

## The cost of hospital care for management of invasive group A streptococcal infections in England

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### SUMMARY

The objective of this study was to estimate the direct financial costs of hospital care for management of invasive group A streptococcal (GAS) infections using hospital records for cases diagnosed in England. We linked laboratory-confirmed cases ( $n = 3696$ ) identified through national surveillance to hospital episode statistics and reimbursement codes. From these codes we estimated the direct hospital costs of admissions. Almost all notified invasive GAS cases (92% of 3696) were successfully matched to a primary hospital admission. Of these, secondary admissions (within 30 days of primary admission) were further identified for 593 (17%). After exclusion of nosocomial cases (12%), the median costs of primary and secondary hospital admissions were estimated by subgroup analysis as £1984–£2212 per case, totalling £4.43–£6.34 million per year in England. With adjustment for unmatched cases this equated to £4.84–£6.93 million per year. Adults aged 16–64 years accounted for 48% of costs but only 40% of cases, largely due to an increased number of surgical procedures. The direct costs of hospital admissions for invasive GAS infection are substantial. These estimated costs will contribute to a full assessment of the total economic burden of invasive GAS infection as a means to assess potential savings through prevention measures.

**Key words:** Cost of disease, hospital costs, streptococcal infections, *Streptococcus pyogenes*, treatment costs.

### INTRODUCTION

Group A streptococcal (GAS) infection causes a diverse range of diseases from common, mild complaints such as pharyngitis, to severe conditions, such as necrotizing fasciitis [1]. While invasive GAS infections (*Streptococcus pyogenes* isolated from a

normally sterile site) are uncommon at around 3/100 000 persons in the UK and other developed countries [2, 3], most result in hospitalization [4–6] and around one fifth will require critical care [2, 6]. Mortality is very high, estimated at 16% at 7 days post-diagnosis [7]. Although risk factors for invasive GAS infection are well established [8], in about a quarter of cases no risk factors are identified [2]. Asymptomatic carriers may be sources of GAS infection [1] and given that most cases occur sporadically, opportunities for prevention are limited [8]. As such, there is a clear need to develop a safe and effective GAS vaccine

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[9]. However, the diversity in serotypes [10], cross-reaction of antibodies with human tissues [11] and the lack of suitable animal models [12] have all restricted vaccine development.

Invasive GAS infection accounts for only part of the global burden of GAS infections [1, 13] yet given the complex care needed for management of invasive GAS infections the financial costs of hospitalization may be considerable. An assessment of the full economic burden will be required before considering the cost-effectiveness of any vaccination programme. The societal costs of GAS pharyngitis in an area of the USA have been estimated to be \$205 per case [13] but the cost of hospital admissions associated with invasive GAS infection are currently unknown. Methods to estimate the cost of hospital admissions for infections can either utilize the actual billing cost [14–16] or use unit costs based on either the type of admission [17, 18] or a diagnosis resource group [19–25].

As a means to assess the economic burden associated with hospital care for the management of invasive GAS infection, we estimated the direct costs of hospital resources associated with admissions for a 3-year period in England (2008–2010). We used a case-based methodology with healthcare resource group codes derived from a national database of hospital admissions (Hospital Episode Statistics; HES). These codes are used to reimburse costs for care provided to patients admitted to hospital in England.

## METHODS

### Case definitions and ascertainment

Cases were defined by the isolation of GAS from a normally sterile site from clinical specimens taken between 1 January 2008 and 31 December 2010. Cases were identified through a national database integrating routine laboratory surveillance reports and records of isolates submitted to the national reference laboratory. For individuals with more than one specimen, the date of the earliest GAS-positive specimen was used and the individual included once in this study. A nosocomial case was defined as one where the date of the positive specimen was  $\geq 2$  days after hospital admission.

Cases were linked to hospital admissions using their unique National Health Service (NHS) number. A primary admission was defined as one where the GAS-positive specimen was taken during the admission or up to 14 days prior to the admission date

