This enables public health specialists to compare the expected number of cases to the number in the outbreak under investigation. However, the calculator was not designed to establish links between iGAS cases or for use in investigations of outbreaks in closed populations such as nursing homes.

In general, GAS infections occur sporadically and have not been associated with outbreaks, though outbreaks of severe infections have occurred in closed environments such as military bases, hospitals and nursing homes.^{14;21;100} Whilst cases of iGAS occur among children attending school, there have been no subsequent cases of iGAS in schools and only a single subsequent case associated with varicella in a child care centre.¹⁰¹

4.4.2 Establishment of the Outbreak Control Team

When an outbreak of iGAS infection is suspected, an outbreak control team (OCT) should be established. The decision to convene an OCT will be made jointly, and as appropriately, by:

- Director of Public Health (DPH)/Medical Officer of Health (MOH)
- Consultant medical microbiologist

The final decision in the case of a community outbreak rests with the DPH/MOH. In the case of a hospital - based outbreak, the decision to convene an outbreak team rests with the consultant microbiologist or other doctor if there is no Consultant microbiologist.

In the case of community, nursing home or other non-acute healthcare facilities, the OCT should be chaired by the DPH/MOH. The DPH/MOH will notify the National Director for Population Health and the HPSC. Membership of the team should include: DPH/MOH, local consultant/GP, occupational health physician, Director of Nursing (or deputy)/Public Health nurse, consultant medical microbiologist, nursing home manager and infection control nurse. Where an outbreak involves more than one HSE-Health Area, the composition of the OCT should reflect this and include a representative from the HPSC. A decision should be taken at the initial stage as to which area takes the lead role.

In acute hospitals, the OCT should be chaired by the hospital chief executive (CEO) or deputy, and liaise closely with the DPH/MOH. Membership of the hospital OCT should include the attending physician/surgeon, consultant medical microbiologist, infectious diseases physician, hospital infection control team, occupational health physician, DPH/MOH, Hospital CEO or Deputy, the Hospital director of nursing and the patient services manager.

The role of the OCT is

- To review the evidence and confirm that there is an iGAS outbreak
- To develop a strategy to deal with the outbreak and to allocate individual responsibilities for implementing action
- To investigate the outbreak by careful assessment of all the epidemiological information available: confirmed and probable iGAS cases, serotyping, dates of onset, links between cases, size of population containing the cases, homogeneity of population containing the cases etc
- To implement control measures and to monitor their effectiveness in dealing with the outbreak and in preventing further spread
- To advise management on the necessary action to control the outbreak
- To decide the approach to antibiotic chemoprophylaxis
- To agree a communications strategy to provide clear, consistent and accurate information and to keep relevant persons within the hospital/nursing home, HSE- Health Area, outside agencies, the general public and the media appropriately informed

- To provide support, advice and guidance to individuals and the various organisations directly involved in dealing with the outbreak
- To declare when the outbreak is over and prepare a report

Effective communication with relevant authorities, other professional groups, the media and the general public during an outbreak is an important aspect of outbreak management. All relevant information should be shared as appropriate with these groups. (Appendix 7) The OCT will endeavour to keep the public and media as fully informed as possible without prejudicing the investigation and without compromising any statutory responsibilities, legal requirements or patient confidentiality.

4.4.3. Management of Outbreaks in Specific Groups

4.4.3.i. Postpartum or Postsurgical iGAS

A common source of GAS transmission needs to be ruled out, if two or more cases of postpartum or postsurgical iGAS with an identical or indistinguishable strain, which are epidemiologically linked, are identified within a one-month period.

Isolates should be sent to the molecular laboratory for GAS typing as outlined in Section 2.3. The following actions are recommended if typing results reveal identical/indistinguishable GAS strains:³

1. Enhanced surveillance for GAS infection, in order to establish if there is an epidemiological link between cases.
2. Screening of HCWs is recommended for all HCWs epidemiologically linked to the case patients. Sites that may be screened vary and include throat and any skin lesions. Perineal swabs may also be taken for screening.
3. Screened HCWs may return to work pending culture results. Colonised HCWs should be suspended from patient care duties until they have received chemoprophylaxis for 24 hours.¹⁰² This suspension should not be counted as leave.
4. The Infection Control Team should review infection control procedures in the relevant areas and re-educate HCWs regarding the use of standard precautions.

4.4.3.ii. Nursing homes and other long-term care facilities

Targeted or mass antibiotic prophylaxis for residents and staff should be considered (depending on factors such as interval between cases, epidemiological links, fatality rate). Infection control measures should be reviewed.

4.4.3.iii. Household outbreaks

If two or more cases of iGAS occur in the same household within a 30-day time period then the entire household should receive chemoprophylaxis.²

4.3.4.iv Community outbreaks

The OCT should decide on the extent of the public health response.

Appendix 1: A draft of this document was sent to the following groups for consultation

Academy of Medical Laboratory Science

Emergency Medicine Association

Irish College of General Practitioners

Irish Society of Clinical Microbiologists

Irish Patients Association

Intensive Care Society of Ireland

Infection Control Nurses Association

Infectious Diseases Consultants Group

Royal College of Physicians of Ireland (RCPI)

RCPI Faculty of Pathology

RCPI Faculty of Public Health Medicine

RCPI Faculty of Paediatrics

RCPI Faculty of Occupational Health Medicine

RCPI Institute of Obstetrics and Gynaecology

Royal College of Surgeons in Ireland (RCSI)

