

# Whole genome sequencing in the investigation of recurrent invasive Group A streptococcus outbreaks in a maternity unit

Running title: Recurrent iGAS outbreaks in a maternity unit

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## Summary

### Background

The clinical manifestations of Group A streptococcus (GAS) – (*Streptococcus pyogenes*) are diverse, ranging from asymptomatic colonisation to devastating

invasive disease. Maternity related clusters of invasive Group A streptococcus (iGAS) infection are complex to investigate and control, especially if recurrent.

## **Aim**

We report on the investigation into three episodes of *emm 75* GAS/iGAS infection in maternity patients at one hospital site over a 4 year period, two with monophyletic ancestry.

## **Methods**

The episodes are described, together with whole genome sequence isolate analyses. Single nucleotide polymorphism differences were compared with contemporaneous *emm 75* genomes.

## **Findings**

Seven mothers had GAS/iGAS in over a 4 year period, *emm 75*, *S.pyogenes* and one had iGAS (in year 4) *emm 3*, *S.pyogenes* (subsequently discounted as linked). Three (clinical/screening samples) of the seven babies of *emm 75* positive mothers and 3 screened healthcare workers were positive for GAS *emm 75*. Whole genome sequence similarity suggests a shared ancestral lineage and suggested a common source transmission but directionality of transmission cannot be inferred. However the findings indicate that persistence of a particular clone in a given setting may be long-term.

## **Conclusions**

Occupational health procedures were enhanced, staff were screened and antibiotic therapy provided to GAS positive staff and patients. The definitive source of infection could not be identified, although staff / patient transmission is the most likely route. The pattern of clonal GAS transmission over 4 years suggests long-term persistence of GAS may have occurred.

**Keywords.** iGAS, Streptococcus, maternity, whole genome sequencing

## **Introduction**

Group A Streptococcal infections have a spectrum of clinical manifestations (asymptomatic colonisation to severe invasive infections) occurring sporadically or in clusters. The incidence of invasive infection ranges from 1-3 cases/100,000 population, with a case fatality of ~17% [1, 2]. Transmission is mostly via respiratory droplets/discharges or infected skin lesions [3]. Most GAS isolates are from the throat, but skin, vaginal, anal and perineal carriage have been noted; asymptomatic throat carriage is 5-12% [4-6].

Onward transmission can be reduced by robust infection prevention and control, prompt treatment of infection in cases and decolonisation through chemoprophylaxis in prolonged close contacts and colonised mother / neonate contacts. Wider chemoprophylaxis may be appropriate in some outbreaks, e.g. closed communities.

After a hospital acquired iGAS case, the probability of a second in the same hospital is ~40% within 12 months and 9.3% of hospital associated GAS infections are linked to others [1].

There is a particular association between iGAS and the peripartum / postpartum period [1, 7]. The age-specific attack rate for peripartum / puerperal period GAS is 20 times that of non-pregnant females [8]. In 2003-2004, 2-11% of all severe GAS infections were associated with childbirth. Likewise between 1997-1999, puerperal GAS constituted 2% of all invasive GAS infections in the US/Canada. [5, 7]. Pregnancy associated iGAS occurs mostly in the peripartum, but has been reported during pregnancy and the later postpartum period. Peripartum iGAS carries a substantial maternal morbidity / mortality burden (25%), however the risk to the baby is greatest in antenatal iGAS, but still poses a substantial hazard to the new-born [9].

GAS strains can be distinguished by *emm* gene sequence analysis. In England between September 2015–March 2016, the most common *emm* types associated with iGAS were *emm* 1 (30%), 12 (12%) and 89 (11%)<sup>[10]</sup>.

Puerperal sepsis is fortunately rare. Indeed there are few reports of outbreaks in maternity settings published in recent years, however they may remain unrecognised; outbreaks have been associated with infected healthcare workers (staff-members) and shared bathroom facilities [11-13].