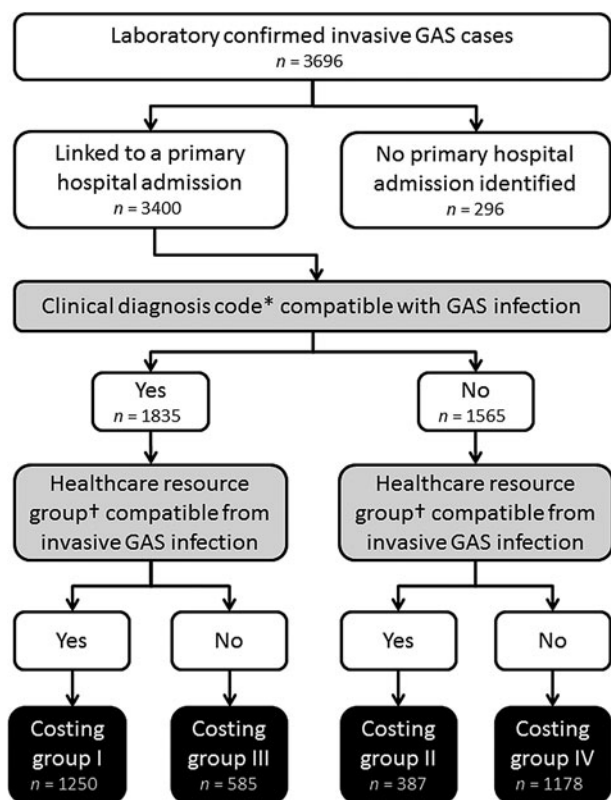
(in order to include cases with a delayed admission, for example patients initially managed in community healthcare facilities). A secondary admission was defined as a subsequent admission  $\leq 30$  days after the primary admission discharge.

### Healthcare resource groups

In order to cost admissions, the ICD-10 primary diagnosis codes and the interventions and procedures (Office of Population Censuses and Surveys classification of interventions and procedures, version 4; OPCS-4) recorded for each case within HES were used to generate a healthcare resource group casemix classification code (version 4, HRG4) using the 2010/2011 NHS Local Payment Grouper (LPG; <http://www.hscic.gov.uk>). The LPG uses codes recorded for a hospital admission and produces a single HRG4 code for that admission. Where an admission was followed by transfer(s) to another hospital, these admissions were combined to generate a single HRG4 code. HRG4 codes were translated into reimbursement costs by referring to the NHS national tariff for 2010/2011 [26]. Extended hospital stays not covered by the standard tariff (long stay trim-point) were identified and costs adjusted using the *per diem* for each code.

Cases with a primary hospital admission were divided into four groups (I–IV) to account for the differing degree of certainty in attributing their hospital costs directly to invasive GAS infection. This group allocation was based on the presence or absence of (1) diagnosis codes for invasive GAS infection combined with the presence or absence of (2) a resource group code compatible with treatment for an invasive GAS infection (creating four groups in total; Fig. 1). For (1), ICD-10 diagnosis codes were used based on those recorded which included mention of: abscess, cellulitis, empyema, endocarditis, endometriosis, fasciitis, gangrene, infective arthritis, meningitis, myositis, osteomyelitis, peritonitis, pneumonia, puerperal sepsis, sepsis, septicaemia, toxic shock syndrome, unspecified streptococcal infection. We excluded ICD-10 codes that specified non-GAS organisms. For (2), we derived a list of HRG4 codes that were associated with ICD-10 codes from (1) in the 2010/2011 NHS HRG4 Code to Group workbook v. 1.0 (<http://www.hscic.gov.uk>).

As a new LPG is released each year, we tested the suitability of using a single LPG for the 3 years of study data by assessing the consistency of coding for



**Fig. 1.** Schematic outlining the attribution of cases to costing groups of invasive group A streptococcal (GAS) cases. \* ICD-10 primary diagnosis code. † Healthcare resource group code, version 4.

primary diagnosis (ICD-10), main operative procedures (OPCS-4) and resource group (HRG4) codes for all primary admissions. For this purpose we compared only the distribution of codes that accounted for  $\geq 1\%$  of primary admissions during a study year and where the code had a hierarchy level  $\geq 3$  (thus excluding low resource expenditure procedures). Study groups were also created for three character OPCS-4 codes for the main operation, excluding subsidiary classification codes (from OPCS-4, chapters Y and Z) from all primary admissions not defined as nosocomial infections.

### Costing critical care

As payments for critical care in the NHS are covered by separate arrangements to other costs for admitted care, these are not reliably identified through HES. In recognition of this, the expected frequency of critical care was determined using the available enhanced surveillance data for invasive GAS in England, for 2003/2004 and 2009 [2, 27]. HES data for

Augmented Care Periods (ACPs) were available for cases with a hospital admission between April 2008 and March 2009 and used to determine the number of organs supported during critical care and the length of stay on intensive-care or high-dependency units. These were then used to cost critical care episodes according to NHS benchmark costs for 2010/2011 [28].

### Sensitivity and age group analysis

A subgroup sensitivity analysis was undertaken in order to account for the inability to determine those admissions with costs directly as a result of invasive GAS infection and uncertainty as to which secondary admissions were truly a consequence of invasive GAS infection. This sensitivity analysis calculated costs with and without costing group IV (Fig. 1).

Analysis of costs was undertaken according to the following age groups: children ( $\leq 15$  years), working age adults (16–64 years), older adults ( $\geq 65$  years).