RCSI Faculty of Radiologists

Surveillance Scientists Association

Appendix 2: Proposed iGAS enhanced Surveillance Form



Invasive Group A Streptococcal (iGAS) Infection Enhanced Data Form



<p>HSE Area / CCA _____</p> <p>Lab Specimen No. _____</p> <p>Hosp Patient /Chart No. _____</p> <p>Name of laboratory _____</p> <p>Name of hospital _____</p> <p>Name of clinician _____</p>	<p>i) PATIENT DETAILS</p> <p>Patient's initials _____ Male <input type="checkbox"/> Female <input type="checkbox"/></p> <p>Date of birth (dd/mm/yyyy) _____ or age _____ <small>Age in Years/Months/Days (please state)</small></p> <p>Date of hospital admission (dd/mm/yyyy) _____</p> <p>County of residence _____</p> <p>Nationality _____</p>																											
<p>ii) ISOLATE DETAILS</p> <p>Date of specimen (dd/mm/yyyy) _____</p> <p>M Serotype (if known) _____</p> <p>Isolate stored? Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Other clinically relevant pathogens associated with this illness/episode? (Please specify) _____ No <input type="checkbox"/> NK <input type="checkbox"/></p>	<table style="width: 100%;"> <tr> <th style="text-align: left; padding: 5px;">For confirmed cases Isolated from:</th> <th style="text-align: left; padding: 5px;">For probable cases (STSS cases only) Isolated from:</th> </tr> <tr> <td style="padding: 5px;">Blood <input type="checkbox"/></td> <td style="padding: 5px;">Throat <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">Joint <input type="checkbox"/></td> <td style="padding: 5px;">Vagina <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">Deep tissue <input type="checkbox"/></td> <td style="padding: 5px;">Sputum <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">CSF <input type="checkbox"/></td> <td style="padding: 5px;">Other non-sterile site (please specify) _____</td> </tr> <tr> <td style="padding: 5px;">Abscess <input type="checkbox"/></td> <td></td> </tr> <tr> <td style="padding: 5px;">Bone <input type="checkbox"/></td> <td></td> </tr> <tr> <td style="padding: 5px;">Other sterile site (please specify) _____</td> <td></td> </tr> </table>	For confirmed cases Isolated from:	For probable cases (STSS cases only) Isolated from:	Blood <input type="checkbox"/>	Throat <input type="checkbox"/>	Joint <input type="checkbox"/>	Vagina <input type="checkbox"/>	Deep tissue <input type="checkbox"/>	Sputum <input type="checkbox"/>	CSF <input type="checkbox"/>	Other non-sterile site (please specify) _____	Abscess <input type="checkbox"/>		Bone <input type="checkbox"/>		Other sterile site (please specify) _____												
For confirmed cases Isolated from:	For probable cases (STSS cases only) Isolated from:																											
Blood <input type="checkbox"/>	Throat <input type="checkbox"/>																											
Joint <input type="checkbox"/>	Vagina <input type="checkbox"/>																											
Deep tissue <input type="checkbox"/>	Sputum <input type="checkbox"/>																											
CSF <input type="checkbox"/>	Other non-sterile site (please specify) _____																											
Abscess <input type="checkbox"/>																												
Bone <input type="checkbox"/>																												
Other sterile site (please specify) _____																												
<p>iii) CLINICAL DETAILS</p> <p>Case definition: Confirmed <input type="checkbox"/> Probable (STSS only) <input type="checkbox"/> Date of onset (dd/mm/yyyy) _____</p> <p>Clinical presentation: Please tick all that apply</p> <table style="width: 100%; border: none;"> <tr> <td style="padding: 5px;">Peritonitis <input type="checkbox"/></td> <td style="padding: 5px;">Septic arthritis <input type="checkbox"/></td> <td style="padding: 5px;">Meningitis <input type="checkbox"/></td> <td style="padding: 5px;">Puerperal sepsis <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">Myositis <input type="checkbox"/></td> <td style="padding: 5px;">Toxic shock-like syndrome <input type="checkbox"/></td> <td style="padding: 5px;">Cellulitis <input type="checkbox"/></td> <td style="padding: 5px;">Erysipelas <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">Bacteraemia <input type="checkbox"/></td> <td style="padding: 5px;">Necrotising fasciitis <input type="checkbox"/></td> <td style="padding: 5px;">Pneumonia <input type="checkbox"/></td> <td></td> </tr> </table> <p>Other (please specify) _____</p> <p>Degree of severity: Please refer to Case Definition for details of diagnostic parameters</p> <table style="width: 100%; border: none;"> <tr> <td style="padding: 5px;">Hypotensive shock <input type="checkbox"/></td> <td style="padding: 5px;">Coagulopathy <input type="checkbox"/></td> <td style="padding: 5px;">Erythematous rash <input type="checkbox"/></td> <td style="padding: 5px;">Respiratory distress <input type="checkbox"/></td> <td style="padding: 5px;">None of these <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">Renal impairment <input type="checkbox"/></td> <td style="padding: 5px;">Liver abnormality <input type="checkbox"/></td> <td style="padding: 5px;">Soft-tissue necrosis <input type="checkbox"/></td> <td></td> <td style="padding: 5px;">Not known <input type="checkbox"/></td> </tr> </table> <p>Clinical management</p> <p>Admitted to ITU? Yes <input type="checkbox"/> No <input type="checkbox"/> NK <input type="checkbox"/> Surgical intervention? Yes <input type="checkbox"/> No <input type="checkbox"/> NK <input type="checkbox"/></p> <p>If YES, number of days spent in ITU (of the 7 days following GAS isolation) _____ Days Please specify procedures _____</p> <p>Outcome (at one week after GAS isolation)</p> <p>Alive <input type="checkbox"/> RIP <input type="checkbox"/> NK <input type="checkbox"/></p> <p>If RIP date of death (dd/mm/yyyy) _____</p> <table style="width: 100%; border: none;"> <tr> <td style="padding: 5px;">RIP - GAS as main cause of death <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">RIP - GAS contributed (not main cause) <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">RIP - GAS contribution unknown <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">RIP - GAS did not contribute (cause unknown) <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">RIP - GAS did not contribute (cause known) <input type="checkbox"/></td> </tr> </table>		Peritonitis <input type="checkbox"/>	Septic arthritis <input type="checkbox"/>	Meningitis <input type="checkbox"/>	Puerperal sepsis <input type="checkbox"/>	Myositis <input type="checkbox"/>	Toxic shock-like syndrome <input type="checkbox"/>	Cellulitis <input type="checkbox"/>	Erysipelas <input type="checkbox"/>	Bacteraemia <input type="checkbox"/>	Necrotising fasciitis <input type="checkbox"/>	Pneumonia <input type="checkbox"/>		Hypotensive shock <input type="checkbox"/>	Coagulopathy <input type="checkbox"/>	Erythematous rash <input type="checkbox"/>	Respiratory distress <input type="checkbox"/>	None of these <input type="checkbox"/>	Renal impairment <input type="checkbox"/>	Liver abnormality <input type="checkbox"/>	Soft-tissue necrosis <input type="checkbox"/>		Not known <input type="checkbox"/>	RIP - GAS as main cause of death <input type="checkbox"/>	RIP - GAS contributed (not main cause) <input type="checkbox"/>	RIP - GAS contribution unknown <input type="checkbox"/>	RIP - GAS did not contribute (cause unknown) <input type="checkbox"/>	RIP - GAS did not contribute (cause known) <input type="checkbox"/>
Peritonitis <input type="checkbox"/>	Septic arthritis <input type="checkbox"/>	Meningitis <input type="checkbox"/>	Puerperal sepsis <input type="checkbox"/>																									
Myositis <input type="checkbox"/>	Toxic shock-like syndrome <input type="checkbox"/>	Cellulitis <input type="checkbox"/>	Erysipelas <input type="checkbox"/>																									
Bacteraemia <input type="checkbox"/>	Necrotising fasciitis <input type="checkbox"/>	Pneumonia <input type="checkbox"/>																										
Hypotensive shock <input type="checkbox"/>	Coagulopathy <input type="checkbox"/>	Erythematous rash <input type="checkbox"/>	Respiratory distress <input type="checkbox"/>	None of these <input type="checkbox"/>																								
Renal impairment <input type="checkbox"/>	Liver abnormality <input type="checkbox"/>	Soft-tissue necrosis <input type="checkbox"/>		Not known <input type="checkbox"/>																								
RIP - GAS as main cause of death <input type="checkbox"/>																												
RIP - GAS contributed (not main cause) <input type="checkbox"/>																												
RIP - GAS contribution unknown <input type="checkbox"/>																												
RIP - GAS did not contribute (cause unknown) <input type="checkbox"/>																												
RIP - GAS did not contribute (cause known) <input type="checkbox"/>																												
<p>Please see next page for last section and notes</p> <p>Form completed by _____</p> <p>Date completed _____</p> <p>CIDR event number (if unknown, please leave blank) _____</p>																												
<p>Use the space below to enter any relevant reference numbers etc, but please do not enter patient name or address</p> <p>_____</p> <p>_____</p> <p>_____</p> <p style="text-align: right;">Continued...</p>																												