Two clusters and an isolated case of infection with *emm* 75 GAS were noted over a 4 year period in an acute hospital maternity unit providing in/outpatient and community maternity services. (These are hereafter named as the initial cluster, the isolated case 2 years later and last cluster 4 years after the initial cluster). We report the investigations into the source, the control measures instigated and the application of whole genome sequencing (WGS).

## Methods

Outbreak control teams for each episode were established to investigate the potential source and implement control measures.

### Case definitions

#### Confirmed

*A maternity staff-member/associated HCW working at the unit, or a maternity inpatient or baby born at the hospital in the 4 year period when cases occurred, with a confirmed isolate of emm 75 GAS from a clinical, i.e. infected or screening isolate, or colonised, isolate.*

#### Probable

*A maternity staff-member/associated HCW working at the unit, or a maternity inpatient or baby born at the hospital in the 4 year period when cases occurred, who had a*

*suspected GAS infection and a GAS isolate identified or colonised with a GAS isolate, but with a non-*emm* 75 strain or no typing data available.*

The initial probable case definition was kept broad to include any *emm* typing positive isolate to maximise case capture until the situation was clear. However, any non-*emm* 75 clone isolates/cases were subsequently discounted as being part of the outbreak.

## **Possible**

*A HCW from/inpatient admitted to, another part of the hospital, with suspected or confirmed GAS infection of any type/strain in the hospital in the 4 year period when cases occurred, with suspected GAS infection but without microbiological confirmation or typing data/matching *emm* type.*

## **Incidents**

Over the 4 year period, 7 mothers, 3 neonates and 3 Staff-members who were all confirmed, clinical cases, were reported with GAS/iGAS *emm* 75 infection. One other mother from the last cluster had *emm* 3 and was subsequently discounted as being part of the outbreak. Six mothers had iGAS and 1 (the index) had GAS infection, One baby and 3 Staff-members had non-invasive disease and 2 babies were colonised only. There were no deaths. The mothers (aged 22-39 years) received all their maternity care from the hospital; their babies were 1-44 days old at diagnosis. No neonatal cases were delivered by caesarean section. All mothers were well at admission for delivery, although one had an elevated white blood cell count. Three had recognised risk factors, other than pregnancy.

In the initial cluster, the index case re-presented to hospital with postnatal complications; GAS was identified from vaginal sampling. Over the next 5 days, 3 maternal iGAS cases occurred. One baby of these mothers developed a GAS skin infection, within 10 days of the presentation of the index, another was found to be colonised and the baby of index was found to have a positive throat swab 7 days after the presentation of the index. All cases in this initial cluster had *emm* 75 isolates. A patient with puerperal sepsis also presented 10 days after the index, but no microbiological isolates were available for that case.

A single, maternal, confirmed case of *emm* 75 iGAS was identified 2 years after the initial cluster, followed by 2 confirmed maternal *emm* 75 iGAS cases 4 years later in the final cluster (symptomatic within 6 days of each other) and a single maternal *emm* 3 case, who became symptomatic 20 days after the first case in this last cluster. This latter case was subsequently discounted as being part of the outbreak. There were no neonatal cases associated with the isolated case that occurred 2 years after the initial cluster or in the last cluster.

## **Investigations and control measures undertaken**

Cases and their close contacts were treated as per standard guidelines.

Staff screening sampling results were obtained. GAS positive staff were excluded from work, treated and rescreened for clearance. Wider staff prophylaxis was not employed.

For the last cluster, risk factors and symptoms, microbiology results and patient-staff interactions (dates/locations) were obtained. Ward movements were examined for staff/case overlaps and mapped against staff sickness absence records. Genome sequencing and *emm* sequence typing were undertaken. Environmental sampling was undertaken on the delivery suite after a deep clean had occurred and a month later (specific sampling site details are not available).

## Microbiological investigation

### ***Emm* gene typing method**

The *emm* types were determined using the Centers for Disease Control protocol (table 1). When sequence data obtained were ambiguous, alternative primers (MF1, 5'-ATAAGGAGCATAAAAATGGCT-3', and MR1, 5'-AGCTTAGTTTTCTTCTTTGCG-3') were used [14].

