



# Invasive group B *Streptococcus* among non-pregnant adults in Brussels-Capital Region, 2005–2019

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## Abstract

To assess the incidence, clinical, microbiological features and outcome of invasive *Streptococcus agalactiae* (GBS) infections in non-pregnant adults in three tertiary hospitals of the Brussels-Capital Region. All bacterial cultures positive for GBS, from 2005 to 2019 from 3 hospitals of the Brussels-Capital Region, were extracted, and only cases of invasive diseases were included. Medical files were retrospectively retrieved for risk factors, clinical manifestations and outcome and also antibiotic-susceptibility testing and GBS serotypes. Incidence rates were calculated based on the hospitals catchment populations. A total of 337 cases of GBS-invasive infections were included. The incidence of invasive GBS for the 3 hospitals increased from 3.7 to 8.2 cases per 100.000 inhabitants between 2009 and 2018 ( $p = 0.04$ ). The most frequently identified risk factors were diabetes (36.8%), obesity (35.0%), cancer (21.7%), renal disease (20.8%), and advanced age ( $\geq 65$  years; 47.2%). Isolated bacteremia (22%), osteoarticular infection (21.4%), abscesses (13.9%), and skin and soft tissue infections (18.4%) were the most frequent manifestations. Intensive care unit admission was required in 21.7% and overall mortality was 9.4%. All strains remained susceptible to penicillin over the years. Up to 20% of strains were resistant to clindamycin. Serotypes Ia, Ib, II, III, IV, and V represented 96.8% of the available serotypes (60/62). As reported in several countries, invasive GBS disease in non-pregnant adults represents an increasing burden, particularly among diabetic, obese, and elderly patients. Almost all serotypes identified are included in the upcoming hexavalent GBS conjugate vaccine.

**Keywords** Group B *Streptococcus* · Non-pregnant adults · Invasive infections · Incidence · Serotypes · Vaccine · Obesity · Diabetes

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## Introduction

*Streptococcus agalactiae* or group B Streptococcus (GBS) is a commensal bacterium of the digestive tract present in 15–35% of men and women of all ages. GBS can secondarily colonize the urinary and genital tracts [1–3].

GBS is a major and well-known cause of severe infections in pregnant women and newborns [1, 2]. Systematic screening for maternal colonization between the 35th and 37th weeks of pregnancy, followed by antibiotic prophylaxis administered during labor in case of testing positive, significantly reduces the incidence of perinatal GBS disease [4].

The first sporadic case reports of GBS infection in non-pregnant adults were described in the 1940s [5]. Several epidemiological studies have reported an increase in the incidence over the last 30 years in this population [1, 2, 6]. For instance, in the United States of America (USA), the overall incidence of invasive GBS infection increased between 2008 and 2016, increasing from 8.1 cases to 10.9 cases per 100,000 inhabitants [6]. These infections are often severe, requiring hospitalization and intensive care unit (ICU) management in 94% and 27% of cases in the USA, respectively [6].

Skin and soft tissue infections (SSTI) (e.g., erysipelas, cellulitis), isolated bacteremia, osteomyelitis, and urinary tract infections are the most common clinical manifestations of invasive GBS infections. Pneumonia, meningitis, endocarditis, and septic shock are also observed [2, 6–9]. Risk factors for invasive GBS infection in adults include immunosuppression, obesity, diabetes, cancer, and cirrhosis [1, 2, 6–10]. The elderly are particularly at risk of severe GBS infections due to significant comorbidities, disruption of anatomical barriers, and modifications of the immune responses secondary to immunosenescence [11].

Regarding antibiotic susceptibility, GBS remains susceptible to penicillin, the first-line treatment. However, reports of reduced susceptibility to penicillin, associated with mutations in penicillin binding proteins, have been published [1, 7, 12, 13]. Since two decades, increased emergence of resistance to clindamycin and erythromycin is reported worldwide [14] and in Belgium [15].

To date, ten serotypes of GBS, based on specific capsular polysaccharide (CPS) antigens have been described: Ia, Ib, and II to IX. Serotypes Ia, Ib, II, III, and V are the most common serotypes found in most countries [2, 6–9]. Some studies report a recent emergence of serotype IV as a causative agent of adult GBS infections [6, 7, 16]. In addition, it has been reported that some serotypes are more virulent than others and that their distribution varies geographically [6–9].

