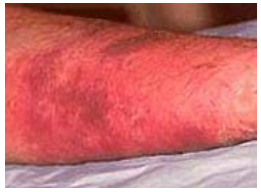
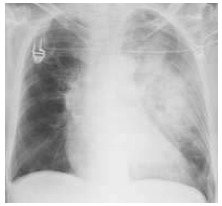
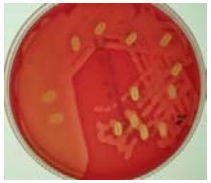
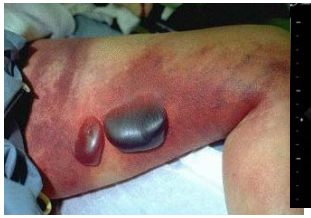
Maternal group A streptococcal infections

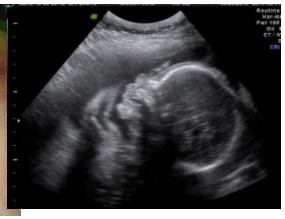
Shiranee Sriskandan
Imperial College London

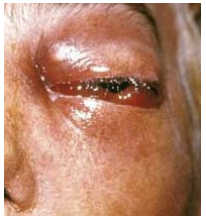

Cellulitis


Pneumonia

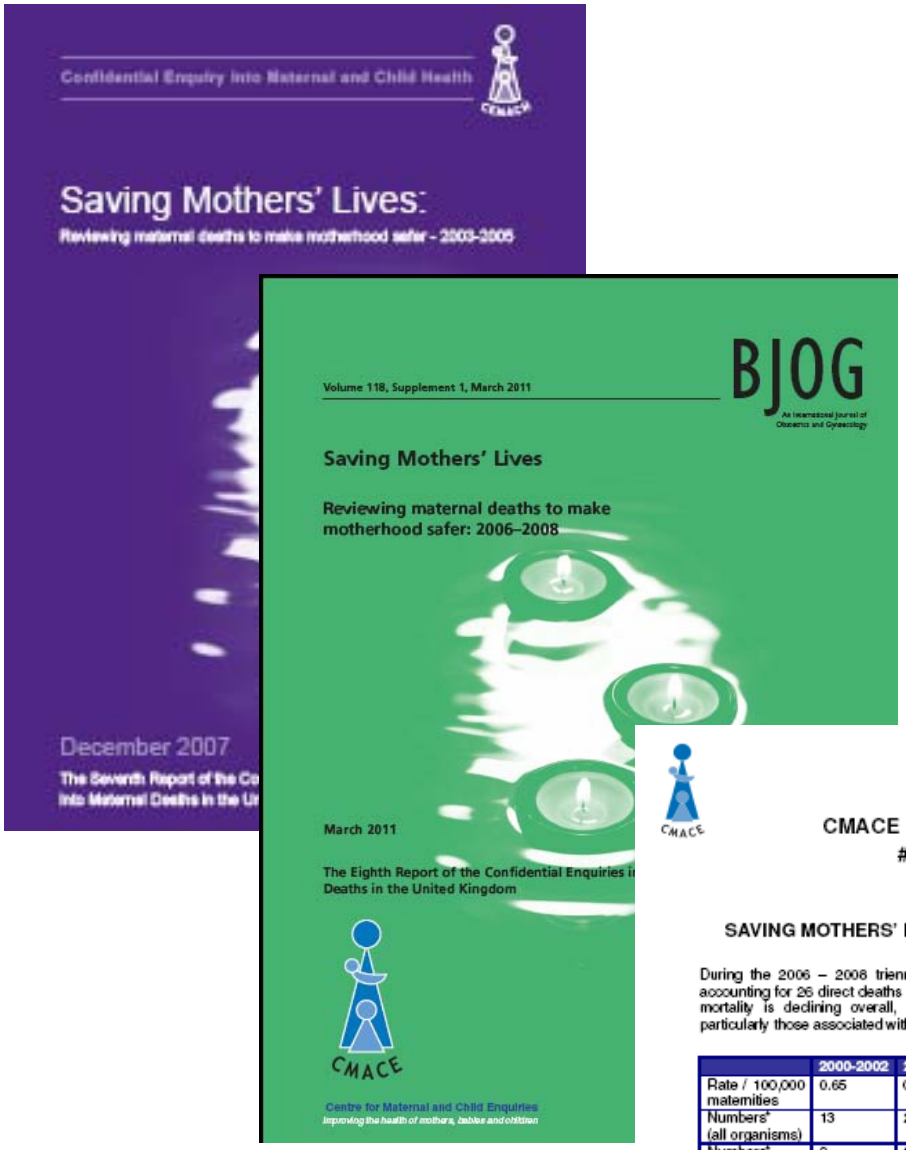

Bacteremia


Necrotising fasciitis


Peripartum sepsis


Toxic shock STSS

- Maternal invasive Group A Streptococcal (iGAS) infection
  - Context
  - Pathophysiology (microbiology, immunology)
  - Recognition & management (antibiotics, IVIG)
  - Preventing nosocomial maternal GAS



"..Sepsis has become the leading cause of Direct maternal deaths in the UK since Confidential Enquiries into Maternal Deaths commenced in 1952"

Linked with increase in Group A Streptococcal infections

Centre for Maternal and Child Enquiries
Improving the health of mothers, babies and children

CMACE

CMACE EMERGENT THEME BRIEFING
#1: Genital Tract Sepsis
September 2010

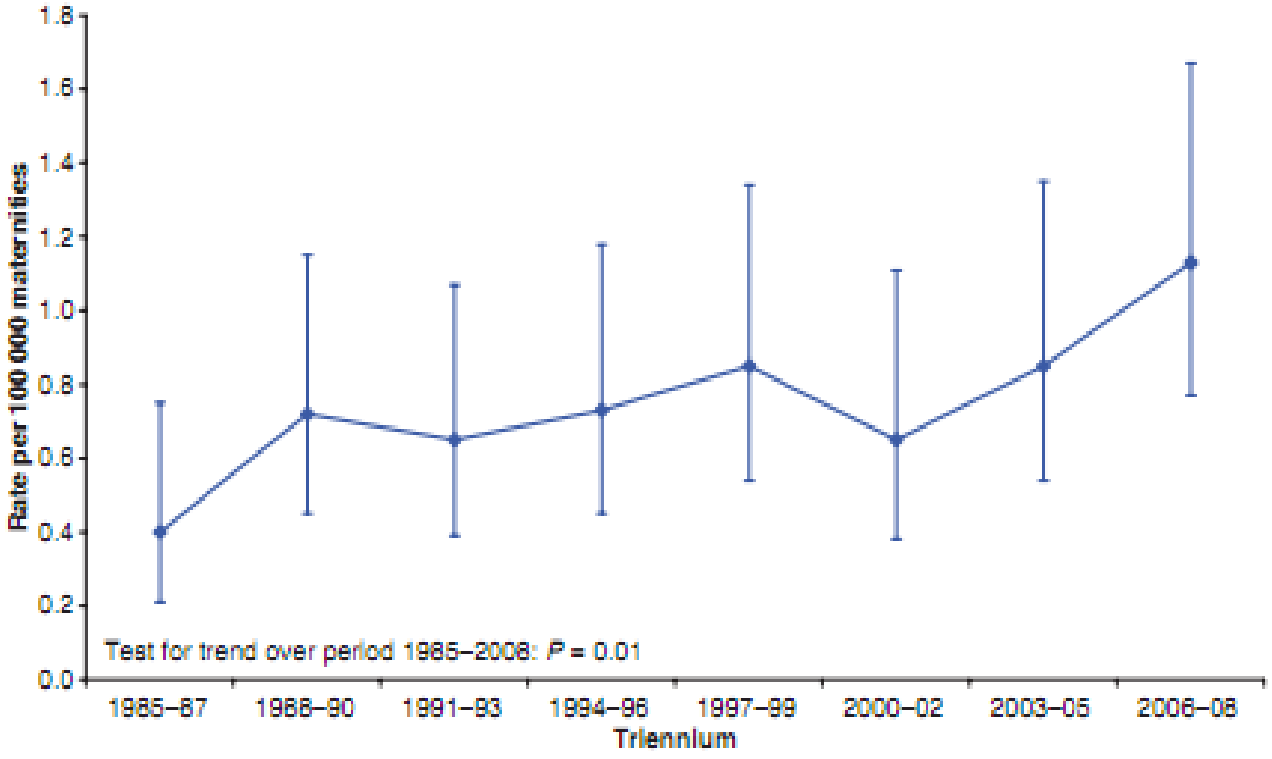
SAVING MOTHERS' LIVES 2006-08: Briefing on genital tract sepsis

During the 2006 – 2008 triennium, sepsis was the leading cause of direct maternal deaths, accounting for 26 direct deaths and a further 3 deaths classified as 'Late Direct'[1]. Whilst maternal mortality is declining overall, maternal deaths due to sepsis have risen in recent triennia, particularly those associated with Gp A streptococcal infection (GAS):