Genome sequencing and single nucleotide polymorphisms (SNP) calling was performed on 13 GAS isolates from the hospital and contemporaneous *emm* 75 isolates from England as previously described using the *emm* 2 MGAS10270 reference genome, RefSeq accession number NC\_008022.1 as the closest available GenBank sequence [15]. This was used in the absence of an *emm* 75 reference genome using bwa-mem 0.7.5a [16]. Gubbins 1.3.3 was used to remove loci with elevated base substitution densities indicative of recombination, producing a multiple sequence alignment file containing only non-recombining variant positions [17]. These data were used to generate a maximum-likelihood tree using RAxML version 8.1.17 using the following parameters:

```
-f a (rapid Bootstrap-analysis and search for best-scoring ML tree in one program run)
-m (substitution-model) GTRGAMMA
-p (random-seed for parsimony inferences) 12345
-x (random-seed for bootstrapping) 12345
-# (number of runs) 1000 [18].
```

## Results

Staffing sickness absence was available for the last cluster only however staff sampling results from the initial cluster (nose/throat swabs only), isolated case 2 years later (sample sites unknown) and last cluster (nose/throat ,+/- perineum sampling if first nose/throat screen was positive) incidents were obtained.

In the initial cluster, at least 170 staff were screened with throat swabs/cultured for GAS; the specialities of the staff sampled were not known; one was positive for GAS *emm* 75 and had become symptomatic with throat symptoms only after all cases were diagnosed excepting the baby of the index, who was detected on screening.

With the isolated case 2 years later, 54 staff were documented as appropriate to screen by throat/wound swabbing and culture for GAS. These included 32 maternity-staff with the remainder from other teams e.g. ITU. Of the 54 eligible staff, 35 were sampled with 25 being from the maternity department and all were screen negative.

In the final cluster, staff screening was undertaken over 3 months. Throat/wound swabs were taken initially with the subsequent addition of nose and perineum samples for those screened later. In the first round, 371 staff (208 maternity-staff) were sampled, and in the 2<sup>nd</sup> to 4<sup>th</sup> rounds, 85, 78 and 72 (37, 35 and 31 maternity staff) were repeat sampled respectively; the number eligible for sampling was not known. Although 4 staff-members were GAS positive on screening, only one maternity staff-member had the *emm 75* strain and became unwell 4 days after the second *emm 75* case in the last cluster, but before the *emm 3* case. The others had strains unrelated to the outbreak. Additionally, a symptomatic staff-member from a different department was identified as having an *emm 75* isolate 3 months later. This suggests *emm 75* may have been circulating more widely in other staff within the hospital and supports the hypothesis that staff were the unwitting source in these incidents.

## Routes of transmission

Four possible transmission routes were investigated:

### 1. Mother-to-mother transmission

No mother was present in more than one cluster (i.e. did not deliver a baby at the maternity unit in each of the affected year clusters); it is therefore unlikely that an individual chronic carrier mother could have been the primary vector responsible for mother-to-mother transmission in all three clusters. Two overlapped for one day in the initial cluster on the delivery suite but were in separate rooms; all 4 had been in the maternity unit within a 7 day period. The first and second mothers in the last cluster overlapped in the delivery-suite on the day the first was readmitted with a positive GAS isolate, occupied the same delivery room during delivery and same postnatal ward bay but with a 3 day separation respectively.

### 2. Staff-patient-staff transmission

*Emm 75* was found on staff-screening in the initial cluster, with one maternity staff-member found to be colonised and in the last cluster, again with one maternity staff-member found to be infected plus an additional non-maternity unit staff-member.

No direct link between a single staff-member and all cases was identified; however two staff had contact with one or more cases in each of the episodes.