The objective of this study is to assess the incidence, clinical, microbiological features and outcome of invasive GBS infections presented by non-pregnant adults in three tertiary hospitals of the Brussels-Capital Region from 2005 to 2019.

## Material and methods

### Study design

This is a multicentric retrospective study carried out in 3 university hospitals in Brussels, Belgium, from January 1, 2005, to November 30, 2019: CUB Erasme—a 858-bed hospital, CHU Brugmann—a 853-bed hospital, and CHU Saint-Pierre—a 582-bed hospital.

### Identification of the cases

All GBS-positive cultures isolated from normally sterile sites collected from patients in the three institutions during the study period were extracted from the respective laboratory information systems. We excluded patients under 18 years of age, women who were pregnant or who delivered within 30 days of the bacterial isolate sample, and also women of childbearing age (estimated age 18–55 years) with unknown pregnancy status. Patients hospitalized less than 24 h and those who had issued a notice of non-use of their data were also excluded. Superficial skin specimens or specimens from a non-sterile site (e.g., intrauterine device) were not retained. In case of duplicate GBS isolated from the same patient and the same site, the first isolate was retained. When several concomitant invasive infections were identified in the same patient (e.g., osteoarticular infection with cellulitis), only the deepest infection was retained (osteoarticular infection). Polymicrobial invasive infections were also retained. GBS infection was considered recurrent if the patient presented 2 positive cultures at least 30 days apart, and it was considered healthcare-associated if GBS was isolated from specimens collected more than 2 days after hospital admission.

### Collection of clinical data

Study data were collected and managed using REDCap hosted at CHU Saint-Pierre [17].

Clinical data for each patient, including clinical manifestations, sociodemographic data (age, sex, weight, height, ethnicity, addictions), comorbidities, date and length of hospital stay, ICU admission, and mortality were obtained directly from review of the medical records. Comorbidities which were not mentioned in the medical records were considered absent. Patients were classified as residents of long-term care facilities if this was their designated place of residence at the time of initial positive culture for GBS. The body mass index was calculated; obesity was defined as a BMI  $\geq 30$  kg/m<sup>2</sup>. The Charlson Comorbidity Index (CCI) was applied to all patients to categorize patients according to their comorbidities and to estimate life expectancy at 10 years (with a maximum score of 37) [18]. Death was considered related to GBS if it occurred

during hospitalization for invasive GBS. Cause of death and response to antibiotherapy were not assessed. Definitions of the clinical manifestations of invasive GBS infections can be found in the [Electronic Supplementary Material](#).

### GBS culture and identification

GBS were isolated from sterile sites by culture of the clinical sample on sheep blood agars such as Columbia agar. Before 2010, the identification of GBS was based on micro- and macroscopic examination (Gram staining, beta-hemolysis) and identification of the group B antigen using a rapid agglutination tests. After 2010, suspected colonies were identified using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) and the Biotyper database (Bruker Daltonics). Invasive strains were referred to the Belgian National Reference Centre (CHU Liège) for further testing including capsular serotyping and/or genotyping, and isolates were kept stored at  $-80^{\circ}\text{C}$  in sterile glycerol-free skimmed milk.

### Antimicrobial susceptibility testing

Routine antimicrobial susceptibility testing (AST) was performed using the disk diffusion technique for the following antibiotics: penicillin, vancomycin, erythromycin, clindamycin, and fluoroquinolones (levofloxacin). In order to categorize the isolate as “susceptible,” “intermediate,” or “resistant” to the tested antibiotic, zone diameters were interpreted using the CLSI or the EUCAST guidelines, if before or after 2010, respectively. For clindamycin, the detection of inducible resistance was performed by double disk diffusion testing (DD-test) as already recommended in Belgium in 2005 [19]. If a flattening of the zone of inhibition adjacent to the erythromycin disk (D-zone) was observed, clindamycin was considered resistant (inducible MLSB phenotype). E-test was not systematically carried out.

### Capsular serotyping

In Belgium, it is recommended but not mandatory for the laboratories to send blood cultures and CSF isolates to the National Reference Laboratory for serotyping. Serotyping of CPS was performed using the modified Strep-B-Latex method (Strep-B-Latex kit, Statens Serum Institut, Copenhagen, Denmark) based on the agglutination of latex beads that display CPS serotype-specific IgGs. In case of double agglutination for different serotypes, the strains were subcultured and further characterized by serotyping. For some strains, the amount of capsule produced was not sufficient for characterization with an agglutination method; therefore, some isolates were “not typable.” Capsular serotyping was also confirmed by genotyping using a multiplex PCR assay for types Ia to VIII [20] and the PCR described by Kong for type IX [21].