	2000-2002	2003-2005	2006-2008
Rate / 100,000 maternities	0.65	0.85	1.13
Numbers* (all organisms)	13	21	29
Numbers* (GAS)	3	8	13

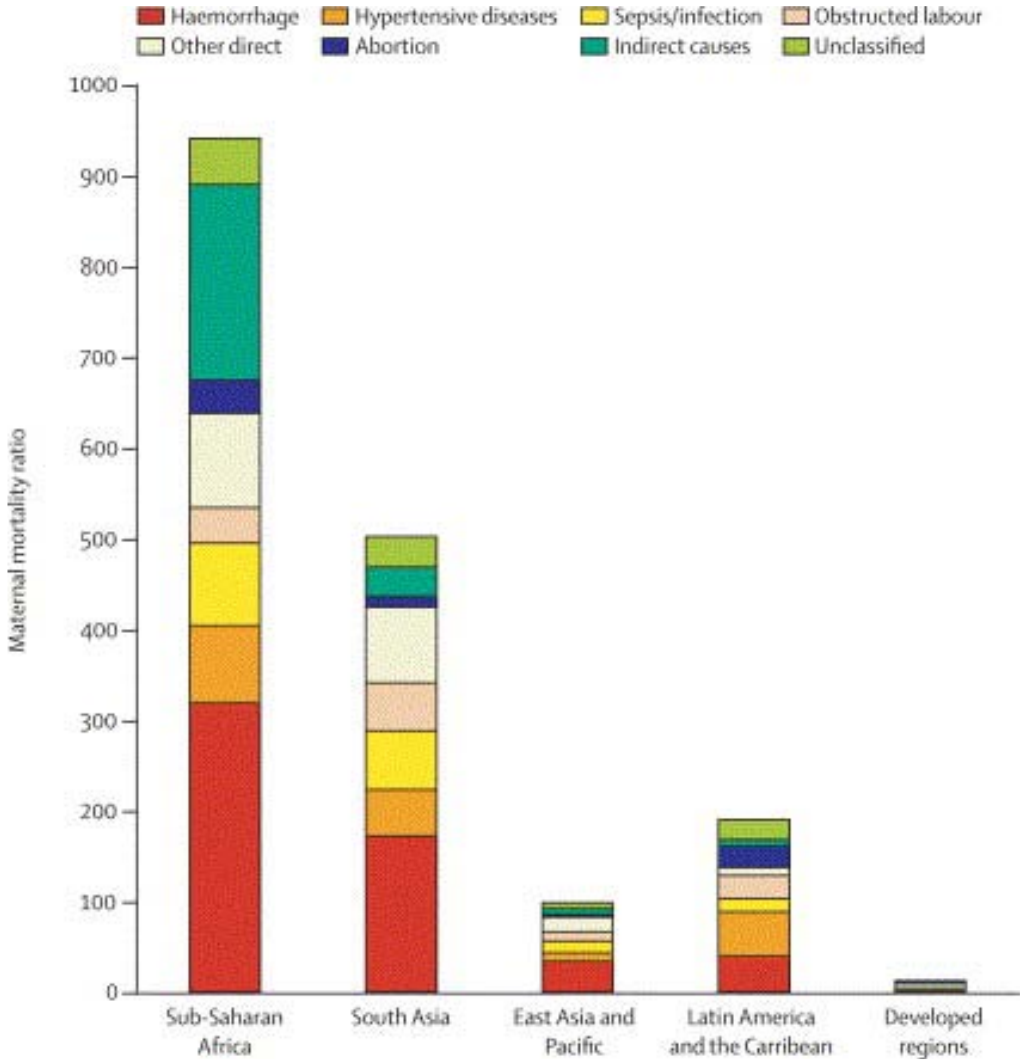
*: Direct and indirect maternal deaths together

The current increase in maternal deaths due to sepsis in the UK



Source: CMACE. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011;118(Suppl. 1):1–203.

Peripartum sepsis: the international context



Ronsmans et al,
Lancet. 2006;368(9542):1189-200

Microbiological context

Severe maternal sepsis/deaths

Group A streptococcus	>50%
Staphylococcus aureus	10-15%
Strep pneumoniae	2-5%
Clostridium spp.	2-5%
E. coli	20-30%
Pseudomonas	2-10%
Klebsiella spp	2-5%
Acinetobacter etc	2-5%

Bacteremia

Group B streptococcus
Group A streptococcus
E.coli, S. aureus, Listeria

Endometritis

Gram positive
Groups A, B, D streptococci
Staphylococcus aureus

Gram negative
Escherichia coli, Enterobacteriaceae
Citrobacter, Pseudomonas aeruginosa,
Proteus mirabilis
Haemophilus , Gardenerella vaginalis

Anaerobes
Peptostreptococcus sp.,Bacteroides
Clostridium spp, Fusobacterium

Miscellaneous
Chlamydia trachomatis
Mycoplasma hominis
Ureaplasma urealyticum

Excess risk of iGAS in peripartum women

- **USA** Deutscher et al Clin Infect Dis. 2011;53:114-23 . Postpartum women have specific x20-fold risk of GAS and GBS bacteremia .

- **E&W**: 52 cases of severe iGAS in postpartum women in 2009
- Overall risk >120 times higher in 28d postpartum period (and >28 times higher if genital infection is excluded) compared to 15-44y women who had not recently delivered a child. (Lamagni et al, XVIII Lancefield Symposium, 2011, Palermo.)

- **Reasons for excess risk unknown**
  - Contact with young children
  - Sore throat in self/near family
  - ?GAS-specific immunological defect
  - Unlikely due to antenatal carriage

Does antenatal carriage of GAS lead to post natal sepsis? Colebrook's 1933-4 study

Incidence of puerperal sepsis approx 30 per 1000 births

855 swabs at onset of labour

- 1 mild fever
- 13 non GAS
- 0 GAS

837 swabs 4d after delivery

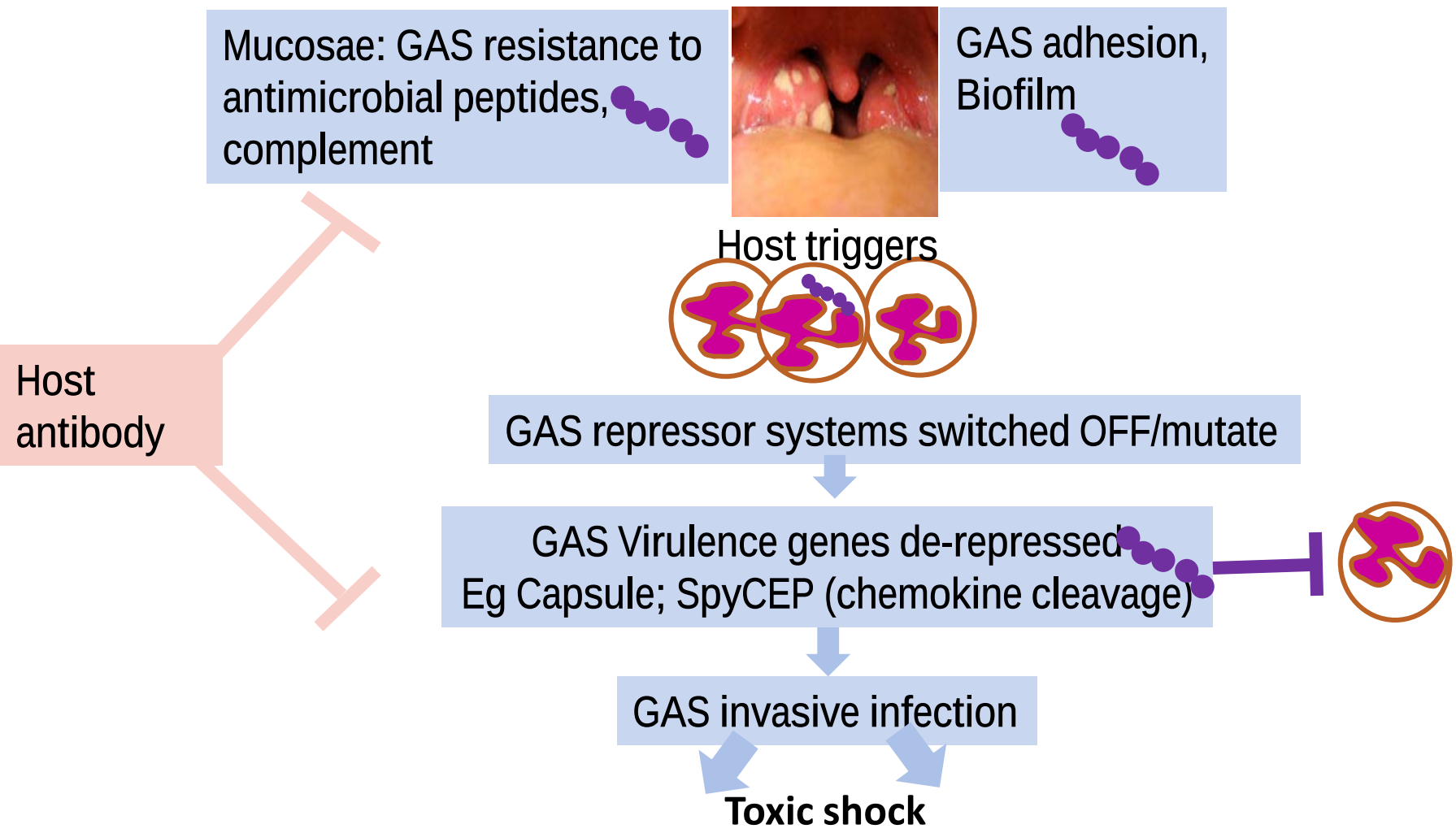
- 11 mild fever
- 50 non GAS
- 2 GAS → 1 severe sepsis