### Statistical analysis

Comparison of continuous variables for independent groups was performed using the Mann–Whitney *U* test.

## RESULTS

### Linkage of cases to hospital admissions

Of the 3696 cases of invasive GAS infection identified through national surveillance in England during 2008–2010, 3555 (96%) were linked to  $\geq 1$  hospital admission. Of these, 3400 (92% of total cases) represented primary admissions, of which 227 involved transfers between hospitals and 593 (17%) had  $\geq 1$  secondary admission. The median interval between primary discharge and secondary admission was 9 days [interquartile (IQR) range 3–20]. Of the 3383 primary admissions, 403 (11.9%) represented nosocomial infections.

### Clinical diagnoses

A wide array of ICD-10 diagnostic codes was associated with primary admissions, reflecting both the spectrum of clinical presentations for invasive GAS infection and comorbidities (Supplementary Fig. S1). Up to six primary diagnosis codes were indicated, although the majority of cases had just one code (2761/3400, 81.2%). Over half (1835/3400, 54%) of

primary admissions were associated with an invasive GAS diagnosis code although only one code specifically mentioned GAS as the causative organism (A40.0, 'Sepsis due to streptococcus, group A'), recorded for 12% (422/3400) of primary admissions. The four highest frequency diagnosis groups were septicæmia (638, 15.2%), skin and soft tissue infection (540, 12.9%), pneumonia (373, 8.9%), and infective arthritis (212, 5.1%). Of the 1756 different ICD-10 diagnosis codes, 117 included a named condition consistent with invasive GAS infection and of these 93 were used as indicators of admission for invasive GAS infection (Supplementary Table S1) and to identify 48 corresponding resource group codes (Supplementary Table S2) to define costing groups (Table 1).

Although the diversity of diagnosis codes for secondary admissions was substantial (Supplementary Fig. S2), 288 (28.9%) of these 994 diagnoses (after excluding those associated with nosocomial cases) were from ICD-10 groups compatible with diagnosis of invasive GAS infection: septicæmia (42, 4.2%), skin and subcutaneous tissue infections (75, 7.5%), pneumonia (42, 4.2%), infective arthritis (73, 7.3%), other groups (56, 5.6%).

### Healthcare resource groups

All primary admissions were successfully assigned a resource group code. Diagnosis, procedure and resultant resource group codes showed a general consistency of use over the study period (Supplementary Fig. S3). HRG4 resource group codes for primary admissions were predominantly those for infectious diseases (502, 14.8%), skin disorders (424, 12.5%), thoracic procedures and disorders (406, 11.9%), and paediatric medicine (404, 11.9%) (Supplementary Fig. S4). The paediatric medicine subchapter contains clinical codes for care of all children  $\leq 18$  years, of the 404 primary admissions with resource group codes within this subchapter >75% were associated with codes for either infections (288, 71.3%) or skin disorders (20, 5.0%).

### Costs of hospital admissions

The costing groups used in this study separate cases based on diagnosis and treatment codes (Table 1), with clear differences in hospital admission costs and length of stay after removing nosocomial cases (Fig. 2). Of the nosocomial infections which could

Table 1. Costing groups for primary admissions of invasive GAS infection cases based on diagnosis and healthcare resource group codes, England 2008–2010

Costing group	Invasive GAS diagnosis code*	Invasive GAS hospital costing code†	Cases (%)‡
I	Yes	Yes	1250 (33.8)
II	No	Yes	387 (10.5)
III	Yes	No	585 (15.8)
IV	No	No	1178 (31.9)
All primary admissions	Yes/No	Yes/no	3400 (92.0)

GAS, Group A streptococcal.

\* One of 93 ICD-10 codes selected as indicative of invasive GAS infection.