### Statistical analysis

Calculation of incidence was based on hospital catchment population and the number of cases observed over the year in consideration. The hospital catchment population was calculated from the hospital’s market share of hospital admissions per year as reported by Belgian Federal Public Service Public Health [22] and from the number of inhabitants per municipality for the year concerned based on the distribution of age classes. As these data were not available before 2009, incidences rate were calculated between 2009 and 2018. Rate of antibiotic resistance was compared over time. Descriptive statistics were used to describe population characteristics, clinical symptoms, and risk factors. Frequencies and percentages were used for categorical data, and median and interquartile range (IQR) for continuous data. We analyzed population characteristics and clinical manifestation by age group. Different patient groups were compared using the Fischer exact test for categorical data and the Wilcoxon-Mann-Whitney test for continuous. We performed multivariate analysis using logistic regression to identify mortality risk factors. The risk factors considered for analysis are as follows: age  $\geq 65$ , CCI  $\geq 4$ , sex, long-term care facilities, and healthcare-associated infection. All  $p$  values are bilateral. A value of  $p < 0.05$  was considered statistically significant. Analyses and graphs were performed using the SAS program (version 9.4; SAS Institute, Cary, NC, USA).

### Ethical aspects

The study was approved by the ethics committees from the three institutions.

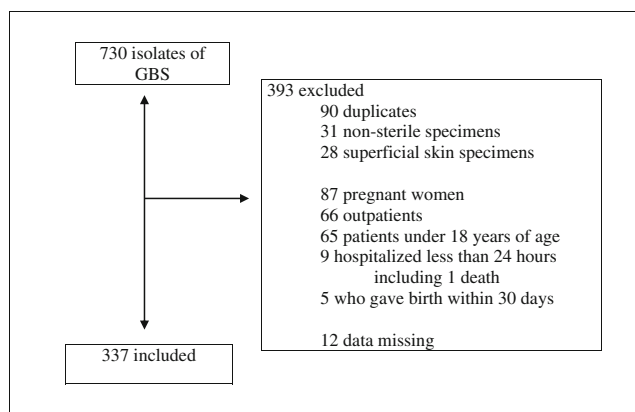
### Results

A total of 730 GBS isolates were extracted from the respective laboratory information systems (CUB Erasme  $n = 312$ , CHU Brugmann  $n = 230$ , and CHU Saint-Pierre  $n = 188$ ). After consulting the medical records and based on the exclusion criteria, 337 cases of invasive GBS infections in non-pregnant adults were identified in the 3 hospitals between 2005 and 2019 (CUB Erasme  $n = 135$  (40.1%), CHU Saint-Pierre  $n = 75$  (22.3%), CHU Brugmann  $n = 127$  (37.7%)) (Fig. 1).

GBS was mainly isolated from blood cultures (205/337; 60.8%) followed by abscess puncture (49/337; 14.5%), bone biopsy (46/337; 13.7%), abdominal fluid (20/337; 6.0%), joint fluid (15/337; 4.5%), pleural fluid (2/337; 0.6%), and cerebrospinal fluid (1/337; 0.3%).

### Sociodemographic features and risk factors

The characteristics of the patient population are reported in Table 1. Patients were predominantly male, with a median



**Fig. 1** Data flowchart of invasive GBS infections in Brussels-Capital Region, 2005–2019

age of 62 years. One or more underlying conditions were present in 88.7% of the patients. Almost one-third of the patients (95/337; 28.2%) had a CCI  $\geq 6$  indicating a life expectancy at 10 years of 0% for these patients. The most common underlying conditions were advanced age (47.2%  $\geq 65$  years), diabetes (36.8%), obesity (35.0%), peripheral vascular disease (23.2%), cancer (21.7%), and renal disease (20.8%) (Table 1). Diabetes and obesity were more common in patients  $\geq 65$  years of age than in younger age groups. Recurrent disease was observed in 4.8% of cases. ICU admission was required in 21.7% (73/337) of the cases and overall mortality was 9.4%.