46 severe puerperal infections

- 1 non-GAS (staph)
- 45 GAS

The strains that give rise to puerperal fever are rarely if ever present in the genital tract at the start of labour

Looking for a GAS-specific immunological defect in pregnancy and puerperium



Case

- 39 year old primagravid, caucasian

- Presented to local emergency dept
- Flu-like illness, diarrhoea 36h
- NVD healthy infant 6d earlier

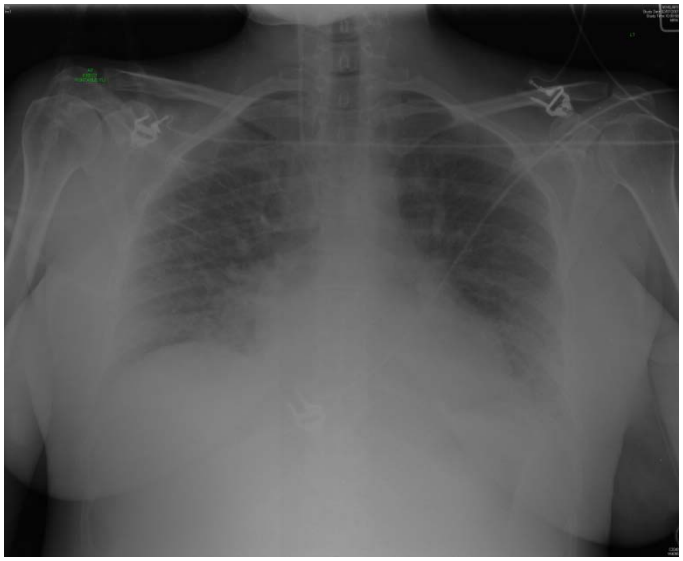
- Clinical signs of severe sepsis
  - HR 130, RR32, BP 86/50; mottling of skin
- Investigations
  - Hb 14.5, plt 94, wcc 6.2; CRP 685; PT 15.2, APTT 39.6

Management

- As for severe sepsis (surviving sepsis guidance)
- Early goal-directed therapy; ICU
- Antibiotics for community-acq sepsis of unknown cause (ceftriaxone)

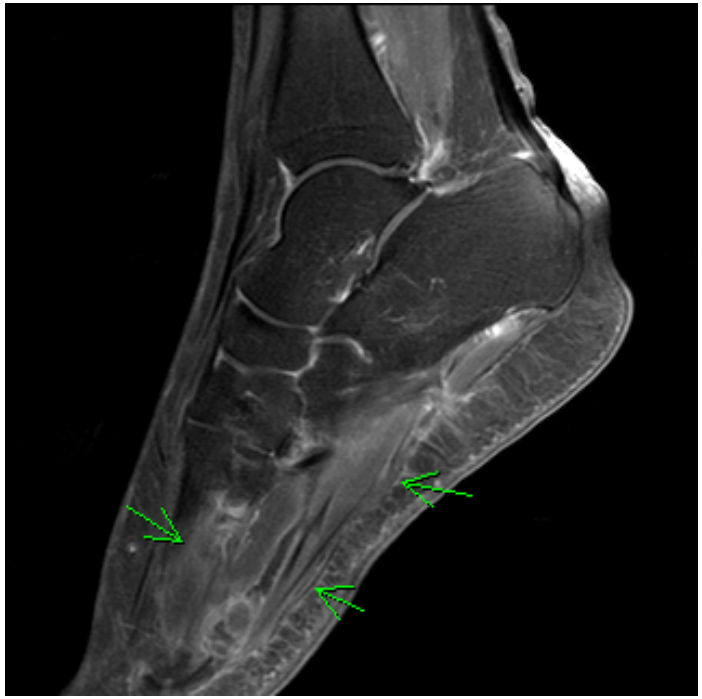
- PT 15.2 – 17 - 18.9
- APTT 39.6 - 43.6 -51

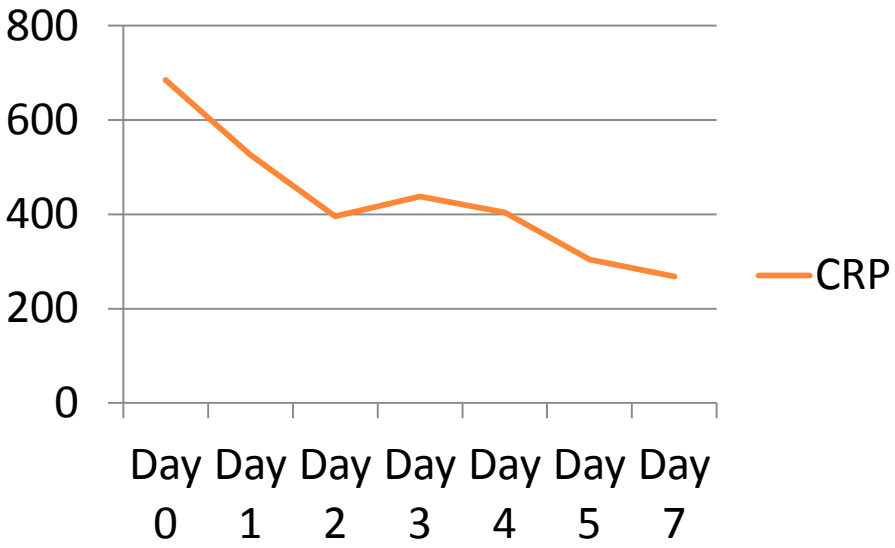
- Increasing hypoxia
- Increasing pain L foot



Progress on ICU

- Severe sepsis -DIC, shock
- MRI L. foot : nec. fasciitis
- **Clindamycin** added
- Further deterioration
- Transferred to 2nd ICU with obstetric and plastic surgery units on site
- Eventual recovery after debridements





Microbiology

HVS (d1)	3+ Group A strep
HVS (d2)	2+ Group A strep
Blood (d1)	No growth

? Genital tract as portal of entry

Foci of peripartum iGAS infection

Focus	No.	(%)
Bacteremia without focus	40	(46)
Endometritis	24	(28)
Peritonitis	7	(8)
Septic abortion	6	(7)
Cellulitis	3	(3)
Septic arthritis	3	(3)
Necrotizing fasciitis	3	(3)
Strept toxic shock	3	(3)
Chorioamnionitis	3	(3)
Pneumonia	1	(1)
Abscesses	0	(0)
Others*	3	(3)

*Meningitis, thrombophlebitis, and septic emboli.

USA (Chuang et al. Clin Infect Dis. 2002; 35:665-70)

Recognition of peripartum GAS sepsis

SIGNS

- Pyrexia OR Hypothermia
- Tachycardia
- Tachypnoea (RR>20)
- Diarrhoea
- Pain (variable degree- opiate req.)
- (Vaginal discharge/abnormal lochia)