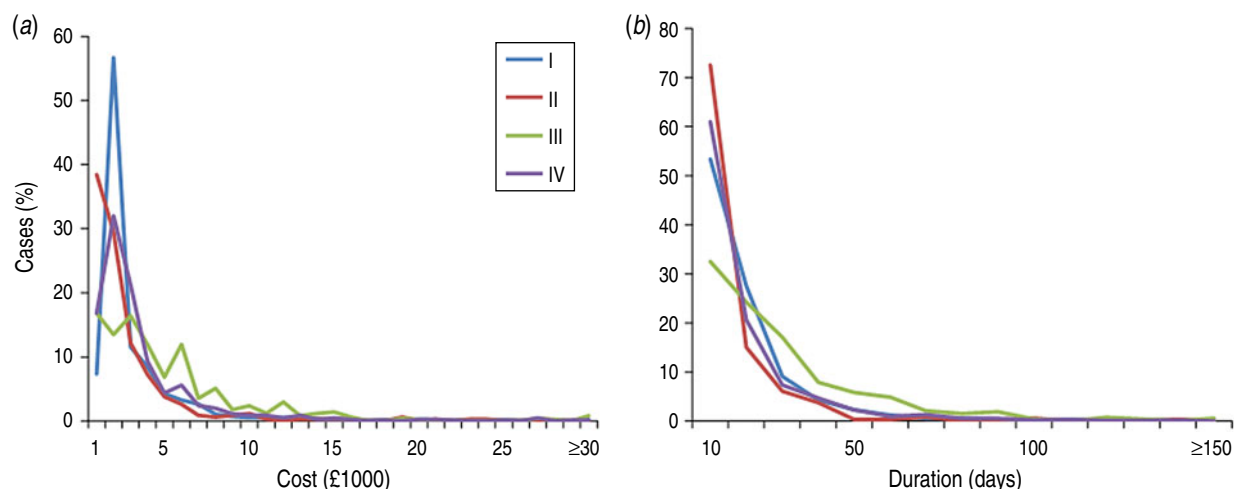
† One of 48 healthcare resource group, version 4 codes associated with the 93 invasive GAS ICD-10 diagnosis codes.

‡ Cases included from the full dataset ( $n = 3696$ ) were those with a linked primary hospital admission ( $n = 3400$ ).

be coded ( $n = 391$ ), 118 (30%) had an HRG4 resource group code not included in our list of invasive GAS infection codes, suggesting costs dominated by management of other conditions.

The highest proportion of cases fell within costing group I (1250, 34% of all cases; Table 2), characterized by both diagnosis and treatment compatible with invasive GAS infection. Median costs of hospital care (entire stay, excluding critical care) were £1707 for these patients. Costing group II, cases without invasive GAS clinical diagnosis codes but whose care was compatible with management of invasive GAS infection, had shorter admissions (median 5 days, Fig. 2) and lower in-hospital mortality rates (7%, Table 1). Conversely, costing group III, patients with invasive GAS clinical diagnosis codes but without resource codes directly attributable to invasive GAS infection (e.g. non-trauma-related procedures), had substantially longer admissions (median 17 days, Fig. 2) and high costs (median £3108, excluding critical care; Fig. 2). Costing group IV represents cases with neither an invasive GAS diagnosis code nor an invasive GAS resource group code and contained the highest proportion of nosocomial cases for any costing group (Table 2).

Invasive GAS cases which died in hospital had reduced lengths of admission and costs, although this was not statistically significant for costing groups II and IV (Table 3). The proportion of nosocomial cases was significantly higher for costing groups where diagnosis of invasive GAS infection could not



**Fig. 2.** Distribution of (a) primary admission costs (Healthcare resource group code version 4 resource groups) and (b) duration of primary admission for cases in costing groups (I–IV). Nosocomial cases have been excluded.

be determined from HES [costing groups I and III: 7.8% (130/1835); costing groups II and IV: 17.4% (273/1565);  $\chi^2 = 86.76$ ,  $P < 0.0001$ ]. The median length of critical care stay for the small proportion of cases where this could be determined (184, 5.4%) was 4 days (IQR 1–10). ACP data identified a median of three organs supported during critical care (pragmatically assumed to be constant during a critical care stay), translating to £1386 per bed-day. For total cost estimates, we adjusted HES costs using external validation of the likely frequency of critical care (20% of cases).

After producing cost estimates for secondary admissions (Table 4), subgroup sensitivity analysis estimated the cost of hospital resources for invasive GAS infections to be £4.43–£6.34 million per year in England (Table 5). After adjusting for cases which could not be linked to a hospital admission, these costs are £4.84–£6.93 million per year in England. The median cost per case was £1984–£2212, with substantial variation in the cost of individual admissions (£247–£358 100). Costs by age group were largely consistent with the distribution of cases, although the expected fraction of costs for working age adults (16–64 years) was slightly higher, while that for children ( $\leq 15$  years) and older adults ( $\geq 65$  years) reduced (Table 6). This would appear to be due to an increased number of operations (particularly abdominal, chest, skin and soft tissue surgeries), procedures related to pregnancy, and higher numbers of cases requiring cardiovascular and respiratory care (Table 7). It was not accounted for by an increased length of stay for working age adults (median 9

days, IQR 4–18), as length of stay was significantly longer for older adults (median 12 days, IQR 4–28,  $Z = -5.17$ ,  $P < 0.0001$ ).