iv) EPIDEMIOLOGICAL INFORMATION

Risk factors: Please tick all that apply No identified risk factors Information not known

Steroid use <input type="checkbox"/>	Alcoholism <input type="checkbox"/>	Skin lesion/wound <input type="checkbox"/>	Recent childbirth (last 4 weeks) <input type="checkbox"/>
Diabetes <input type="checkbox"/>	Malignancy <input type="checkbox"/>	If YES: trauma <input type="checkbox"/>	If YES: date <input type="text"/>
Injecting drug user <input type="checkbox"/>	Non-steroidal anti-inflammatory drugs <input type="checkbox"/>	insect bite <input type="checkbox"/>	Vaginal delivery <input type="checkbox"/>
Varicella <input type="checkbox"/>		Surgical wound <input type="checkbox"/>	Caesarian section <input type="checkbox"/>

Surgery (please specify procedure, date and name of hospital)

Other relevant risk factors including immunosuppression or previous GAS

Other epidemiological information

Occupation of patient

Recent overseas travel (in the last 2 weeks before onset)?
 Yes No NK If YES, which countries?

Was the patient admitted from a closed institution directly (e.g. transfer from hospital, nursing home, prison)? Please also state country if transferred from outside Ireland.
 Yes No NK If YES, please specify type

Was this infection hospital-acquired? (Defined as infection occurring 48 hrs or more after admission, including time in originating hospital in case of transfer)
 Yes No NK

Was this case related/contact of other case(s) of GAS disease? Yes No NK If YES, please provide details -
 Relationship to this case Date of onset
 Specimen no. of related case Clinical presentation of related case

Is this case part of an outbreak/cluster?
 Yes No NK If YES, outbreak identifier

v) COMMENTS

Guidance on the completion of the form – please complete one reporting form for each case diagnosed, meeting the case definition of invasive group A streptococcal disease as outlined below. Please complete as much of this form as possible. All information supplied will be treated as confidential, anonymised data will be analysed at HPSC.

CASE DEFINITION

Clinical Description

- An acute febrile illness which may be associated with Streptococcal Toxic Shock Syndrome (STSS). STSS is characterised by hypotension (5th percentile of systolic blood pressure in children, or <90mmHg systolic pressure in adolescents and adults) and two or more of the following:
 - Ranae equipment (swatens greater than twice upper limit of normal for age)
 - Coagulopathy (platelets <100,000/10⁹) or evidence of disseminated intravascular coagulation)
 - Liver dysfunction (ALT, AST or bilirubin more than twice upper limit of normal for age)
 - Adult respiratory distress syndrome (pulmonary infiltrates and hypoxaemia without cardiac failure or generalised oedema)
 - Generalised erythematous rash that may desquamate
 - Soft tissue necrosis (necrotising fasciitis, myositis, gangrene)

Laboratory criteria for diagnosis

Isolation of group A streptococcus (S. pyogenes) from a normally sterile site (e.g. blood, cerebrospinal fluid, pleural fluid)

For probable case (STSS only)

Isolation of group A streptococcus from a nonsterile site (e.g. throat, sputum, vaginal)

Case classification

- | | |
|-----------------|---|
| Possible | N/A |
| Probable (STSS) | A clinically compatible case and meeting the probable laboratory criteria |
| Confirmed | A case that is laboratory confirmed |

Thank you for your assistance

Please forward to Director of Public Health / Medical Officer of Health and then from Departments of Public Health to the Health Protection Surveillance Centre (HPSC Fax 01 856 1299).