The staff-member who was GAS positive in the initial cluster was present and cared for 5 of the cases then, but only became symptomatic after all the cases had presented, except the baby of the index whose isolate was detected on screening. This staff member was also involved in the care of the single case 2 years later, but was not present for the last cluster. The GAS-positive maternity staff-member in the last cluster had contact with the index case of that last cluster >2 weeks before onset, but didn't develop symptoms until after the last cluster index case had presented, but did have contact with 3 of the cases (2 mothers, 1 baby) in the initial cluster within 3

days of their infection being identified. One staff-member was common to 2 cases in the last cluster and another to all 3 cases in that cluster, but no positive isolates were obtained from them.

### **3. Staff-staff transmission**

In the last cluster, some staff-members had worked while symptomatic with potential GAS infections, e.g. sore-throat. However, this was only after the index and second case in the last cluster had already presented, making it less likely they were the primary vectors (more likely to have been downstream recipients). In the first round of screening in the last cluster, 371 staff were sampled; follow-up sampling was attempted for a further three-rounds to try to increase detections, however fewer were re-sampled on each occasion, 85, 78 and 72 respectively, meaning that other asymptomatic staff who were not sampled could have been the primary vectors, but remained undetected, or that where negative results were obtained that the organisms present were below the limit of detection.

### **4. Environmental transmission**

During the investigations of the last cluster the unit was examined for infection prevention and control compliance; some deficiencies were noted, e.g. blood contaminating a privacy curtain, clinical equipment placed on waste bin tops. Recommendations for improvements were made. GAS was not isolated from environmental sampling (however the sites sampled were not available to the outbreak team, so the appropriateness of sampled sites or the sampling methods used was not known).

### **Genomic sequencing analysis**

Whole genomic sequence analysis showed the initial and last cluster isolates were located within a clade with a shared ancestral lineage suggesting common source transmission; however transmission directionality could not be inferred. The isolates were separated from all others by at least 9 SNPs. No other contemporaneous isolates from national *emm 75* GAS strains were located within this clade (Figure 1). The single case isolate that arose 2 years after the initial cluster did not have an immediate common ancestor to the initial or last cluster isolates.

## **Discussion**

No mother was present in more than one cluster; it is therefore unlikely that an individual chronic carrier mother could have been the primary vector responsible for mother-to-mother transmission in all the clusters. However mother-to-mother transmission may have occurred within the individual cluster, e.g. 2 mothers overlapped in the initial cluster on delivery suite for one day but had no direct contact, making this less likely and in the last cluster two occupied the same bay/bathroom and delivery-suite room but on different days. It is also unlikely the mothers were separately importing GAS leading to multiple re-introductions into the hospital environment as there was little evidence of circulating community *emm 75*; nationally only 3.2% and regionally 3% were *emm 75* during the period and all of the regional *emm 75* isolates

resulted from this incident, suggesting *emm 75* is relatively uncommon in invasive disease.

The recurrence of clonal GAS clusters over such an extended 4 year period is unusual. The initial and final cluster isolates were closely related, with a common ancestor and are distinct from other *emm 75* isolates. The variation observed between the initial and final cluster isolates is indicative of acquired variation consistent with genetic drift over time. The number of single point mutations (single nucleotide polymorphisms or SNPs) estimated to occur in the GAS genome (based on analysis of *emm 1/12* type strains) has been estimated at 1.37 to 1.8 SNPs per core genome per year. [19, 20]. The genetic distance between the initial and last cluster maternity unit clade of isolates is consistent with these estimates. The 9 SNPs that separate the maternity unit clade from all other isolates in this study represent an approximate time of 6.5 years.

It is possible the initial cluster strain could have persisted in the hospital environment and/or in one or more colonised staff until the last cluster; however such a long-duration (greater than two years) of clonal-persistence has not been previously described.

There are three possible explanations for the emergence of a second clonally linked cluster four years after the first infection episode:

1. Treatment / screening failure in the initial cluster with one or more staff-members retaining asymptomatic *emm 75* GAS colonisation/shedding, leading to ongoing staff-staff, staff-patient, staff-environment transmission. It has previously been demonstrated that asymptomatic carriage is less effectively cleared by treatment, than for symptomatic cases [21].
2. A persistent external source/s reintroducing GAS to the hospital, e.g. staff-members / relatives.
3. Persistence of environmental contamination. GAS has been documented to persist in fomites for up to 6½ months [22].

