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Integration of Genomic and Other Epidemiologic Data to Investigate and Control Cross-Institutional *Streptococcus* p*yogenes* Outbreak

Technical Appendix

Full Literature Review Results

Seventy-two iGAS outbreaks in LTCFs were identified, from individual outbreak reports (*1*–*14*) or summary data identified in surveillance studies or reviews (*6*,*13*,*15*–*20*), or laboratory studies (*16*). These 72 include 31 clusters defined as outbreaks based on shared subtypes among 2 or more cases occurring at a facility within 1 year (*15*,*18*). One of these found 13 clusters which shared sub-type, institution and time period among 134 cases, and eight instances of two isolates from the same time period and institution but with distinguishable subtypes which did not meet their subtype based outbreak definition. Among outbreaks identified by other means 22 reported subtyping. Nineteen of these identified a single or dominant strain (*1*,*3*,*5*–*13*,*16*), and three multiple strains (*2*,*4*,*14*).

Treatment restricted to those ill or to cases and direct contacts of cases with laboratory confirmed infection was associated with control in some outbreaks (*5*,*7*,*13*), although in one mass chemoprophylaxis was applied following recurrence after two rounds of this selective treatment (*1*). Screening all staff and residents with chemoprophylaxis if positive (*2*–*4*,*6*,*8*,*9*,*11*–*14*) was associated with recurrence and repeated screening and treatment in two reports (*2*,*8*). Further cases of iGAS were diagnosed between decisions to screen and chemoprophylax and the implementation of chemoprophylaxis (*1*,*11*). Mass chemoprophylaxis of all staff and residents was associated with control of iGAS (*1*,*3*,*10*,*13*) although in one incident persistent infection was shown in one resident with a gastrostomy tube (*1*). Screening detected carriage rates were below 10% among residents with two exceptions (20% (*5*) and 16% (*11*)) with lower rates among staff than residents as reviewed elsewhere (*6*,*13*).

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Technical Appendix Table. Genes of interest, presence and absence

Gene name	Accession no. used for comparison	Protein and Function	Presence/absence in study isolates
Capsule			
HasA		Hyaluronase, production of hyaluronic acid capsule	+
HasB		Production of hyaluronic acid capsule	+
HasC		Production of hyaluronic acid capsule	+
PrtS		Cell envelope proteinase	+
Phage			
AbiR		Abortive infection phage resistance protein	+
MF4		Mitogenic factor - phage associated	– (except ERR027369 +)
Spd3		DNase (Similar to mitogenic factor), phage associated)	+ (except ERR027369 –)
Spy1438		Phage associated cell wall hydrolase	+ (except ERR027369 –)
SpyM3–1302	SpyM3_1302, gi|21909536:c1315318–1314461 *Streptococcus pyogenes* MGAS315 chromosome, complete genome	Phage protein	–
Regulatory proteins			
CcpA		Regulatory protein	+
CovR	gb|EU726239.1|:241–927 *S. pyogenes* strain H342 CovR	Two-component regulation	+
CovS	gb|EU726239.1|:933–2435 *S. pyogenes* strain H342 CovS	Two-component regulation	+
MsmR	gb|DQ984656.1|:6744–7949 *S. pyogenes* strain ALAB49 MsmR	Operon regulatory protein, msm	–
MtsR		Transcriptional regulator of metal ABC transporter MtsR-like Metalloregulator – manganese	+
Nra	gb|DQ984656.1|:126–1661 *S. pyogenes* strain ALAB49 Nra	Negative transcriptional regulator	–
PerR		Ferric uptake regulation protein	+
Rgg		Rgg regulator, production of SpeB Cysteine protease	+
RopB		Rgg regulator, production of SpeB Cysteine protease	+
Attachment			
Cpa	gb|DQ984656.1|:2092–3675 *S. pyogenes* strain ALAB49 Cpa	Fimbrial minor sturctural protein Cpa/FctA	–
FctA	gb|DQ984656.1|:4211–5158 *S. pyogenes* strain ALAB49 FctA	Fimbrial minor sturctural protein Cpa/FctA	–
FctB	gb|DQ984656.1|:6014–6583 *S. pyogenes* strain ALAB49 Nra FctB	Fimbrial minor structural protein	–
Toxins/pathogenicity factors			
ABC-transporter	gb|AF227521.1|:4607–6070	ABC-transporter	–
Emm1		M protein	+
EndoS		Endoglycoside, immunoglobulin degrading enzyme	+
Fba		Fructose-bisphosphate aldolase	+
GRAB		G protein-related a2-macroglobulin binding protein	+
IdeS		Immunoglobulin G endopeptidase, CD11b homologue	–
LaCD		Tagatose 1,6-diphosphate aldolase	+
Mac		Immunoglobulin G-endopeptidase (IdeS)	–
PrtF2	gb|DQ984656.1|:8334–10535 *S. pyogenes* strain ALAB49 PrtF2	Fibrinonectin binding protein	–
SagA		Streptolysin S precursor	+
SagB		Streptolysin S production	+
SagC		Streptolysin S production	+
Scl1		Collagen-like surface protein	–
Scl2		Collagen-like surface protein	–
ScpA		C5a peptidase	+
Sda1		Extracellular streptodornase S, DNase	+
SpeA		Exotoxin A superantigen	+
SpeB		Streptococcal pyrogenic exotoxin B, cysteine protease	+

Gene name	Accession no. used for comparison	Protein and Function	Presence/absence in study isolates
SpeC		Exotoxin C	– (except H130620574, H130620575 +)
SpeJ		Exotoxin J	+
Sic		Streptococcal inhibitor of complement	+
Ska		Streptokinase	–
Slo		Streptolysin O	+
Sof		Serum opacity factor	–
Spd		DNase	+
SpeG		Pyrogenic exotoxin	+
Spy1063		Iron(III) binding protein	+
Spy1064		Unknown	+
Spy1066		Hydrolase (HAD superfamily)	+
Spy1065		O-Acetyltranseferase (cell wall biosynthesis)	+
SpyCEP	gi|94989509:345557–351976 *S. pyogenes* MGAS10270 chromosome, complete genome	Interleukin-8 protease, cell envelope protein	–
SpyA	gi|71909814:c358588–357610 *S. pyogenes* MGAS5005 chromosome, complete genome	C3 family ADP-ribosyltransferase	+
SrtC2	gb|DQ984656.1|:5254–5979 *S. pyogenes* strain ALAB49 SrtC2	Sortase	–
UmuC-MucB	gb|AF227521.1|:6839–8128	Lesion-replicating DNA polymerases	–
Antimicrobial resistance			
FbaA		Fibrinonectin binding protein	+
GyrA		Fluoroquinalone resistance	+
Mef		Macrolide resistance	–
MefA	gb|AF227521.1|:3270–4487	Macrolide resistance macrolide-efflux protein A (mefA)	–
MefMB56Spyo029		Macrolide resistance	–
MefV1		Macrolide resistance	–
MefV2		Macrolide resistance	–
MefV3		Macrolide resistance	–
Nga		NAD glycohydrolase	+
ParC		Fluoroquinalone resistance	+
TetM		Tetracycline resistance	–
TetO		Tetracycline resistance	–