Appendix 3: 'At-risk' populations for invasive group A streptococcal infection^{17;57;107-113}

- Extremes of age: young children, adults greater than 65 years
- Skin trauma
- Young adults exposed to children
- Immunocompromised patients (e.g. underlying malignancy, HIV infection and high-dose steroid use)
- Diabetes mellitus
- Underlying heart or chronic lung disease
- Alcohol abuse
- Intravenous drug users
- Pregnant women
- Concomitant varicella infection

The development of iGAS after use of non-steroidal anti-inflammatory drugs is a controversial topic.

Several reports had suggested a relationship^{112;114} but equally others have refuted it.^{17;115} At this time there is insufficient evidence on which to base a clinical decision about the use or restriction of non-steroidal anti-inflammatory drugs in children with varicella infection.

Appendix 4: Antibiotic dosing for invasive group A streptococcal infection in children

IV Clindamycin:

Age:	1 month-12 years	40mg/kg in 3-4 divided doses
	12-18 years	600-900mg every 8 hours
		Life-threatening infection 1.2g every 6 hours

IV Flucloxacillin:

Age:	1 month-18 years	50mg/kg every 6 hours (Maximum dose, 2g every 6 hours)	
	Neonate:	<7 days	50-100mg/kg every 12 hours
		7-20 days	50-100mg/kg every 8 hours
		21-28 days	50-100mg/kg every 6 hours

IV Benzyl penicillin:

Age:	1 month-18 years	50mg/kg/dose every 4-6 hours (Maximum, 2.4g every 4 hours)	
	Neonate:	Preterm	50mg/kg every 12 hours
		<7 days	50mg/kg every 12 hours
		7-28 days	50mg/kg every 8 hours

Oral Penicillin V:

Not routinely recommended, consider use in immunocompromised contacts.

Age:	< 1 year	62.5mg every 6 hours
	1-5 years	125mg every 6 hours
	6-12 years	250mg every 6 hours
	> 12 years	500mg every 6 hours

Appendix 5: Patient Information Leaflet:

Available at <http://www.hpsc.ie/A-Z/Other/GroupAStreptococcalDiseaseGAS/>

• What is group A streptococcus?

Group A streptococcus (GAS) is often found in the throat and on the skin. People may carry it in their throat or on their skin and not be ill. Most GAS infections are fairly mild illnesses such as "strep throat" and impetigo (skin infection). It is very unusual for it to cause other severe and even life-threatening diseases.

• How is it spread?

GAS spreads between people through sneezing, kissing and skin contact. People who are already sick with GAS are most likely to spread the infection. Healthy people who carry the bacteria but have no symptoms are much less contagious.

• What kinds of illnesses are caused by GAS?

GAS causes a range of mostly mild illnesses, such as "strep throat" and impetigo (skin infections). It is very unusual for it to cause more severe and life-threatening illness but it can happen. Rare complications include acute rheumatic fever and post-streptococcal glomerulonephritis (heart and kidney diseases).

• What is invasive GAS disease?

Severe, sometimes life-threatening, disease can happen when GAS gets into parts of the body where it is usually not found, such as blood, muscle or the lungs. These infections are called "invasive GAS disease". Two of the most severe, but least common forms are necrotising fasciitis and streptococcal toxic shock syndrome. Necrotising fasciitis destroys muscles, fat and skin tissue. Streptococcal toxic shock syndrome causes a rapid drop in blood pressure which causes organ failure (e.g. kidneys, liver, lungs).

• Why does invasive GAS disease happen?

Invasive GAS infections happen when the bacteria get past the defences of the person who is infected. This may happen when someone has sores or other breaks in the skin that allow the bacteria to get into the tissue, or when someone can't fight off infection because of chronic illness or an illness that affects the immune system. Some strains of GAS are more likely to cause severe disease than others.

Who is most at risk of getting invasive GAS disease?

Most people who come in contact with GAS will not develop invasive GAS disease. Most will have no symptoms at all, but some may have a throat or skin infection. Although healthy people can get invasive GAS disease, people with chronic illnesses like cancer, diabetes and kidney dialysis patients, and those who use medications such as steroids, are more at risk.

• How can GAS infection be prevented?

Washing your hands - especially after coughing and sneezing - and before preparing foods or eating - reduces the spread of all types of GAS infection. People with 'strep throats' should stay at home for 24 hours after taking an antibiotic. Anyone with signs of an infected wound, especially if fever occurs, should seek medical care.

• How is GAS disease treated?

GAS infections are treated with antibiotics. The earlier these can be taken the better. People with necrotising fasciitis, may need surgery to remove damaged tissue.

• What is the situation in Ireland?

Invasive Group A streptococcus infection has been a notifiable disease in Ireland since the beginning of 2004. This means that, by law, any cases must be reported to the Medical Officer of Health. Before 2004, data on GAS was not collected regularly. Since 2004, 84 cases of iGAS have been notified to the Health Protection Surveillance Centre, which is the agency responsible for collecting information on notifiable disease in Ireland: thirty-five in 2004 and 49 in 2005. It affected almost equal numbers of males and females. Cases occurred in all age groups but were most common in elderly people. The numbers show that invasive GAS was detected in around one in 100,000 people (0.9 per 100,000 population in 2004, 1.25 per 100,000 population in 2005) in Ireland every year. This is much lower than reported from the UK and USA, where more than 3 per 100,000 population have developed the infection.