## DISCUSSION

This study provides the first estimate of the cost of hospital care for invasive GAS infection. The generation of these costs has included careful consideration of both the clinical nature of the infection and the methodological approach to costing admissions using routinely collected hospital admission data. With a study of this kind, a single point estimate of costs will be unlikely to satisfactorily represent the full complexity of the analysis undertaken and the accompanying uncertainty. With this in mind, we have estimated the cost of hospital resources associated with admissions for treatment of invasive GAS infection to be £4.43–£6.34 million per year in England. This reflects uncertainty in directly attributing costs to treatment of invasive GAS infection for both primary and secondary hospital admissions. Conservatively we have excluded all nosocomial infections from our costing estimates. However, clinical management of invasive GAS infection may have dominated the treatment costs for some of these cases and their removal will represent an underestimate. We have also likely excluded some community-acquired cases where there was late diagnosis. Our estimate is for cases that we have been able to successfully link to a primary hospital admission and could be 8% higher (£4.84–£6.93 million per year) if we failed to identify corresponding

Table 2. *Costs of primary hospital admissions for cases of invasive GAS infection, England 2008–2010*

Costing group	<i>n</i>	Median duration of primary admission (IQR)	Hospital care (HRG4) costs (£)		Critical care costs			Adjusted† annual (million £)	Combined annual HRG4 and critical care cost (million £)	Nosocomial GAS infections		Annual costs adjusted for nosocomial GAS infections (million £)
			Median (IQR)	Annual* (millions)	<i>n</i> (%)	Median (£, IQR)	Annual (million £)			Cases (%)	Costs of admissions (million £)	
I	1250	9 (4–17)	1707 (1324–3092)	1·20	65 (5·2)	5544 (1386–12470)	0·18	0·74	1·94	77 (6·2)	0·13	1·81
II	387	5 (3–13)	1527 (842–2872)	0·34	12 (3·1)	4851 (2772–12820)	0·04	0·17	0·51	41 (10·6)	0·10	0·41
III	585	17 (8–32)	3108 (1653–5599)	0·87	61 (10·4)	8316 (1386–29110)	0·35	1·38	2·26	53 (9·1)	0·24	2·01
IV	1161	9 (3–20)	2141 (1132–4086)	1·39	46 (3·9)	4158 (1386–9702)	0·14	0·58	1·96	220 (18·9)	0·49	1·47
All primary admissions‡	3383	9 (3–20)	1980 (1292–3872)	3·80	184 (5·4)	5544 (1386–14210)	0·72	2·87	6·67	391 (11·6)	0·96	5·71

GAS, group A streptococcal; HRG4, Healthcare resource group, version 4; IQR, interquartile range.

\* Annual costs are an average for the three years of the study.

† Costs adjusted on basis of expected overall critical care frequency.

‡ Cases from the full dataset ( $n = 3696$ ) were those with a linked primary hospital admission ( $n = 3400$ ) after removal of cases which could not be costed ( $n = 17$ ).

Table 3. Duration of primary admission and hospital care costs for cases of invasive GAS infection which died in hospital, England 2008–2010

Costing group	n*	Cases who died in hospital (%)	Median duration of primary admission in days (IQR)				Median hospital care (HRG4) costs (IQR)			
			Non-fatal cases	Fatal cases	Comparison†		Non-fatal cases	Fatal cases	Comparison†	
					Z score	P value			Z score	P value
I	1173	219 (18.7)	10 (5–18)	2 (1–6)	13.04	<0.0001	1729 (1324–3128)	1707 (1324–1707)	5.06	<0.0001
II	346	19 (5.5)	5 (2–11)	0 (0–3)	5.02	<0.0001	1425 (842–2597)	1324 (751–1707)	1.55	0.0123
III	532	83 (15.6)	18 (9–33)	2 (1–14)	8.28	<0.0001	3359 (1836–5940)	1999 (1092–3906)	3.72	0.0002
IV	941	161 (17.1)	8 (3–16)	1 (1–6)	8.70	<0.0001	2051 (1076–3568)	1921 (1130–2900)	0.47	0.6400
All primary admissions	2992	482 (16.1)	10 (1–19)	2 (1–7)	17.60	<0.0001	1944 (1175–3666)	1707 (1324–2294)	4.42	<0.0001

HRG4, Healthcare resource group, version 4; IQR, interquartile range.

\* Cases included from the full dataset ( $n = 3696$ ) were those with a linked primary hospital admission ( $n = 3400$ ) after removal of nosocomial cases ( $n = 403$ ) and/or those that could not be costed ( $n = 17$ , of which 12 were also nosocomial cases).

† Mann–Whitney  $U$  test.