Definitively confirming any of these hypotheses is not possible, however the first is the most plausible, since staff colonisation was found, no inanimate reservoir was detected and *emm 75* GAS / iGAS disease is rare. Supporting this; asymptomatic, colonised staff-members and symptomatic staff-members have been previously demonstrated to account for 34% and 8.2% of all GAS outbreaks respectively and carriage with the same strain in close contacts of a GAS-infected case can approach 30% [5, 23]. Staff may have unwittingly transmitted GAS to each other leading to persistence in multiple staff-members. Control measures were therefore targeted at interrupting transmission from staff, including the screening of staff to detect carriers, attention to handwashing and infection control procedures.

WGS was useful for supporting the linkage of cases and determining that the clusters were genetically distinct from other *emm 75* isolates, however more contemporaneous isolates would have been helpful to indicate more clearly the incidence of infections / prevalence of carriage of this particular clade.



Although staff screening was undertaken, the logistics of sampling and particularly repeat sampling a large group of individuals was challenging; screening effectiveness is also limited by sample quality and false negative results. Data quality was also an issue; data on the location of mothers was incomplete, not all staff-patient interactions were documented and staff signatures were frequently unclear. Increased duration and proximity of staff / patient interactions may increase the chances of transmission; however it is unusual for these details to be noted in clinical records.

While environmental surfaces have been recognised as the source of maternity GAS outbreaks, for example, GAS remain viable on fomites for up to 6½ months and shower heads, curtains, baths, bidets and toilet seats have been previously implicated and transmission vectors, and there were some infection control deficiencies identified, sampling nonetheless found no evidence of environmental GAS contamination [5, 22, 24]. Environmental sampling was performed with dry swabs after deep-cleaning which may have reduced detections. The sites sampled were also not available to the outbreak team so their relevance was not known. Moistened / specific environmental swabs or directly applied plates may have produced more meaningful results [24]. Although speculative in the absence of clearer environmental sampling data, it is unlikely a single persistent environmental source was responsible due to the time between the two episodes. It is more likely the environment acted as a temporary, intermediate vector. Even with systematic, environmental sampling using moistened swabs, areas of contamination may be missed, so negative swabs are not necessarily indicative of a non-contaminated environment. The focus therefore should be on assuming that there may be temporary contamination of the care environment and robust cleaning to reduce such contamination to a minimum. GAS prevention and control guidelines recommend 'communal facilities, including bathrooms / toilets, are cleaned and decontaminated after each use especially on delivery-suites, post-natal wards and other high-risk areas' [5]. At the time of the last cluster the cleaning regime was consistent with other NHS practice, namely twice daily cleaning, however cleaning was subsequently increased to decontaminate after each patient use. Further research on the optimal cleaning frequency for such high risk areas is warranted.

## Conclusions

Recurrent clonal outbreaks of GAS/iGAS spanning comparable durations to this incident and *emm 75* outbreaks related to childbirth appear rare. We postulate that recurrent infections seen with isolates within the *emm 75* monophyletic group occurred over a four year period due to asymptomatic carriage in maternity staff-members, with transmission to patients. However, other modes of transmission cannot be excluded. Increased monitoring and vigilance is essential, particularly if more cases with the *emm 75* type are identified. Staff and patient education will be a valuable tool in preventing any future cases. No further cases have been noted at the time of writing, (March 2018).

Authorities investigating maternity related outbreaks should be aware that prolonged, clonal isolate outbreaks are possible over a period of years, indicating that robust efforts to identify, control and eradicate the common source are needed, particularly given the seriousness of puerperal sepsis. Fortunately all invasive cases recovered in these incidents, but some were very ill, so the outcome could have been very different.

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Conflicts of interest: HD is currently employed by GlaxoSmithKline and holds GSK shares. At the time this work was done she was employed by Public Health England.