Appendix 6: Pathogenesis - Bacterial virulence factors of group A streptococcus

Beta-haemolytic streptococci can be classified into serogroups based on precipitin reactions to the cell membrane M-protein. Most strains pathogenic for humans belong to serogroup A (*S. pyogenes*). GAS may be further subdivided on the basis of antigenic differences in the surface M-protein and on the basis of nucleotide differences in the *emm* gene, which encodes it.¹⁰³

The M protein plays an important role in inhibiting phagocytosis by polymorphonuclear leucocytes by binding complement control factors, thereby preventing activation of the alternate pathway.¹⁰⁴ More than 90 serotypes of GAS have been identified. Serotypes M-1, M-3, M-12 and M-28 are particularly associated with iGAS.^{13;105}

The GAS polysaccharide capsule also contributes to antiphagocytic function and is a poor immunogen.¹⁰⁶ Surface structures such as the M protein family, the capsule and a number of adhesion molecules including fibronectin, vitronectin, and collagen-binding proteins and lipoteichoic acid, allow the organism to adhere to and colonise the skin and mucus membranes.¹⁶ In addition, extracellular toxins, including superantigenic streptococcal pyrogenic exotoxins, contribute to tissue invasion and are thought to be responsible for the rash in scarlet fever and play a role in STSS.¹⁶ Continued carriage after appropriate antimicrobial therapy is thought to be related to intracellular localization of some GAS strains.¹⁵ Expression of GAS virulence factors under different environmental conditions, and over time, are controlled by a complex system of global genetic modulators.¹⁶

Appendix 7: Communications with the media by the iGAS Outbreak Control Team (OCT)

1. The OCT will endeavour to keep the public and media as fully informed as possible without prejudicing the investigation and without compromising any statutory responsibilities, legal requirements or patient confidentiality.
2. At the first meeting of the OCT arrangements for dealing with the media should be discussed and agreed. A decision should be made as to whether a member from the Communications Department should be in attendance at OCT meetings.
3. Timely press statements should be agreed by the OCT or by a small sub-group, with the agreement of the OCT.
4. No other member of the OCT will release information to the press without the agreement of the Team.
5. Contents of press statements should be given to hospital medical and nursing staff and field workers to ensure that consistent advice is being provided to the public.

Reference List

1. Group A Streptococcal Disease Surveillance Protocol for Ontario Hospitals. Ontario Hospital Association and the Ontario Medical Association . 2004.
Ref Type: Electronic Citation
2. Health Protection Agency. Interim UK guidelines for management of close community contacts of invasive group A streptococcal disease -Health Protection Agency,Group A Streptococcus Working Group. *Commun Dis Public Health* 2004;7:354-61.
3. Prevention of invasive group A streptococcal disease among household contacts of case patients and among postpartum and postsurgical patients: recommendations from the Centers for Disease Control and Prevention. *Clin Infect Dis* 2002;35:950-959.
4. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323:334-36.
5. Hoge CW, Schwartz B, Talkington DF, Breiman RF, MacNeill EM, Englander SJ. The changing epidemiology of invasive group A streptococcal infections and the emergence of streptococcal toxic shock-like syndrome. A retrospective population-based study. *JAMA* 1993;269:384-89.
6. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance. Centers for Disease Control and Prevention. Last accessed on 17/11/2005. 2005.
Ref Type: Electronic Citation
7. Schalen C. European surveillance of severe group A streptococcal disease. *Eurosurveillance weekly* 2005;6.
8. National Disease Surveillance Centre. Case Definitions for Notifiable Diseases. Infectious Diseases (Amendment) (No 3) Regulations 2003 (SI No.707 of 2003). National Disease Surveillance Centre . 2004.
Ref Type: Electronic Citation
9. Coakley P, Bergin C. Invasive Group A Streptococcal Infection. *Epi-Insight* 2003;4:4.
10. Davies HD, McGeer A, Schwartz B, Green K, Cann D, Simor AE, Low DE. Invasive group A streptococcal infections in Ontario, Canada. Ontario Group A Streptococcal Study Group. *N Engl J Med* 1996;335:547-54.
11. Demers B, Simor AE, Vellend H, Schlievert PM, Byrne S, Jamieson F, Walmsley S, Low DE. Severe invasive group A streptococcal infections in Ontario, Canada: 1987-1991. *Clin Infect Dis* 1993;16:792-800.
12. American Academy of Pediatrics. Committee on Infectious Diseases. Severe invasive group A streptococcal infections: a subject review. *Pediatrics* 1998;101:136-40.
13. Stevens DL. Invasive group A streptococcus infections. *Clin Infect Dis* 1992;14:2-11.
14. Stevens DL. Streptococcal toxic-shock syndrome: spectrum of disease, pathogenesis, and new concepts in treatment. *Emerg Infect Dis* 1995;1:69-78.
15. Neeman R, Keller N, Barzilai A, Korenman Z, Sela S. Prevalence of internalisation-associated gene, *prtF1*, among persisting group-A streptococcus strains isolated from asymptomatic carriers. *Lancet* 1998;352:1974-77.
16. Bisno AL, Brito MO, Collins CM. Molecular basis of group A streptococcal virulence. *Lancet Infect Dis* 2003;3:191-200.
17. Factor SH. Invasive group A streptococcal disease: risk factors for adults. *Emerg Infect Dis* 2003;9:970-977.