Table 4. Costs of secondary hospital admissions within 30 days of primary admission for cases of invasive GAS infection, England 2008–10

Costing group	n*	Secondary admissions per case (no. of cases)								Total number of secondary admissions	Hospital care (HRG4) costs (£)			Invasive GAS infection admissions§	
		0	1	2	3	4	≥5	≥1	Median (IQR)		Annual† (millions)	Combined annual cost‡ (million £)	n (%)	Annual cost (million £)	
I	1173	957	173	25	7	3	8	216	315	1568 (935–2293)	0.21	0.22	125 (39.7)	0.10	
II	346	286	43	10	3	3	1	60	92	1449 (742–2031)	0.06	0.06	15 (16.3)	0.01	
III	532	415	94	15	3	4	1	117	159	1648 (1024–2886)	0.14	0.14	78 (49.1)	0.08	
IV	941	741	151	29	3	3	14	200	377	1190 (630–1774)	0.22	0.22	66 (17.5)	0.05	
All primary admissions	2992	2399	461	79	16	13	24	593	943	1449 (796–2061)	0.63	0.63	284 (30.1)	0.25	

GAS, Group A streptococcal; HRG4, healthcare resource group, version 4; IQR, interquartile range.

\* Cases included from the full dataset ( $n = 3696$ ) were those with a linked primary hospital admission ( $n = 3400$ ) after removal of nosocomial cases ( $n = 403$ ) and/or those that could not be costed ( $n = 17$ , of which 12 were also nosocomial cases).

† Annual costs are an average for the 3 years of the study.

‡ Includes costs for critical care.

§ Admissions defined by the recording of an invasive GAS infection ICD-10 diagnosis code.

Table 5. Subgroup sensitivity analysis of hospital care costs for cases of invasive GAS infections, England 2008–2010

Estimate level	Primary hospital admission costing groups ( <i>n</i> *)	Percentage of total cases†	Total annual‡ costs of primary hospital admissions (million £)	Secondary hospital admissions included	Total costs of secondary hospital admissions (million £)	Combined costs of primary and secondary admissions (million £)	Median total costs (£) per costed case (IQR)
Lower	I–III (2 051)	55.5	4.23	Invasive GAS diagnosis§	0.20	4.43	1984 (1324–4458)
Upper	I–IV (2992)	81.0	5.71	All	0.63	6.34	2212 (1324–4952)

GAS, Group A streptococcal; IQR, interquartile range.

\* Cases included from the full dataset (*n* = 3696) were those with a linked primary hospital admission (*n* = 3400) after removal of nosocomial cases (*n* = 403) and/or those that could not be costed (*n* = 17, of which 12 were also nosocomial cases), for the lower estimate cases from costing group IV (*n* = 941) were also excluded.

† For the entire study (*n* = 3696).

‡ Annual costs are an average for the 3 years of the study.

§ Includes only secondary hospital admissions with a diagnosis code for invasive GAS infection.

Table 6. Distribution of cases and total annual hospital care costs by age group for invasive GAS infections, England 2008–2010

Age group	No. of cases (%)	Total annual costs (million £)	
		Lower estimate (%)	Upper estimate (%)
All ages	3383* (100.0)	4.43 (100.0)	6.34 (100.0)
0–15 years	539 (15.9)	0.53 (12.0)	0.72 (11.4)
16–64 years	1346 (39.8)	2.11 (47.6)	3.03 (47.8)
≥65 years	1498 (44.2)	1.80 (40.6)	2.58 (40.7)

GAS, Group A streptococcal.

\* Cases included from the full dataset (*n* = 3696) were those with a linked primary hospital admission (*n* = 3400) after removal of cases which could not be costed (*n* = 17).

hospital records for cases that were in fact treated within a hospital setting. Published percentages of cases requiring hospitalization range from 98–99% in Australia and New Zealand [4, 6] to 91% in the USA [5].

The lower range of our estimated costs is based on cases with invasive GAS infection diagnosis codes and/or invasive GAS infection healthcare resource group codes (for the associated primary hospital admission). The exclusion of other cases was made to remove admissions which may have been dominated by condition(s) independent to invasive GAS infection. However, this excludes a substantial proportion of cases (32%) with laboratory-confirmed invasive GAS infection, some of which will undoubtedly have been

admitted to hospital because of that invasive GAS infection. Although exclusion of these cases is logical when wishing to reduce the risk of overestimating costs, such a step is reliant on accurate and relevant coding within HES and the *a priori* selection of appropriate invasive GAS infection defining codes. Although we have been thorough in our reduction of error from the latter, we have not determined the influence of inaccurate HES codes [29] or the dominance of other conditions with regard to diagnosis. Ultimately, these cases either reflect those where treatment for invasive GAS infection truly did not dominant hospital care or where the nature of HES coding has obscured direct recognition of that care.