### Incidence of invasive GBS infection

Between 2009 and 2018, the incidence of invasive GBS for the 3 hospitals significantly increased from 3.7 to 8.2 cases per 100,000 inhabitants ( $p = 0.04$ ) (Fig. 2).

### Clinical manifestations

Isolated bacteremia, osteoarticular infection, SSTI, and abscess were the most frequent manifestations of invasive GBS infection. Of the 15 endocarditis cases, 5 (33.3%) required heart surgery. Of the 337 cases, 6.5% developed a septic shock. Patients aged  $\geq 65$  years were more likely to have non-focal bacteremia and SSTI as compared with younger patients. In contrast, bone and joint infections, and abscesses, were more common in patients aged 40–64 years (Table 2). Patients with diabetes were more likely to have osteoarticular infection (36/124; 29%), SSTI (26/124; 21%), and bacteremia without focus (25/124; 20.2%) than to have other manifestations. Obese patients were more likely to have SSTI (19/76; 25%) or abscess (17/76; 22.4%) as compared with other manifestations. Cases with recurrent diseases were significantly more likely to manifest osteoarticular infection (6/15; 40%) and to be associated with diabetes (6/15; 40%),

obesity (4/15; 26.7%), and peripheral vascular disease (5/15; 33.3%).

### Mortality risk factors

The CCI showed that the percentage of death increased markedly with age, from 2.1% (2/94) in those under 50 years to 27.9% (17/61) in those over 80 years. There was no statistical difference in mortality between the three hospitals (8.3% CUB Erasme, 9.6% CHU Saint-Pierre, and 10.4% CHU Brugmann). Mortality was slightly but significantly higher in men as compared with women (51.6% vs. 48.4%;  $p = 0.03$ ). More than half (17/31; 54.8%) of the observed deaths occurred in patients over 80 years old and 20.7% (6/29) occurred in long-term care facility residents. Among the fatal cases, 32.3% (10/31) were healthcare-associated. The more frequent clinical manifestations among deceased patients were isolated bacteremia (15/31; 48.4%), SSTI (7/31; 22.6%), endocarditis (4/31; 12.9%), intra-abdominal infection (3/31; 9.7%), and pneumonia (2/31; 6.5%). The following factors were independently associated with mortality: CCI  $\geq 4$  (OR 9.0; IC 95% 2.1–34.5), and healthcare-associated infection (OR 6.1; IC 95% 2.1–17.5) (Table 3).

### Antibiotic-susceptibility testing results

Table 4 describes the results of AST. No penicillin- or vancomycin-resistant strain was identified. Resistance to erythromycin and clindamycin varied over the years but regularly reached peaks of up to more than 20% resistance. There was no statistically significant difference in antibiotic resistance between the 3 hospitals.

### Serotype distribution

From 2005 to 2019, serotyping was performed on a total of 62 (18.4%) collected isolates (Table 5). The available serotypes were mainly determined on isolates from positive blood culture ( $n = 61$ ). One serotype was identified on a CSF culture. Serotypes Ia, Ib, II, III, IV, and V represented 96.8% of the serotypes in our study. The four main serotypes identified were III (21%), Ia, II, and V (each 19.4%), followed by Ib and IV (8.1% for both). Serotypes VII, VIII, and IX were rarely identified.

### Discussion

We performed a retrospective, multicentric study to assess the incidence, clinical, microbiological features and outcome of invasive GBS infections in non-pregnant adults of the Brussels-Capital Region.