THINK of possibility

Not all postpartum sepsis is genital tract

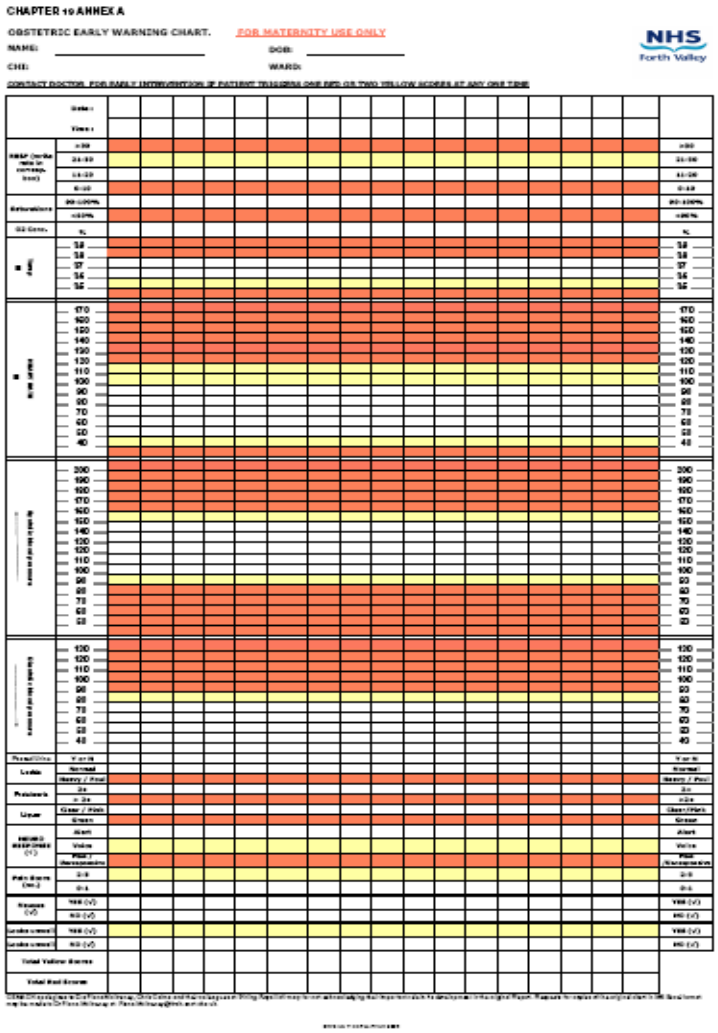
May present to any team

Any other focus?

TESTS

- Leucopenia
- Raised CRP
- Raised lactate/low pH
- Thrombocytopenia
- Coagulopathy

Recognition of illness severity


CHAPTER 19 ANNEX A

OBSTETRIC EARLY WARNING CHART. FOR MATERNITY USE ONLY

NAME: DOB:

CHI: WARD:

NHS Forth Valley

MEOWS charts: Who should use them?

Community?
A&E depts

Must be linked to clear action plans when patients trigger

If a maternity patient is not improving (heart rate, lactate, blood pressure, pain) then she is inadequately resuscitated and may need intervention
?surgical
?adequate level of care and hydration
?choice of antibiotics

Empiric management of peripartum infection

- Antibiotics as early as possible (<1h) i.v. full dose
  - **MODERATE** Co-amoxiclav (plus metronidazole)
  - OR Cefuroxime (plus metronidazole)
  - OR if ESBL risk Carbapenem

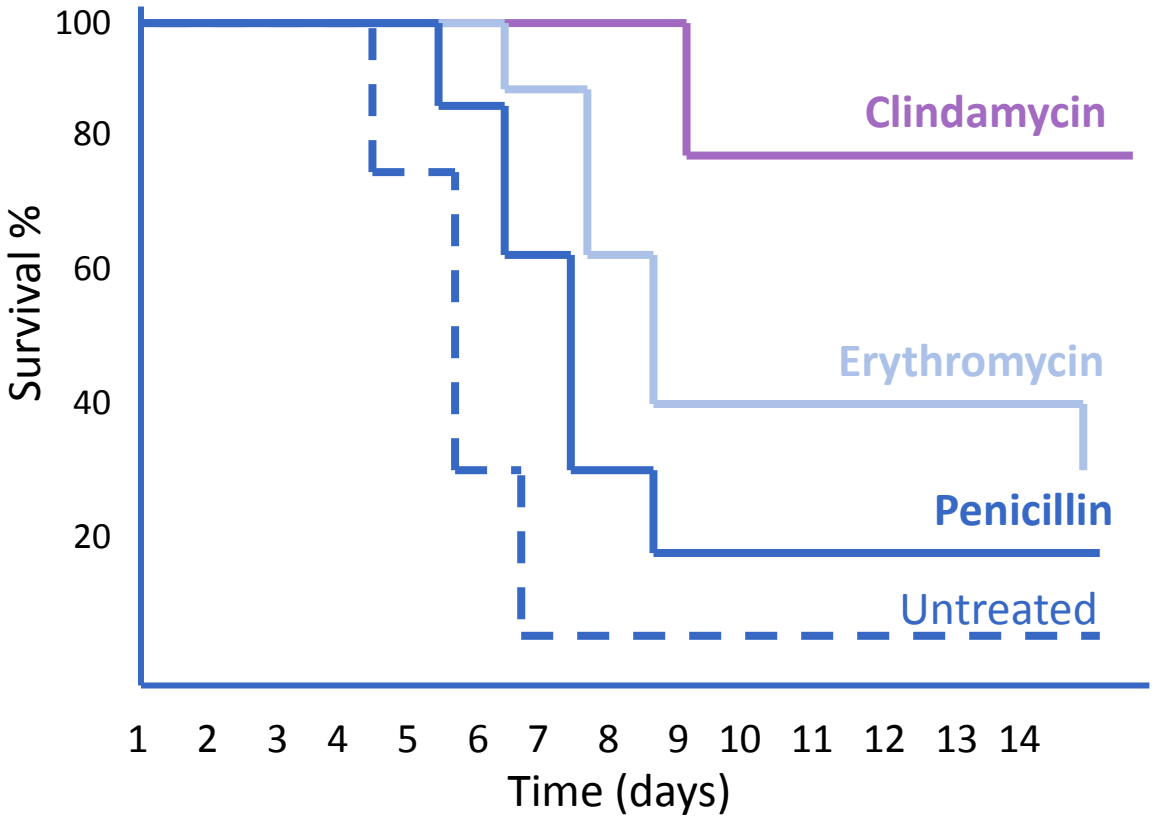
  - **SEVERE:** Piperacillin/Tazobactam/gent or Carbapenem
    CLINDAMYCIN,
    IVIG if group A strep likely
    (cover MRSA if screening +ve)

RCOG guidelines 2012

- Cultures beforehand (blood), also HVS, throat, urine
- Refine antibiotics once culture results known
- Source control, repeat imaging if swinging pyrexia
- Supportive care – fluids (cvp, catheter), oxygen, ICU- Rpt physiology and bloods
- Infection control- side room (nb iGAS is notifiable in UK)

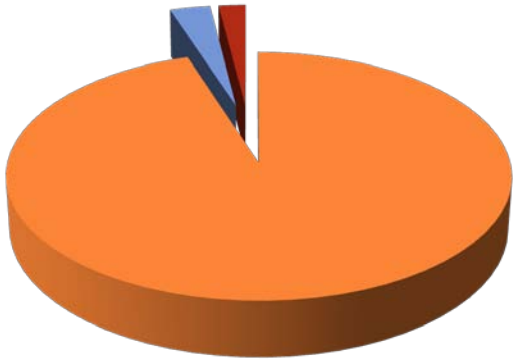
Rationale for use of clindamycin: toxin inhibition and enhancement of bacterial clearance

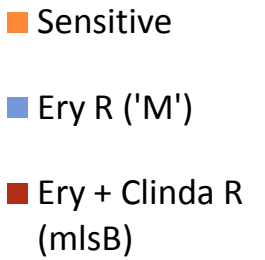
Data: in vivo (MOUSE) models of iGAS SSTI but no RCT



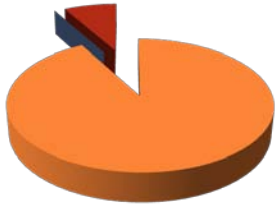
Adapted from: Stevens DL, J. Infect Dis.1993 Jun;167(6):1401-5.

Macrolide and lincosamide resistance UK...