18. Mazon A, Gil-Setas A, Sota de la Gandara LJ, Vindel A, Saez-Nieto JA. Transmission of *Streptococcus pyogenes* causing successive infections in a family. *Clin Microbiol Infect* 2003;9:554-59.
19. Weiss K, Laverdiere M, Lovgren M, Delorme J, Poirier L, Beliveau C. Group A *Streptococcus* carriage among close contacts of patients with invasive infections. *Am J Epidemiol* 1999;149:863-68.
20. Robinson KA, Rothrock G, Phan Q, Saylor B, Stefonek K, Van Beneden C, Levine OS. Risk for severe group A streptococcal disease among patients' household contacts. *Emerg Infect Dis* 2003;9:443-47.
21. Schwartz B, Elliott JA, Butler JC, Simon PA, Jameson BL, Welch GE, Facklam RR. Clusters of invasive group A streptococcal infections in family, hospital, and nursing home settings. *Clin Infect Dis* 1992;15:277-84.
22. Ridgway EJ, Allen KD. Clustering of group A streptococcal infections on a burns unit: important lessons in outbreak management. *J Hosp Infect* 1993;25:173-82.
23. Stamm WE, Feeley JC, Facklam RR. Wound infections due to group A streptococcus traced to a vaginal carrier. *J Infect Dis* 1978;138:287-92.
24. Berkelman RL, Martin D, Graham DR, Mowry J, Freisem R, Weber JA, Ho JL, Allen JR. Streptococcal wound infections caused by a vaginal carrier. *JAMA* 1982;247:2680-2682.
25. Lamagni TL, Efstratiou A, Vuopio-Varkila J, Jasir A, and Schalen C. Strep-Euro. *Eurosurveillance weekly* 10[9]. 2005.
Ref Type: Electronic Citation
26. The Ontario Group A Streptococcal Study. <http://microbiology.mtsinai.on.ca/research/gas/default.asp> . 6-2-0006.
Ref Type: Electronic Citation
27. Jasir A, Schalen C on behalf of the Strep-EURO study group. Strep-EURO: progress in analysis and research into severe streptococcal disease in Europe, 2003-2004. *Eurosurveillance weekly* 10[2]. 2005.
Ref Type: Electronic Citation
28. CDC. Updated guidelines for evaluating public health surveillance systems: recommendations from the guidelines working group. *MMWR* 2005; 50.
29. Pitt TL. Bacterial typing systems: the way ahead. *J Med Microbiol* 1994;40:1-2.
30. Pitt TL. Molecular typing in practice. *J Hosp Infect* 1999;43 Suppl:S85-S88.
31. van Belkum A. High-throughput epidemiologic typing in clinical microbiology. *Clin Microbiol Infect* 2003;9:86-100.
32. Tenover FC, Arbeit RD, Goering RV, Mickelsen PA, Murray BE, Persing DH, Swaminathan B. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. *J Clin Microbiol* 1995;33:2233-39.
33. Efstratiou A. Group A streptococci in the 1990s. *J Antimicrob Chemother* 2000;45 Suppl:3-12.
34. Cunningham MW. Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev* 2000;13:470-511.
35. Facklam R, Beall B, Efstratiou A, Fischetti V, Johnson D, Kaplan E, Kriz P, Lovgren M, Martin D, Schwartz B, Totolian A, Bessen D, Hollingshead S, Rubin F, Scott J, Tyrrell G. *emm* typing and validation of provisional M types for group A streptococci. *Emerg Infect Dis* 1999;5:247-53.
36. Tanaka D, Gyobu Y, Kodama H, Isobe J, Hosorogi S, Hiramoto Y, Karasawa T, Nakamura S. *emm* Typing of group A streptococcus clinical isolates: identification of dominant types for throat and skin isolates. *Microbiol Immunol* 2002;46:419-23.

37. McGregor KF, Bilek N, Bennett A, Kalia A, Beall B, Carapetis JR, Currie BJ, Sriprakash KS, Spratt BG, Bessen DE. Group A streptococci from a remote community have novel multilocus genotypes but share *emm* types and housekeeping alleles with isolates from worldwide sources. *J Infect Dis* 2004;189:717-23.
38. Facklam RF, Martin DR, Lovgren M, Johnson DR, Efstratiou A, Thompson TA, Gowan S, Kriz P, Tyrrell GJ, Kaplan E, Beall B. Extension of the Lancefield classification for group A streptococci by addition of 22 new M protein gene sequence types from clinical isolates: *emm*103 to *emm*124. *Clin Infect Dis* 2002;34:28-38.
39. Vitali LA, Zampaloni C, Prenna M, Ripa S. PCR m typing: a new method for rapid typing of group a streptococci. *J Clin Microbiol* 2002;40:679-81.
40. McGregor KF, Spratt BG, Kalia A, Bennett A, Bilek N, Beall B, Bessen DE. Multilocus sequence typing of *Streptococcus pyogenes* representing most known *emm* types and distinctions among subpopulation genetic structures. *J Bacteriol* 2004;186:4285-94.
41. Upton M, Carter PE, Orange G, Pennington TH. Genetic heterogeneity of M type 3 group A streptococci causing severe infections in Tayside, Scotland. *J Clin Microbiol* 1996;34:196-98.
42. Gruteke P, van Belkum A, Schouls LM, Hendriks WD, Reubsaet FA, Dokter J, Boxma H, Verbrugh HA. Outbreak of group A streptococci in a burn center: use of pheno- and genotypic procedures for strain tracking. *J Clin Microbiol* 1996;34:114-18.
43. Kim S, Lee NY. Epidemiology and antibiotic resistance of group A streptococci isolated from healthy schoolchildren in Korea. *J Antimicrob Chemother* 2004;54:447-50.
44. McGregor KF, Spratt BG. Identity and prevalence of multilocus sequence typing-defined clones of group A streptococci within a hospital setting. *J Clin Microbiol* 2005;43:1963-67.
45. Raymond J, Schlegel L, Garnier F, Bouvet A. Molecular characterization of *Streptococcus pyogenes* isolates to investigate an outbreak of puerperal sepsis. *Infect Control Hosp Epidemiol* 2005;26:455-61.
46. Felkner M, Pascoe N, Shupe-Ricksecker K, Goodman E. The wound care team: a new source of group a streptococcal nosocomial transmission. *Infect Control Hosp Epidemiol* 2005;26:462-65.
47. Martin PR, Hoiby EA. Streptococcal serogroup A epidemic in Norway 1987-1988. *Scand J Infect Dis* 1990;22:421-29.
48. Adams EM, Gudmundsson S, Yocum DE, Haselby RC, Craig WA, Sundstrom WR. Streptococcal myositis. *Arch Intern Med* 1985;145:1020-1023.
49. Yoder EL, Mendez J, Khatib R. Spontaneous gangrenous myositis induced by *Streptococcus pyogenes*: case report and review of the literature. *Rev Infect Dis* 1987;9:382-85.
50. Urschel JD. Necrotizing soft tissue infections. *Postgrad Med J* 1999;75:645-49.
51. Facklam R. What happened to the streptococci: overview of taxonomic and nomenclature changes. *Clin Microbiol Rev* 2002;15:613-30.
52. European agreement concerning the international carriage of dangerous goods by road (ADR) SI No 29 2004. 2004.
Ref Type: Bill/Resolution
53. Hospital Planning Office and Department of Health and Children. Segregation Packaging and Storage Guidelines for Healthcare Risk Waste. Hospital Planning Office, Department of Health and Children April 2004[3rd Edition]. 2004.
Ref Type: Electronic Citation