**Table 1** Characteristics of non-pregnant adults with invasive GBS infections per age group

Variables	All <i>n</i> = 337 (100 %)	18–39 years <i>n</i> = 56 (16.6%)	40–64 years <i>n</i> = 122 (36.2%)	≥ 65 years <i>n</i> = 159 (47.2%)	<i>p</i> value* <sup>1</sup>
Sex					
Male	196 (58.1%)	34 (60.7%)	81 (66.4%)	81 (50.9%)	0.031
Female	141 (41.8%)	22 (39.3%)	41 (33.6%)	78 (49.1%)	0.031
Median age (years)	62 (IQR 48–95)	31 (IQR 25–39)	53 (IQR 48–63)	77 (IQR 70–95)	< 0.0001
Median BMI (kg/m <sup>2</sup> )	26 (IQR 22–45)	25 (IQR 22–44)	27 (IQR 23–43)	27 (IQR 22–45)	0.418
Ethnic group					
Europe	240/320 (75%)	26/51 (51.0%)	84/113 (74.3%)	130/156 (83.3%)	< 0.0001
North Africa	50/320 (15.6%)	13/51 (25.5%)	17/113 (15.0%)	20/156 (12.8%)	
Sub-Saharan Africa	24/320 (7.5%)	10/51 (19.6%)	9/113 (8.0%)	5/156 (3.2%)	
Others	6/320 (1.9%)	2/51 (3.9%)	3/113 (2.7%)	1/156 (0.6%)	
Median length of stay (days)	12	7	11.5	14	0.005
Healthcare-associated	44/327 (13.5%)	3/54 (5.6%)	17/118 (14.4%)	24/155 (15.5%)	0.171
Recurrent disease	15/314 (4.8%)	3/51 (5.9%)	7/115 (6.1%)	5/148 (3.4%)	0.547
Long-term care facilities resident	21/322 (6.5%)	0	0	21/151 (13.9%)	< 0.0001
ICU	73/337 (21.7%)	12 (21.4%)	28 (23.0%)	33 (20.8%)	0.916
Death	31/330 (9.4%)	3/56 (5.4%)	4/120 (3.3%)	24/154 (15.6%)	0.001
Underlying condition					
≥ 1 conditions	299 (88.7%)	33 (58.9%)	105 (86.1%)	159 (100%)	<0.0001
Diabetes	124 (36.8%)	12 (21.4%)	46 (37.7%)	66 (41.5%)	0.050
Obesity	76/217 (35.0%)	8/30 (26.7%)	32/89 (36.0%)	36/98 (36.7%)	0.844
Cancer* <sup>2</sup>	77 (21.7%)	3 (5.4%)	20 (16.4%)	50 (31.5%)	0.004
Renal disease	70 (20.8%)	9 (16.1%)	20 (16.4%)	41 (25.8%)	0.100
Neurologic disease* <sup>3</sup>	47 (14.0%)	2 (3.6%)	8 (6.6%)	37 (23.3%)	0.028
Heart failure disease	67 (19.9%)	1 (1.8%)	16 (13.1%)	50 (31.4%)	0.031
Chronic obstructive pulmonary disease	45 (13.4%)	3 (5.4%)	13 (10.7%)	29 (18.2%)	0.028
Current smoker	90/305 (29.5%)	14/50 (28%)	48/115 (41.7%)	28/140 (20%)	0.001
Liver disease	37 (11.0%)	5 (8.9%)	21 (17.2%)	11 (6.9%)	0.058
Peripheral vascular disease	78 (23.2%)	6 (10.7%)	26 (21.3%)	46 (28.9%)	0.018
IVDU	9/303 (3.0%)	4/50 (8%)	5/113 (4.4%)	0	0.009
Alcohol	69/306 (22.6%)	7/50 (14%)	41/115 (35.7%)	21/141 (14.9%)	< 0.0001

Data are expressed as numbers and percentages for categorical data and median (IQR) for continuous data. Denominators are smaller for ethnic group, obesity, addictions, healthcare-associated, recurrent disease, ICU, deaths, and long-term care facility residents because we did not have all data in medical records for all 337 patients

BMI, body mass index; ICU, intensive care unit; IVDU, intravenous drug use

\*<sup>1</sup> For the comparison of results among the groups of cases in patients aged 18–39 years, 40–64 years, and ≥ 65 years. *p* < 0.05 was considered statistically significant

\*<sup>2</sup> Cancer includes Hodgkin and non-Hodgkin lymphoma, leukemia, and solid organ tumor