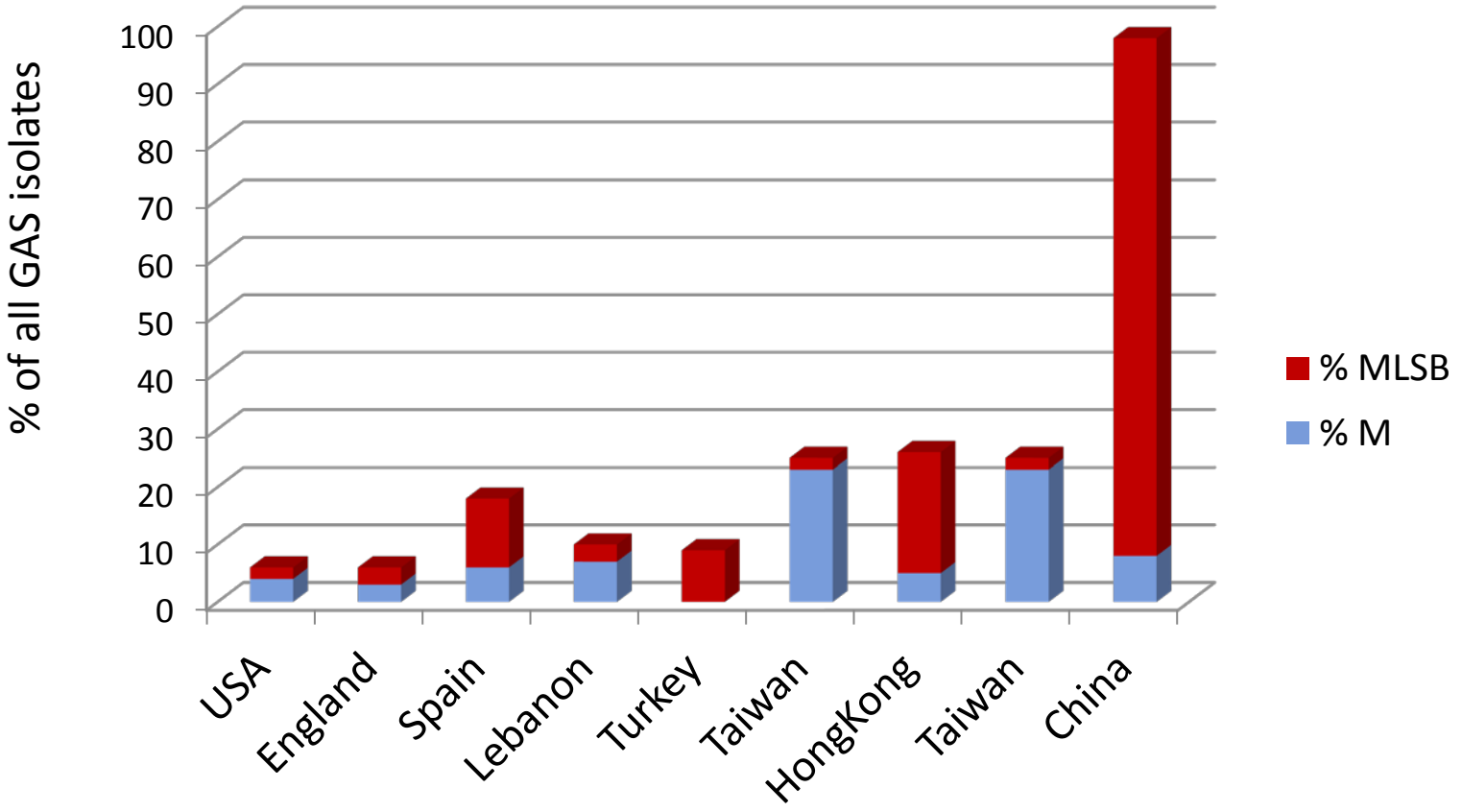
Group A Strep 4% clinda R



Group A Strep
2010: London 8%

2010: England, Wales, N. Ireland
Health Protection Report Vol. 5 No. 46 – 18 November 2011

But may be problematic elsewhere



Extracted from individual published studies 2008-2011

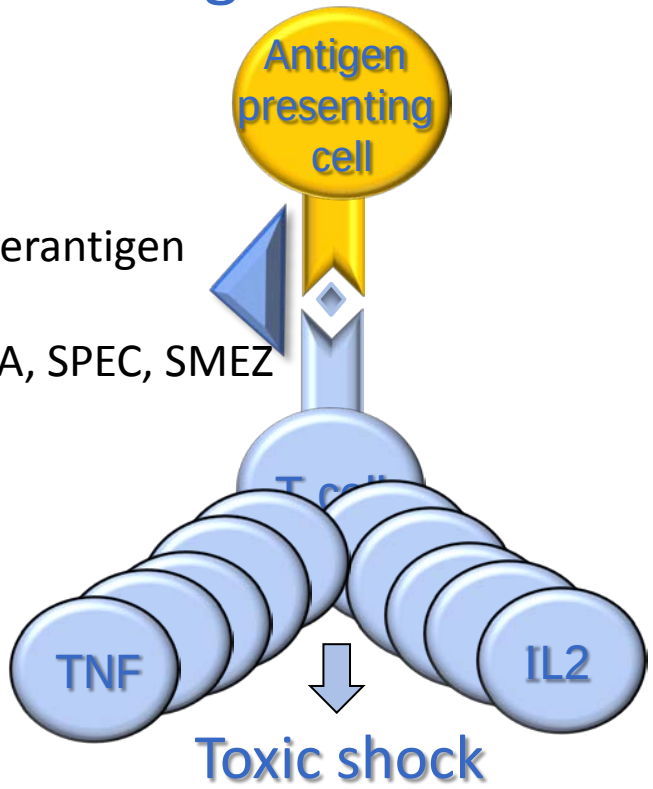
Specific Emm types associated with emergence of MLSB phenotype eg emm12 and 22 in China

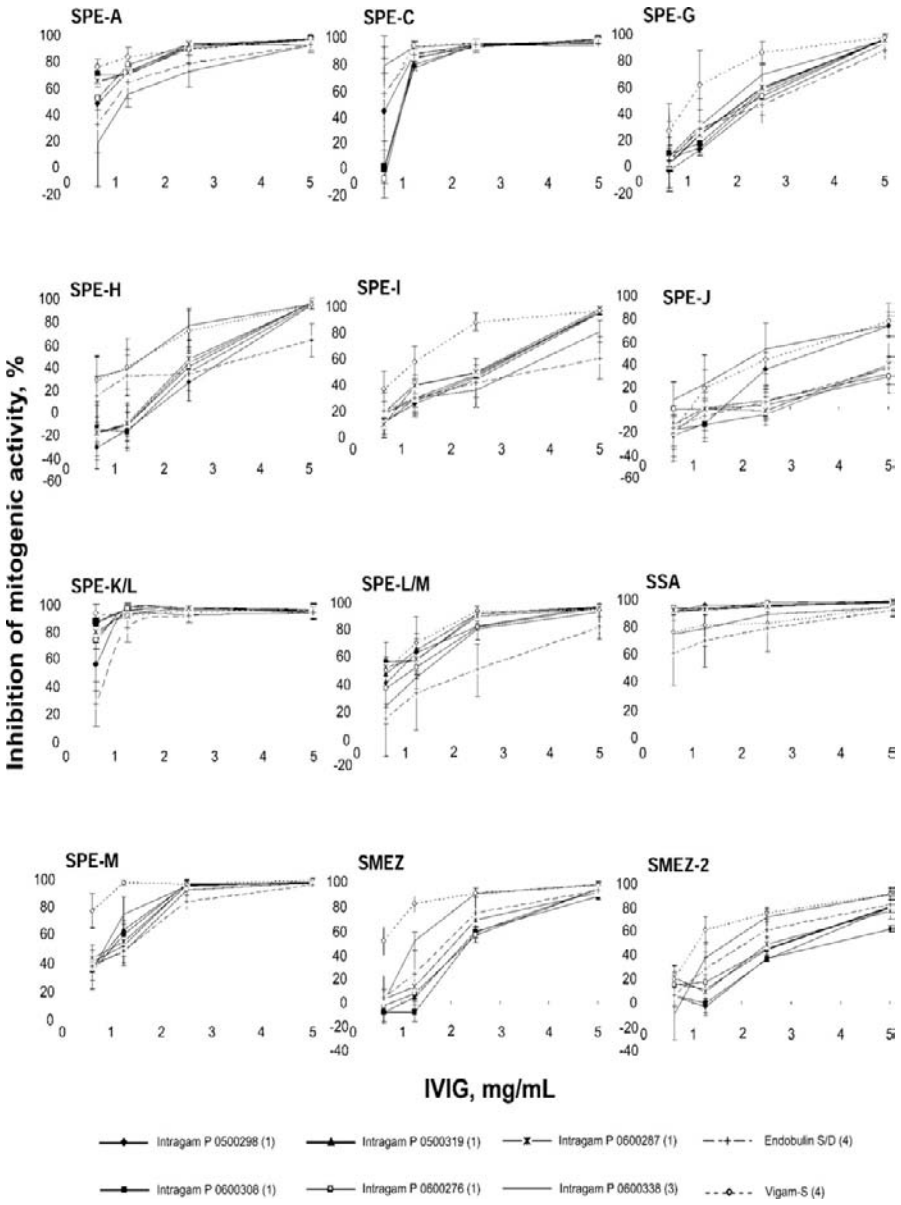
Intravenous Immunoglobulin (IVIG)

- Purified IgG from pooled donors
- Screened for HIV, HBV and HCV
  - Concerns about risks of Prion disease transmission-supply
- >97% monomeric IgG
- Products vary between manufacturers
  - Variety of (rare) adverse side effects
  - IgA and IgM content (Pentaglobin 12% IgM)

Rationale for IVIG.