54. Safety, Health and Welfare at Work (Biological Agents) Regulation 1998. SI No 248 (Amends SI No 146 of 1994) 2005. 2005.
Ref Type: Bill/Resolution
55. Pickering LK, and the Committee on Infectious Diseases. *Red Book. Report of the Committee on Infectious Diseases. American Academy of Pediatrics.* 2006.
56. Chelsom J, Halstensen A, Haga T, Hoiby EA. Necrotising fasciitis due to group A streptococci in western Norway: incidence and clinical features. *Lancet* 1994;344:1111-15.
57. Kaul R, McGeer A, Low DE, Green K, Schwartz B. Population-based surveillance for group A streptococcal necrotizing fasciitis: Clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases. Ontario Group A Streptococcal Study. *Am J Med* 1997;103:18-24.
58. Buchanan CS. Necrotizing fasciitis due to group A beta-hemolytic streptococci. *Arch Dermatol* 1970;101:664-68.
59. Barker FG, Leppard BJ, Seal DV. Streptococcal necrotising fasciitis: comparison between histological and clinical features. *J Clin Pathol* 1987;40:335-41.
60. Guibal F, Muffat-Joly M, Terris B, Pocard JJ, Morel P, Carbon C. Necrotising fasciitis. *Lancet* 1994;344:1771.
61. Seal DV, Kingston D. Streptococcal necrotizing fasciitis: development of an animal model to study its pathogenesis. *Br J Exp Pathol* 1988;69:813-31.
62. Howe PM, Eduardo FJ, Orcutt MA. Etiologic diagnosis of cellulitis: comparison of aspirates obtained from the leading edge and the point of maximal inflammation. *Pediatr Infect Dis J* 1987;6:685-86.
63. Lebre C, Girard-Pipau F, Roujeau JC, Revuz J, Saiag P, Chosidow O. Value of fine-needle aspiration in infectious cellulitis. *Arch Dermatol* 1996;132:842-43.
64. Epperly TD. The value of needle aspiration in the management of cellulitis. *J Fam Pract* 1986;23:337-40.
65. Kaplan EL. The group A streptococcal upper respiratory tract carrier state: an enigma. *J Pediatr* 1980;97:337-45.
66. Chapin KC, Blake P, Wilson CD. Performance characteristics and utilization of rapid antigen test, DNA probe, and culture for detection of group a streptococci in an acute care clinic. *J Clin Microbiol* 2002;40:4207-10.
67. Liang H, Cordova SE, Kieft TL, Rogelj S. A highly sensitive immuno-PCR assay for detecting Group A Streptococcus. *J Immunol Methods* 2003;279:101-10.
68. Louie L, Simor AE, Louie M, McGeer A, Low DE. Diagnosis of group A streptococcal necrotizing fasciitis by using PCR to amplify the streptococcal pyrogenic exotoxin B gene. *J Clin Microbiol* 1998;36:1769-71.
69. Muldrew KL, Simpson JF, Stratton CW, Tang YW. Molecular Diagnosis of Necrotizing Fasciitis by 16S rRNA Gene Sequencing and Superantigen Gene Detection. *J Mol Diagn* 2005;7:641-45.
70. Shet A, Kaplan EL. Clinical use and interpretation of group A streptococcal antibody tests: a practical approach for the pediatrician or primary care physician. *Pediatr Infect Dis J* 2002;21:420-426.
71. Kaplan EL, Rothermel CD, Johnson DR. Antistreptolysin O and anti-deoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. *Pediatrics* 1998;101:86-88.
72. Kaplan EL, Anthony BF, Chapman SS, Ayoub EM, Wannamaker LW. The influence of the site of infection on the immune response to group A streptococci. *J Clin Invest* 1970;49:1405-14.