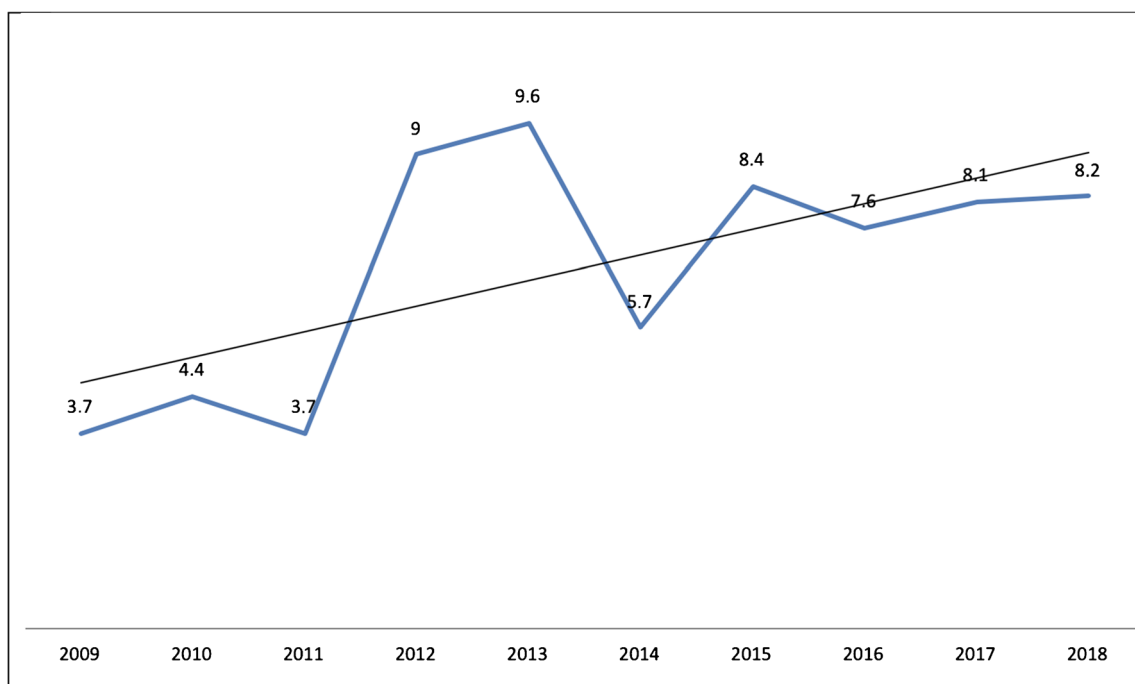
\*<sup>3</sup> Neurologic disease includes dementia or stroke

Over 80% of the clinical manifestations of invasive GBS infection were bacteremia without focus, osteoarticular infection, SSTI, and abscesses. Over 80% of these patients presented an underlying condition, diabetes and obesity being the most frequent. These infections were severe, as almost one quarter of patients were admitted to the ICU and an almost 10% mortality rate was observed. Over 50% of deaths occurred in patients over 80 years old. In our study, the risk factors associated with higher mortality were a CCI ≥ 4, and healthcare-associated infections. Our results are similar to

those reported in the literature as global in-hospital mortality for non-pregnant adults is estimated to range from 3 to 23.7% worldwide [1, 2, 16]. Other factors previously associated with mortality are cancer, septic shock, peritonitis, endocarditis, and meningitis [8, 23].

During the study period, GBS strains remained fully susceptible to penicillin and vancomycin. Resistance to erythromycin and clindamycin varied over the years but regularly reached peaks of 20–30%, in accordance with data reported by the GBS National Center in 2016 [15]. Clindamycin





**Fig. 2** Incidence per 100,000 person-years of invasive GBS disease among non-pregnant adults from 2009 to 2018 in the three Brussels hospitals

resistance is worrisome as it is used as a second-line agent in case of allergy to penicillin [9, 14, 24].

Since the 1990s, serotype V has emerged in the USA and became the most common serotype causing invasive GBS disease in non-pregnant adults [25]. Later, other serotypes such as Ia, Ib, II, III, and IV were also recognized worldwide

as common serotypes [25]. However, the distribution of serotypes varies geographically over time: an increase in the incidence of serotypes Ib, II, and IV in the USA [6], serotypes IV and V in Iceland [7], and serotype III in France [9]. In a 1-year survey in Belgium, during the year 2018, the most prevalent serotypes were Ia (25.1%), V (23%), and III (19.6%) coming