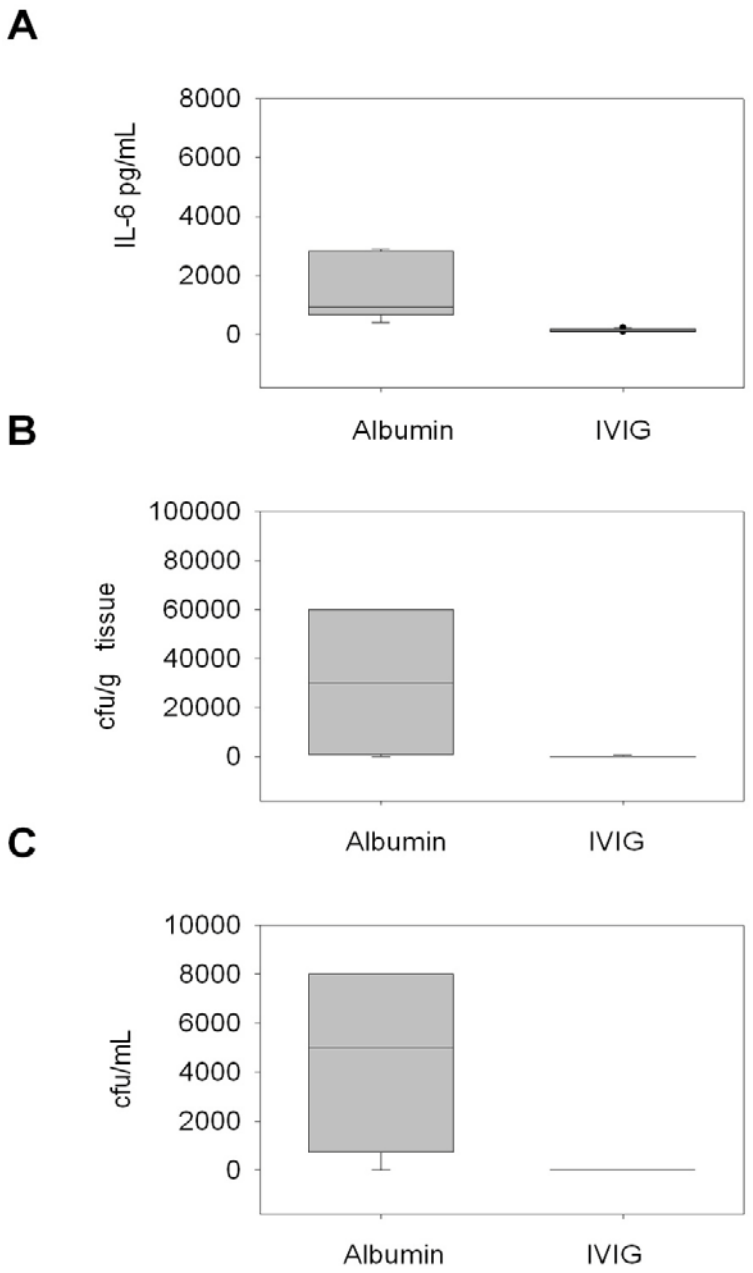
Bacterial opsonisation AND in vitro neutralisation of GAS superantigens





Schrage B et al. Clin Infect Dis. 2006;43:743-746

In GAS-infected superantigen-sensitive HLA-transgenic mice, polyclonal IVIG can reduce systemic inflammation and bacterial load in spleen and blood



J Antimicrob Chemother 2006;58:117-24

Clinical trial of IVIG in STSS

Primary and secondary end points assessing efficacy of administration of high-dose intravenous polyspecific IgG.
Trial stopped due to low recruitment.

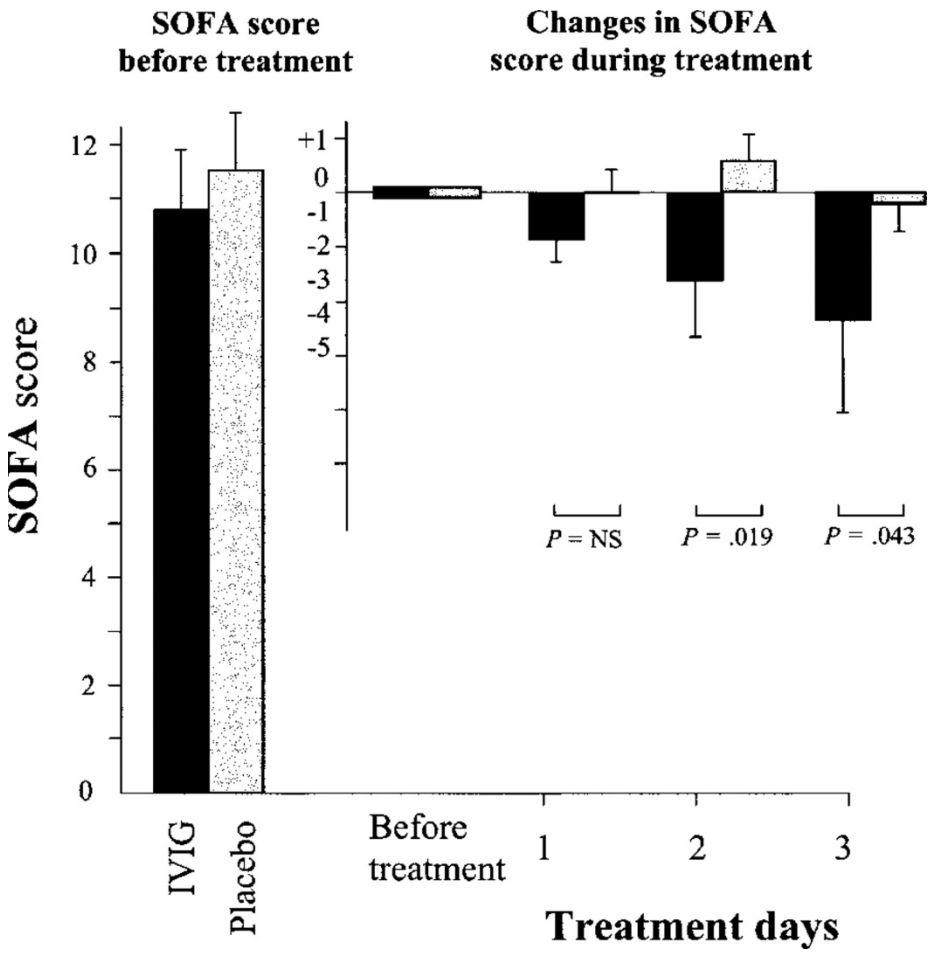
	All included patients		Patients with GAS only	
End point	IVIG group (n = 10)	Placebo group (n = 11)	IVIG group (n = 8)	Placebo group (n = 10)
Primary: mortality day 28, no. (%) of patients	1 (10)	4 (36)	1 (12.5)	3 (30)
Secondary				
Time to resolution of shock,[a] h				
Mean	88	122	100	122
Median (range)	96 (2–159)	108 (47–294)	108 (2–159)	108 (47–294)
Time to no further progression of NF/cellulitis, h				
Mean	68[b]	36[c]	69[c]	36[c]
Median (range)	20 (2–168)[b]	24 (19–72)[c]	20 (2–168)[c]	24 (19–72)[c]
Mortality day 180, no. (%) of patients	2 (20)	4 (36)	1 (12.5)	3 (30)

NOTE. GAS, group A streptococci; IVIG, intravenous IgG; NF, necrotizing fasciitis.

[a] In the survivors.
[b] Seven patients.
[c] Five patients.

Darenberg J et al. Clin Infect Dis. 2003;37:333-340

Initial Sepsis-related Organ Failure Assessment (SOFA) scores and changes during treatment in polyspecific intravenous IgG (IVIG)– and placebo-treated patients.



Darenberg J et al. Clin Infect Dis. 2003;37:333-340

Immunoglobulin is authorised for use in iGAS but only when failing 1st line treatment in UK

Diagnosis	*n*	Volume used (g)	Average dose (g/patient)
Severe invasive group A streptococcal disease	31	4451	144
Necrotising (PVL-associated) staphylococcal sepsis	20	2673	134
Severe or recurrent *Clostridium difficile* colitis	67	2297	34
Staphylococcal toxic shock syndrome	11	1388	126
Toxin-related infection in paediatric intensive care	19	719	38
Sepsis in the intensive care unit not related to specific toxins or *Clostridium difficile*	3	384	128
Neonatal sepsis (prevention or treatment)	2	10	5
Other (Infectious diseases)	31	4096	132
Total	**184**	**16,018**	