73. Klein GC, Baker CN, Jones WL. "Upper limits of normal" antistreptolysin O and antideoxyribonuclease B titers. *Appl Microbiol* 1971;21:999-1001.
74. Seal DV. Necrotizing fasciitis. *Curr Opin Infect Dis* 2001;14:127-32.
75. Simonart T, Simonart JM, Derdelinckx I, De Dobbeleer G, Verleysen A, Verraes S, de Maubeuge J, Van Vooren JP, Naeyaert JM, de la BM, Peetermans WE, Heenen M. Value of standard laboratory tests for the early recognition of group A beta-hemolytic streptococcal necrotizing fasciitis. *Clin Infect Dis* 2001;32:E9-12.
76. Kellogg JA. Suitability of throat culture procedures for detection of group A streptococci and as reference standards for evaluation of streptococcal antigen detection kits. *J Clin Microbiol* 1990;28:165-69.
77. Murray P.R. *Manual of Clinical Microbiology*. ASM Press, 2005.
78. Ellner PD, Stoessel CJ, Drakeford E, Vasi F. A new culture medium for medical bacteriology. *Tech Bull Regist Med Technol* 1966;36:58-60.
79. Petts DN. Colistin-oxolinic acid-blood agar: a new selective medium for streptococci. *J Clin Microbiol* 1984;19:4-7.
80. Mandell GL, Bennett JE, Dolin R. *Principles & Practice of Infectious Diseases*. Elsevier Inc, Churchill Livingstone; 2005.
81. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing: Fifteenth Informational Supplement: updated tables for the Clinical and Laboratory Standards Institute (CLSI)/NCCLS antimicrobial susceptibility testing standards M2-A8 and M7-A6. M100-S15*. 2005.
82. British Society for Antimicrobial Chemotherapy. BSAC Disc Diffusion Method for Antimicrobial Susceptibility Testing. British Society for Antimicrobial Chemotherapy (BSAC) . 29-11-2005.
Ref Type: Electronic Citation
83. Macris MH, Hartman N, Murray B, Klein RF, Roberts RB, Kaplan EL, Horn D, Zabriskie JB. Studies of the continuing susceptibility of group A streptococcal strains to penicillin during eight decades. *Pediatr Infect Dis J* 1998;17:377-81.
84. Health Protection Agency.Centre for Infections. Pyogenic and non-pyogenic streptococcal bacteraemias. England, Wales and Northern Ireland. 2003. *Commun Dis Rep CDR Wkly* [serial online] 16th April 2004 14[16]. 4.
Ref Type: Electronic Citation
85. Herrera L, Salcedo C, Orden B, Herranz B, Martinez R, Efstratiou A, Saez Nieto JA. Rifampin resistance in *Streptococcus pyogenes*. *Eur J Clin Microbiol Infect Dis* 2002;21:411-13.
86. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858-73.
87. Sessler CN, Perry JC, Varney KL. Management of severe sepsis and septic shock. *Curr Opin Crit Care* 2004;10:354-63.
88. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive *Streptococcus pyogenes* infection. *Pediatr Infect Dis J* 1999;18:1096-100.
89. Stevens DL, Madaras-Kelly KJ, Richards DM. *In vitro* antimicrobial effects of various combinations of penicillin and clindamycin against four strains of *Streptococcus pyogenes*. *Antimicrob Agents Chemother* 1998;42:1266-68.
90. Stevens DL, Gibbons AE, Bergstrom R, Winn V. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. *J Infect Dis* 1988;158:23-28.

91. Stevens DL, Yan S, Bryant AE. Penicillin-binding protein expression at different growth stages determines penicillin efficacy in vitro and in vivo: an explanation for the inoculum effect. *J Infect Dis* 1993;167:1401-5.
92. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. *Am Surg* 1998;64:397-400.
93. Darenberg J, Ihendyane N, Sjolín J, Aufwerber E, Haidl S, Follin P, Andersson J, Norrby-Teglund A. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2003;37:333-40.
94. Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* 2002;CD001090.
95. Norrby-Teglund A, Ihendyane N, Darenberg J. Intravenous immunoglobulin adjunctive therapy in sepsis, with special emphasis on severe invasive group A streptococcal infections. *Scand J Infect Dis* 2003;35:683-89.
96. Patel R, Rouse MS, Florez MV, Piper KE, Cockerill FR, Wilson WR, Steckelberg JM. Lack of benefit of intravenous immune globulin in a murine model of group A streptococcal necrotizing fasciitis. *J Infect Dis* 2000;181:230-234.
97. Ayliffe GA, Fraise AP, Geddes AM, Mitchell K. *Control of Hospital Infection - Practical Handbook*. Hodder Arnold, 2000.
98. Garner JS. Guideline for isolation precautions in hospitals. The Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1996;17:53-80.
99. Investigating clusters of group A streptococcal disease . Centers for Disease Control and Prevention . 2005.
Ref Type: Electronic Citation
100. DiPersio JR, File TM, Jr., Stevens DL, Gardner WG, Petropoulos G, Dinsa K. Spread of serious disease-producing M3 clones of group A streptococcus among family members and health care workers. *Clin Infect Dis* 1996;22:490-495.
101. Outbreak of invasive group A Streptococcus associated with varicella in a childcare center. *MMWR* 1997;46:994-48.
102. Snellman LW, Stang HJ, Stang JM, Johnson DR, Kaplan EL. Duration of positive throat cultures for group A streptococci after initiation of antibiotic therapy. *Pediatrics* 1993;91:1166-70.
103. Beall B, Facklam R, Thompson T. Sequencing *emm*-specific PCR products for routine and accurate typing of group A streptococci. *J Clin Microbiol* 1996;34:953-58.
104. Gillespie SH. New tricks from an old dog: streptococcal necrotising soft-tissue infections. *Lancet* 2004;363:672-73.
105. Johnson DR, Stevens DL, Kaplan EL. Epidemiologic analysis of group A streptococcal serotypes associated with severe systemic infections, rheumatic fever, or uncomplicated pharyngitis. *J Infect Dis* 1992;166:374-82.
106. Moses AE, Wessels MR, Zalcmán K, Alberti S, Natanson-Yaron S, Menes T, Hanski E. Relative contributions of hyaluronic acid capsule and M protein to virulence in a mucoid strain of the group A Streptococcus.



Féilímeannacht na Seirbhíse Sláinte
Health Service Executive



Health Protection Surveillance Centre

25-27 Middle Gardiner Street
Dublin 1, Ireland

Ph +353 1 876 5300
Fx +353 1 856 1299
E info@mailx.hse.ie

www.hpsc.ie