**Table 2** Clinical manifestations of non-pregnant adults with invasive GBS infections

	All <i>n</i> = 337 (100%)	18–39 years <i>n</i> = 56 (16.6%)	40–64 years <i>n</i> = 122 (36.2%)	≥ 65 years <i>n</i> = 159 (47.2%)	<i>p</i> value* <sup>1</sup>
Bacteremia without focus	74 (22.0%)	7 (12.5%)	22 (18%)	45 (28.3%)	0.021
Osteoarticular infection	72 (21.4%)	11 (19.6%)	34 (27.9%)	27 (17%)	0.088
SSTI	62 (18.4%)	7 (12.5%)	10 (8.2%)	45 (28.3%)	< 0.0001
Soft tissue abscess	47 (13.9%)	15 (26.8%)	25 (20.5%)	7 (4.4%)	< 0.0001
Intra-abdominal infection	25 (7.4%)	4 (7.1%)	14 (11.5%)	7 (4.4%)	0.075
Endocarditis	15 (4.5%)	2 (3.6%)	5 (4.1%)	8 (5%)	0.939
Pneumonia* <sup>2</sup>	13 (3.9%)	2 (3.6%)	4 (3.3%)	7 (4.4%)	0.929
Invasive urinary tract infection	12 (3.6%)	2 (3.6%)	2 (1.6%)	8 (5%)	0.408
Others* <sup>3</sup>	12 (3.6%)	5 (8.9%)	4 (3.3%)	3 (1.9%)	0.417
Meningitis	5 (1.5%)	1 (1.79%)	2 (1.64%)	2 (1.26%)	1.00
Septic shock-associated	22/337 (6.5%)	3 (5.4%)	6 (4.9%)	13 (8.2%)	0.558

Definitions of the clinical manifestations are found in the [Electronic Supplementary Material](#)

SSTI, skin and soft tissue infection

\*<sup>1</sup> For the comparison of results among the groups of cases in patients aged 18–39 years, 40–64 years, and ≥ 65 years

\*<sup>2</sup> Includes empyema

\*<sup>3</sup> Other clinical syndrome included pelvic infection (*n* = 2), post myomectomy sepsis (*n* = 2), sinusitis (*n* = 1) and infection of an indwelling or implanted medical device (*n* = 7)

**Table 3** Mortality risk factors in hospitalized patients with invasive GBS infection

	Death (n = 31) (9.4%)	Alive (n = 299) (90.6%)	p value	Univariate analysis		Multivariate analysis	
				OR	IC 95%	OR	IC 95%
Age ≥ 65	24 (77.4%)	127 (42.5%)	< 0.001	4.6	1.9–11.5	1.9	0.5–7.4
CCI ≥ 4	26 (83.9%)	138 (46.2%)	< 0.001	6.1	2.2–20.7	9.0	2.1–34.5
Sex: male	16 (51.6%)	178 (59.5%)	< 0.394	0.7	0.3–1.6		
Long-term care facilities* <sup>1</sup>	6/29 (20.7%)	15/286 (5.2%)	< 0.015	4.7	1.3–14.3	2.9	0.8–10.0
Healthcare-associated* <sup>2</sup>	10 (32.3%)	33/293 (11.3%)	0.002	4.6	1.7–11.7	6.1	2.1–17.5

Data are expressed as numbers and percentages. A multivariate analysis using logistic regression was performed to identify mortality risk factors. Denominators are lower than n when there was a lack of data in the medical records

CCI, Charlson Comorbidity Index

\*<sup>1</sup> Denominators are 29 for death patients and 286 for alive patients

\*<sup>2</sup> Denominators are 293 for alive patients

from 143 GBS-positive samples from invasive disease among non-pregnant adults [26]. In our study, serotypes Ia, Ib, II, III, IV, and V accounted for over 95% of the available serotypes.

The incidence of invasive GBS infections in non-pregnant adults in the Brussels-Capital Region almost tripled between 2009 and 2018 (p = 0.04). The increase in the incidence of invasive GBS infection in non-pregnant adults is observed in many countries and is associated with an increase in mortality over time [1, 2, 6, 9, 25]. The aging of the population but also the increasing prevalence of obesity and diabetes could contribute to this increase in invasive GBS infections [27, 28]. In England, the incidence tripled between 1991 and 2016 and was mainly attributable to the elderly [10]. Recent studies

performed in the USA [6, 29] and France [30] reported incidences of GBS-invasive disease that were higher than that of invasive pneumococcal diseases (IPD) in adults. In Belgium, the incidence for IPD in adults in 2018 was 17 cases per 100,000 inhabitants which is higher than the incidence of invasive GBS infections observed in our study. Various factors could explain these differences. In Belgium, there is a good surveillance of IPD, covering about 85–90% of the Belgian population, which is different compared with other countries where data is collected only from hospitals/regions and then extrapolated to the whole country. Also, vaccine coverage against *Streptococcus pneumoniae* is high in children but low in older persons and at risk patients. (Stefanie Desmet, personal communication).