Immunoglobulin database, 2010, UK Dept Health

Preventing transmission of iGAS in maternity settings

Cluster of GAS infection

Case 1 -

- Delivered baby 1.10 am
- 21/12/07
- Died 23/12/07

Blood Culture
Group A Streptococcus M1

Post mortem HVS and
Cervical swab
Group A Streptococcus M1

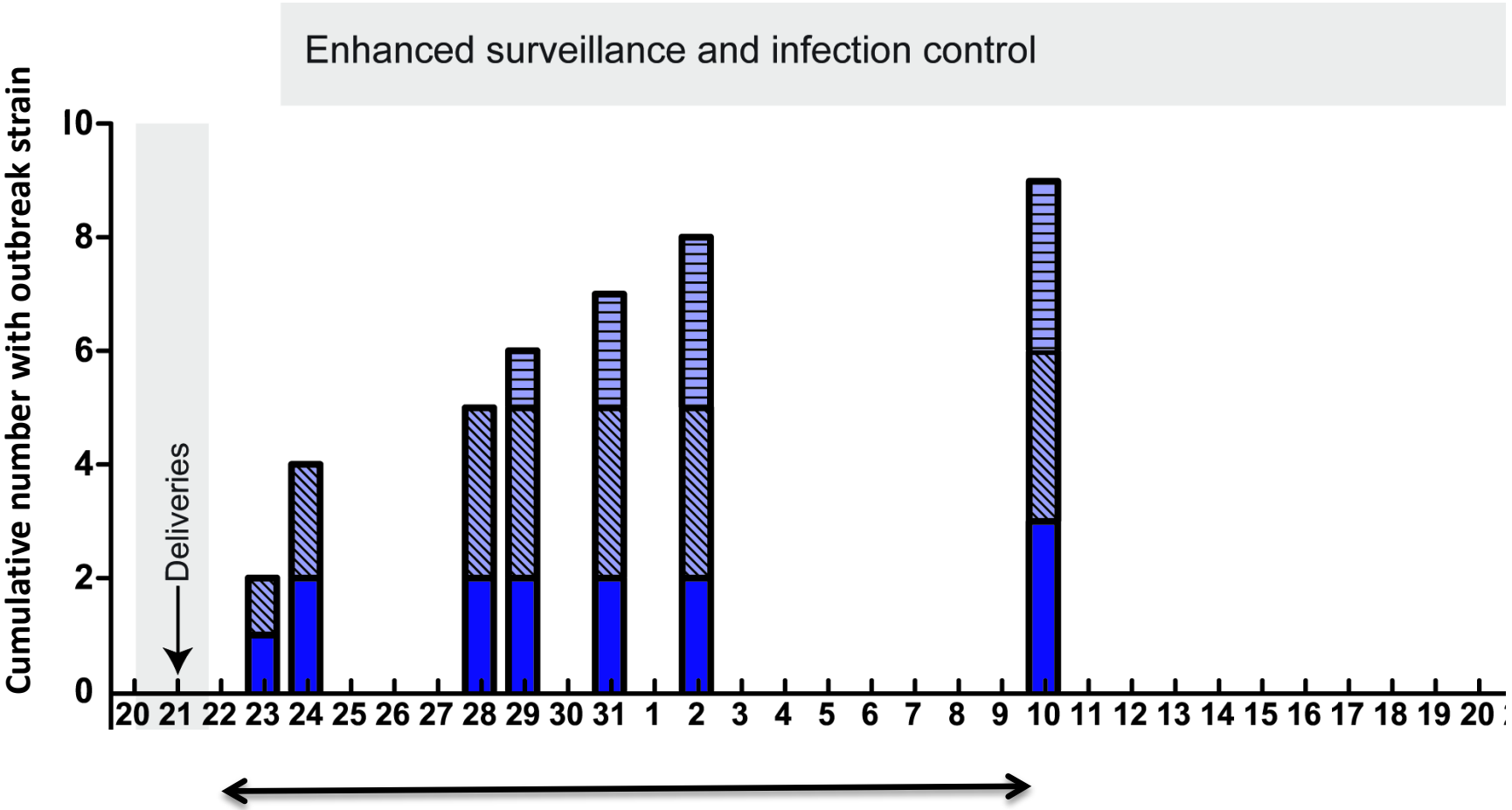
Case 2 -

- Delivered baby 1.08 am same unit
- 21/12/07
- Died 24/12/07

Post mortem ENT swab
Group A Streptococcus M1

Post mortem uterine swab and L+R Lung
Group A Streptococcus M1

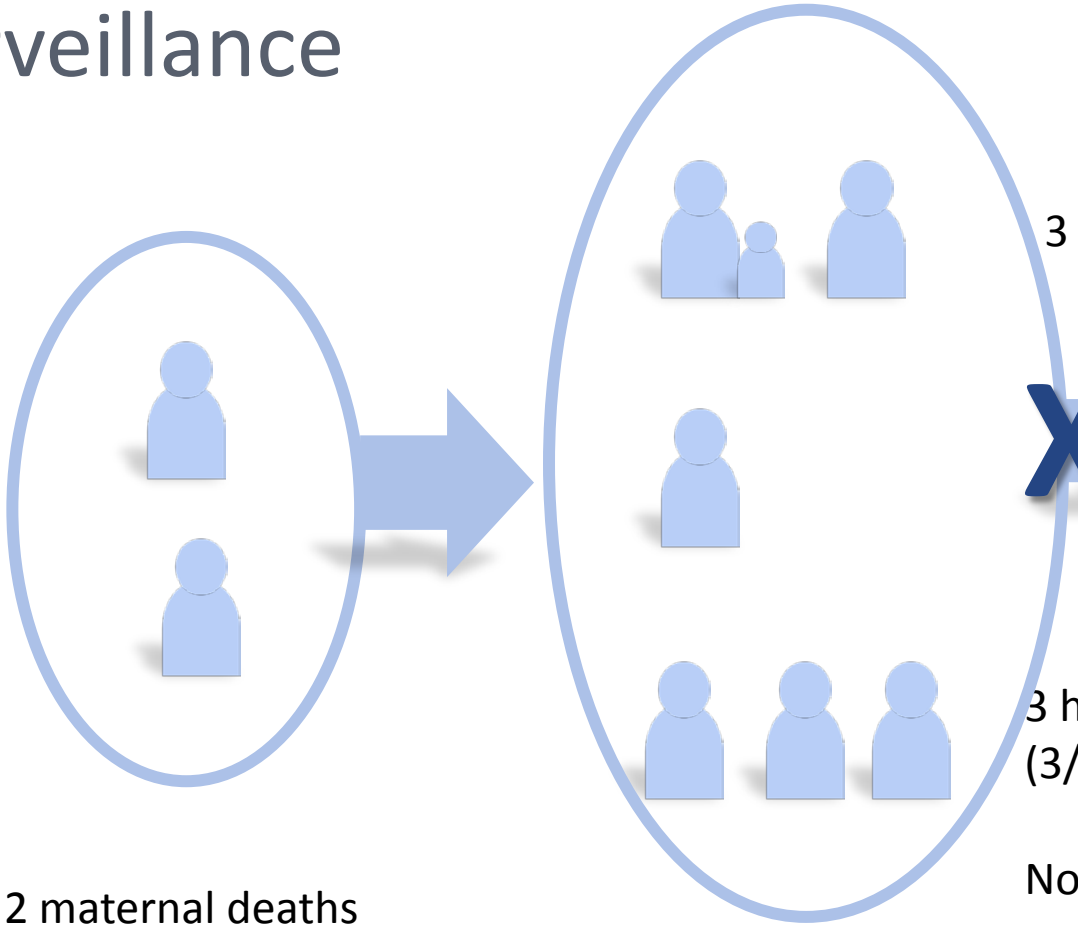
GAS can spread rapidly- preventing transmission requires speed



Exposures limited to single interactions

18 days from first isolate to last isolate

The importance of intense and immediate surveillance



2 maternal deaths

3 househ

3 healthca
(3/69 =4%

Not in 200 control HCWs

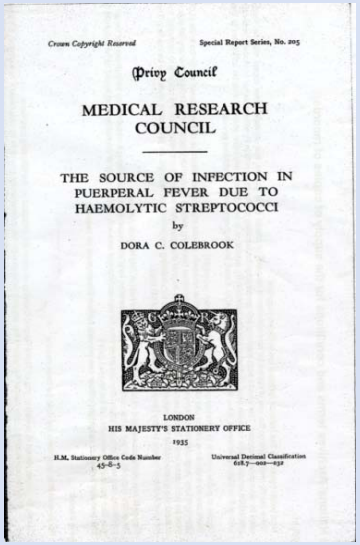
Confirmed by SOLEXA whole geno
sequencing