We are not aware of any published studies which have applied this case level methodology to comparative invasive bacterial infections in England. A small study published over 20 years ago for invasive *Haemophilus influenzae* infection found costs for hospital admissions using base reference costs (£2300 without critical care, £4300 with) [30] to be not dissimilar to those found here, but this comparison does not consider inflation. Costs of hospital admissions for invasive pneumococcal infection (£903–£1547, depending on clinical presentation) [20] and invasive meningococcal infection (£2337) [31] have been produced for cost-effectiveness estimates and are also not widely different from our estimates for invasive GAS. However, the lack of a case list independent to hospital admission data prevents such aggregate studies accounting for variance in costs at an individual level. Moreover, the clinical diversity and distribution of comorbidities for



Table 7. Types of main operative procedures recorded for primary hospital admissions of cases of invasive GAS infection by age group and by number of main procedures, England 2008–2010

OPCS-4 study group*	OPCS-4 study subgroup	No. of primary admissions undergoing $\geq 1$ main procedure (%†)				No. of primary admissions according to the number of main procedures recorded‡						Total no. of procedures
		All ages (n = 2997)	0–15 yr (n = 511)	16–64 yr (n = 1207)	$\geq 65$ yr (n = 1279)	0	1	2	3	4	$\geq 5$	
Cardiovascular care	Cardiac interventions	15 (0.5)	1 (0.2)	8 (0.7)	6 (0.5)	2982	12	3				18
	Echocardiography	229 (7.6)	15 (2.9)	129 (10.7)	85 (6.6)	2768	182	35	6	6		294
	Intravenous and intra-arterial procedures	407 (13.6)	58 (11.4)	197 (16.3)	152 (11.9)	2590	273	101	18	6	9	612
Diagnostics	Biopsies	28 (0.9)	3 (0.6)	14 (1.2)	11 (0.9)	2969	27	1				29
	Diagnostic imaging and tests	882 (29.4)	116 (22.7)	410 (34.0)	356 (27.8)	2115	131	267	214	111	159	2807
Gastrointestinal care	Endoscopy or intubation of gastrointestinal tract	105 (3.5)	1 (0.2)	36 (3.0)	68 (5.3)	2892	76	26	3			137
Gynaecology and obstetric care	Female genital tract procedures	10 (0.3)	0 (0.0)	8 (0.7)	2 (0.2)	2987	8	2				12
	Pregnancy and delivery (excluding surgical delivery)	29 (1.0)	0 (0.0)	29 (2.4)	0 (0.0)	2968	21	7	1			38
Renal care	Catheterization and endoscopic examination of bladder	40 (1.3)	1 (0.2)	9 (0.7)	30 (2.3)	2957	33	4	2	1		51
Respiratory care	Dialysis for renal failure	121 (4.0)	4 (0.8)	66 (5.5)	51 (4.0)	2876	86	16	6	4	9	230
	Endoscopy of respiratory tract	74 (2.5)	8 (1.6)	44 (3.6)	22 (1.7)	2923	57	13	2	2		97
	Invasive ventilations and associated procedures	109 (3.6)	0 (0.0)	65 (5.4)	44 (3.4)	2888	80	25	1	2	1	146
	Non-invasive ventilations and associated procedures	274 (9.1)	38 (7.4)	135 (11.2)	101 (7.9)	2723	215	48	7	3	1	352
	Pleural drainage and respiratory tests	128 (4.3)	22 (4.3)	86 (7.1)	20 (1.6)	2869	79	33	10	5	1	201
Surgery and associated procedures	Abdominal surgery	72 (2.4)	3 (0.6)	55 (4.6)	14 (1.1)	2925	49	15	7	1		104
	Amputations	55 (1.8)	1 (0.2)	27 (2.2)	27 (2.1)	2942	38	11	4	1	1	88
	Chest surgery including heart and lung	21 (0.7)	5 (1.0)	13 (1.1)	3 (0.2)	2976	13	5	1	1	1	35
	Female genital tract and pregnancy-related operations	36 (1.2)	1 (0.2)	34 (2.8)	1 (0.1)	2961	29	5	1	1		46
	Gastrointestinal tract surgery	41 (1.4)	5 (1.0)	21 (1.7)	15 (1.2)	2956	31	9	1			52
	Head and neck surgery	64 (2.1)	17 (3.3)	29 (2.4)	18 (1.4)	2933	35	11	6	10	2	125
	Skin surgery	191 (6.4)	11 (2.2)	115 (9.5)	65 (5.1)	2806	80	44	22	22	23	469
	Soft tissue and musculoskeletal surgery	339 (11.3)	55 (10.8)	164 (13.6)	120 (9.4)	2658	171	85	44	19	20	670
	Unclassified operative procedures	170 (5.7)	16 (3.1)	102 (8.5)	52 (4.1)	2827	130	34	3	2	1	221

Table 7 (cont.)