We found a high proportion of healthcare-associated infections. We used an arbitrary definition usually used for other healthcare-associated infections (> 48 h) [31]. Clusters of

**Table 4** Antibiotic-susceptibility test results for GBS-invasive strains

		n (%)
Penicillin	S	335/335 (100)
	I	0/335 (0)
	R	0/335 (0)
Erythromycin	S	219/334 (65.6)
	I	22 (6.6)
	R	93 (27.8)
Clindamycin	S	251/332 (75.6)
	I	9 (2.7)
	R	72 (21.7)
Vancomycin	S	334/334 (100)
	I	0
	R	0
Levofloxacin	S	89/106 (84.0)
	I	10/106 (9.4)
	R	7/106 (6.6)
	NA	224/337(66.5)

S, sensitive; I, intermediate; R, resistant; NA, not available

**Table 5** Serotype distribution of 62 isolates of GBS-invasive isolates from 2005 to 2019

Serotypes	n = 62 (100%)
Ia	12 (19.4)
Ib	5 (8.1)
II	12 (19.4)
III	13 (21)
IV	5 (8.1)
V	12 (19.4)
VI	0
VII	0
VIII	1 (1.6)
IX	1 (1.6)

Data are expressed as numbers and percentages. Data are limited to cases with available isolates: isolates were available for 62 of 337 cases from the 3 hospitals

invasive GBS infections linked to nosocomial transmission have been reported in neonatal intensive care units [32]. The evidence for nosocomial transmission of invasive GBS infection is however much weaker in hospitalized adults [32]. Healthcare-associated GBS infections could be related to delay in acquisition of the sample or secondary to intra-hospital procedures such as surgery. We found an association between healthcare-associated infections and mortality. This observation warrants further prospective studies on healthcare-associated invasive GBS.

Invasive GBS infection in adults is responsible for a significant health burden. Vaccination against GBS may offer a solution to diminish morbidity and mortality. In recent years, significant progress has been made in vaccine development, primarily to prevent neonatal diseases. Administered during pregnancy, vaccines aim to protect newborns by transplacental transfer of specific antibodies against these polysaccharides [33]. A hexavalent polysaccharide (GBS6) conjugate vaccine, containing the 6 serotypes responsible for 98% of invasive infections in neonates and adults (Ia, Ib, II, III, IV, and V), is being evaluated in healthy adults after encouraging protective effects have been demonstrated in animals [34]. Although there is no clinical evidence that antibodies can prevent GBS infection in adults, healthy and infected older adults are able to produce anti-GBS CPS antibodies. This has been shown both in vaccine trials and following GBS infection [34]. The development of a GBS6 vaccine as a new preventive strategy could potentially prevent these infections in at-risk adults as 97% of the serotypes identified in our study are included in the GBS6 vaccine.

## Limitations

Our study has several limitations. First, this is a retrospective study, but this is the first study to describe GBS-invasive infection in non-pregnant adults in the Brussels-Capital Region. Second, the focus of this study was limited to invasive GBS disease and invasive samples. GBS also causes many non-invasive diseases, including SSTI, the vast majority of which do not lead to documented bacteremia. In the present study, only SSTI infections with concomitant bacteremia or skin abscesses requiring drainage were included. The overall burden of GBS-invasive infections in adults is likely to be much higher [6]. Third, we excluded patients hospitalized less than 24 h due to lack of data, but this did not change data on mortality because only one of the patients excluded from the study died. Fourth, only 18.4% of strains were submitted to serotyping, so we were not able to assess the incidence variations of specific serotypes.

## Conclusions

In the Brussels-Capital Region, similarly as reported in several other countries, invasive GBS disease in non-pregnant adults

represents an increasing burden, particularly among older persons and patients with chronic diseases, such as obesity and diabetes. GBS also causes many non-invasive diseases so the overall burden in adults is likely to be much higher. Ongoing monitoring of serotype distribution and antibiotic resistance is warranted. Reducing risk factors through hygienic-dietary rules and maintaining skin integrity may help for the prevention of invasive GBS infections. The development of a GBS6 vaccine as a new preventive strategy could also prevent these infections in at-risk adults. Future studies are needed to assess the potentially positive impact of this vaccine on invasive GBS infections.

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## Compliance with ethical standards

**Conflict of interest** Dr Dauby has received a travel grant from Pfizer (outside of the submitted work).

**Ethical approval** The study was approved by the three institutions' ethics committee.

**Informed consent** Informed consent is not required because of the retrospective design of this study.

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