Immediate treatment

Intense surveillance

Environment,

Patients, staff



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MEDICAL RESEARCH COUNCIL

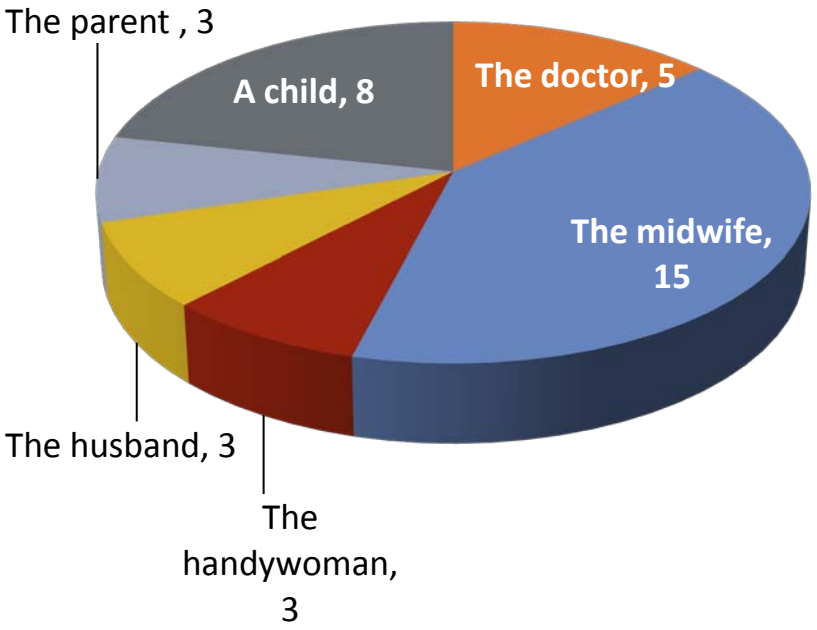
THE SOURCE OF INFECTION IN PUERPERAL FEVER DUE TO HAEMOLYTIC STREPTOCOCCI

by

DORA C. COLEBROOK

LONDON
HIS MAJESTY'S STATIONERY OFFICE
1935

H.M. Stationery Office Code Number 45-6-3 Universal Decimal Classification 618.7—002—032



1935 Recommendations (Dora Colebrook)

- Symptomatic URTI should be kept away from women in the puerperium
- Prophylactic measures-scrupulous hygiene incl disinfectants and masks
- **Investigate every case and exclude those affected (frequent nosocomial spread)**
- Estimated that 576 of 900 deaths per year were preventable

Journal of Infection (2012) 64, 1–18

ELSEVIER

PRACTICE GUIDELINES

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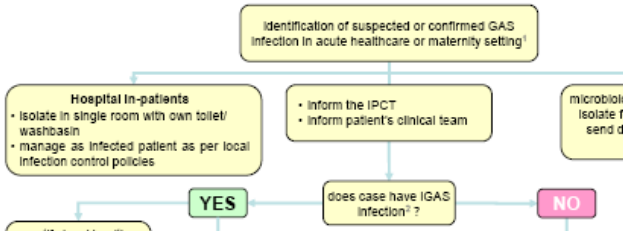
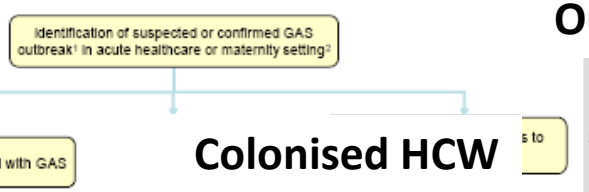
Single case



2. Invasive GAS infection (IGAS) is defined through isolation of GAS from normally sterile body site. Infections where GAS isolated from non-sterile site in combination with severe clinical presentation, should be managed as per IGAS infection.

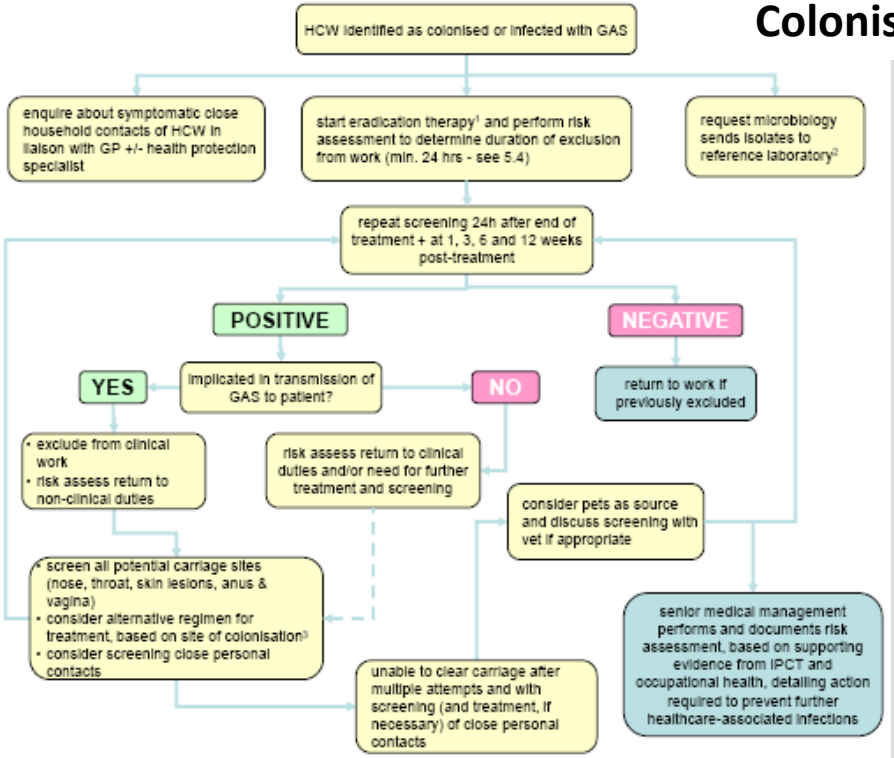
Outbreak



a month of each other but the interval may extend to six months.

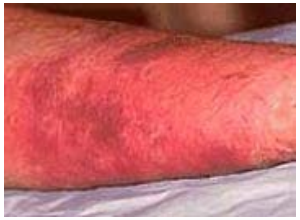
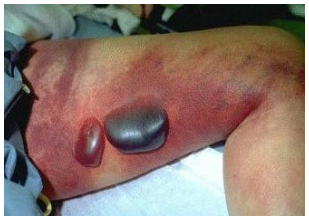
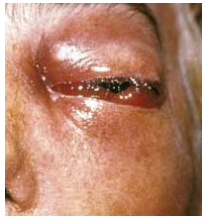
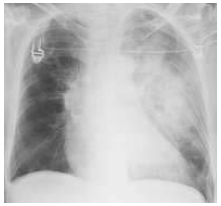
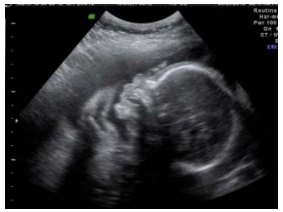
2. Includes hospital in-patients, patients recently discharged (<7 days) and women who gave birth in any setting including at home.
3. Clearly label isolates sent to the reference laboratory as being part of a suspected outbreak to prioritise processing. Epidemiological investigations and preventive measures should not await results of typing.
4. Outbreak control team may include infection control doctor and nurses, consultant microbiologist, consultant from the specialty involved, occupational health adviser, local health protection specialist, cleaning manager, bed manager, appropriate healthcare manager, local commissioning lead and communications adviser.
5. Other patients, HCWs and the environment are possible sources of outbreaks. Develop time lines and in-patient journeys to identify overlaps of hospital stays and common exposures.

Colonised HCW



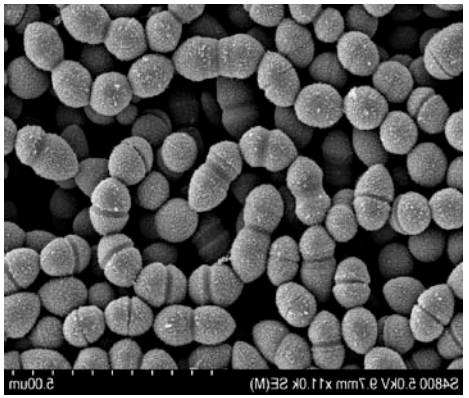
amoxicillin (500mg tds for 10 days), clindamycin (300 mg qds for 10 days), or azithromycin 500mg /day for 3 days. Non-pharyngeal carriage - Penicillin treatment alone may not be sufficient. Treatment options include clindamycin 300mg qds for 10 days, or azithromycin 500mg/day for 5 days with some limited reports in literature of combining with oral rifampicin or oral vancomycin.

2. Clearly label isolates sent to the reference laboratory as being part of a suspected outbreak to prioritise processing. Epidemiological investigations and preventive measures should not await results of typing.
3. Clindamycin (300mg QDS for 10 days) should be used for eradication of throat carriage in cases where first-line therapy with penicillin has been unsuccessful.

- Managing severe invasive GAS (peripartum sepsis)
  - If severe sepsis, likely to be GAS- prompt action
  - Not always genital tract sepsis
  - Use of clindamycin but beware resistance
  - Consider pooled intravenous immunoglobulin
  - No RCTs but plausible mode of action
  - Prompt strategies to prevent nosocomial spread and be concerned about even a single case

Acknowledgements



- Claire Turner
- Frances Davies

- Matthew Dryden, Royal Hampshire County Hospital
- Matt Holden, WT Sanger Institute
- Androulla Efstratiou, HPA
- Theresa Lamagni, HPA
- Joe Kearney, HPA & Working Party Guideline group

- UK CRC Centre for Infection Prevention and Management, Imperial College London