OPCS-4 study group*	No. of primary admissions undergoing $\geq 1$ main procedure (%†)				No. of primary admissions according to the number of main procedures recorded‡						Total no. of procedures
	All ages (n = 2997)	0–15 yr (n = 511)	16–64 yr (n = 1207)	$\geq 65$ yr (n = 1279)	0	1	2	3	4	$\geq 5$	
OPCS-4 study subgroup											
Treatment and rehabilitation											
High cost drugs	35 (1.2)	4 (0.8)	21 (1.7)	10 (0.8)	2962	26	8	1			46
Injections, infusions and transfusions	47 (1.6)	11 (2.2)	20 (1.7)	16 (1.3)	2950	40	5	1	1		62
Other treatments (including anaesthetic drugs)	54 (1.8)	9 (0.3)	30 (1.0)	15 (0.5)	2943	39	14	1			70
Rehabilitation	35 (1.2)	0 (0.0)	6 (0.5)	29 (2.3)	2962	31	3	1			40
Resuscitation	30 (1.0)	1 (0.2)	10 (0.8)	19 (1.5)	2967	28	2				32
Any costing group	1688 (56.3)	231 (45.2)	794 (65.8)	663 (51.8)	1309	370	333	243	187	555	7084

GAS, Group A streptococcal; OPCS-4, Office of Population Censuses and Surveys classification of interventions and procedures, version 4.

\* Grouping according to Supplementary Table S3.

† Cases included from the full dataset (n = 3696) were those with a linked primary hospital admission (n = 3400) after removal of nosocomial cases (n = 403) (n = 3400–403 = 2997).

‡ Zeroes have been omitted for ease of presentation.

invasive GAS infection restricts the application of definitions on the basis of diagnostic coding. Diagnoses made on admission to hospital may involve recording of underlying conditions and risk factors for invasive GAS infection such as cancer and chronic diseases [8] which do not preclude the presence (recognized or not) of a concomitant invasive GAS infection. This situation is further complicated for secondary hospital admissions where there is the combination of invasive GAS infection, post-operative care, post-infection care and post-infection sequelae. For this reason, we adopted a pragmatic approach to defining secondary admissions, applying a simple definition with the acceptance that both the inclusion of unrelated admissions and censoring of invasive GAS-related ones were likely. Nevertheless, we feel that the majority of re-admissions as a direct consequence of a previous invasive GAS infection will occur within 30 days of the end of the primary admission.

Critical care resources made up a substantial contribution to our estimates of costs, upon which we have made three assumptions. First, we have made a fixed adjustment based on the assumption that the HES-based methodology has under-ascertained critical care cases by a factor of 4 (due to the use of a dedicated separate data stream for critical care admissions). This assumption is based on published data for England [2, 27], Australia [4], Denmark [32] and New Zealand [6]. While the principle and magnitude of the adjustment are reasonable, we were unable to assess the level of adjustment separately for each costing group. As such, these subgroup-specific critical care estimates are not likely to be robust. Second, we have assumed that the duration of critical care episodes when recorded in HES is an accurate duration of critical care provided generally for invasive GAS patients. As the median duration of these episodes (4 days) appears to be broadly consistent with that reported in Canada [33] and New Zealand [6], this would appear to be sensible. Third, we have based costs on support for three organs during critical care, which is validated by limited data from our study and elsewhere [33]. After the discontinuation of the ACP dataset, critical care episodes are not routinely or consistently recorded in HES and a separate dataset now exists for that purpose [34].

The total economic burden of invasive GAS infections will of course include general practice consultations/other primary care costs and further costs associated with lost working days and life years. The latter will be substantial for invasive GAS infection

given the associated high mortality, although for these cases healthcare costs will ultimately be reduced as death tends to occur rapidly after diagnosis [7]. We have limited our study to invasive infections caused by GAS and have not attempted to estimate the financial costs associated with the management of less severe GAS infections by primary care services or those costs associated with public health actions, such as the management of outbreaks and close contacts of cases. All of these costs are to our knowledge unknown yet vital should a full estimate of cost-effectiveness for vaccination be required. Invasive GAS infection has a high mortality rate and affects all ages, including the otherwise healthy [2], and the burden is likely to be considerable. Despite the modest progress in vaccine development for GAS infection [12], it seems likely that a commitment to development of a vaccine for GAS will continue [35]. The costing estimates from this study will contribute towards a full cost-effectiveness estimate as and when it is undertaken, but for now provides valuable knowledge of the financial costs of invasive GAS infections to secondary healthcare in England.

## SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0950268814002489>.

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## DECLARATION OF INTEREST

None.

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