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ARTICLE

Invasive group B streptococcus (GBS) disease in Norway 1996–2006

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Abstract The aim of this study was to survey the occurrence of invasive group B streptococcus (GBS) disease in Norway and detect possible trends in characteristics of invasive GBS strains from1996 to 2006. Data from national monitoring systems for infectious diseases in Norway were analysed. Of 638,452 live births in the period, 434 cases of invasive GBS disease in infants were reported. In adults and children older than 1 year of age, 969 cases were reported. The incidence of invasive GBS disease increased significantly in the elderly, while the incidence of neonatal early-onset disease was stable with 0.46 cases per 1,000 live births. The incidence of late-onset disease increased in 2005 and 2006. The lethality of GBS in infants increased from an average of 6.5% in 1996–2005 to 20% in 2006. Serotypes III and V were predominant in 839 invasive GBS strains characterized—type III in infants and type V in the elderly. The distribution of serotypes did not change throughout the period. The distribution of detected surface proteins was stable from 1996 to 2005, but the detection rates in types III and V were low. Molecular methods for GBS typing introduced in 2006 made characterization of nearly all strains possible and appear more applicable to epidemiological studies of GBS than conventional methods. Resistance to erythromycin and clindamycin increased significantly in 2006. The increased incidence in the elderly, the increased lethality in infants in 2006, and the increased resistance to erythromycin and clindamycin the same year might indicate changing characteristics of invasive GBS strains.

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Introduction

Streptococcus agalactiae (group B streptococcus, GBS) has been an important cause of morbidity and mortality in newborns over the last four decades. The reported incidence of neonatal GBS disease from 1990 to 2005 ranges from <0.5 to 2 per 1,000 live births in different geographic areas [1–3]. Neonatal GBS disease presents as early-onset disease (EOD) or late-onset disease (LOD). In EOD (age at onset 0–6 days), the neonate is infected by exposure to GBS before or during birth. In LOD (age at onset 7–89 days) the pathogenesis is not clear. Intrapartum antibiotics given to women with risk factors for EOD has reduced the incidence of invasive GBS disease in newborns, and different prophylactic strategies to detect women at risk have been recommended [4, 5]. During recent decades, an increasing incidence of invasive GBS disease in adults has been

reported worldwide [6–8]. Disease rates increase with age, and disease occurs mainly in those with an underlying medical condition [9].

Almost all clinical isolates of GBS carry a capsular polysaccharide (CPS) and can be classified into nine distinct serotypes or CPS types: Ia, Ib, and II-VIII [10]. In addition, a capsular type IX was proposed in 2007 [11]. Antibodies against CPS provide type-specific protection [12], and conjugate vaccines composed of CPS and tetanus toxoid have been evaluated in healthy adults [13, 14]. The prevalence of serotypes varies with time and geographical location; thus, knowledge of serotype distribution is necessary for the selection and development of serotype-based vaccines in a given geographic area [15, 16]. By combining serotyping with subtyping (testing for expression of strain variable surface proteins or genes that encode the surface proteins), the characterization of GBS can be more precise. Some of the best characterized surface proteins are the c proteins (alpha and beta) and the R proteins (R1, R3, and R4) [17], where R4 is identical to rib [18, 19]. The genes *bca, bac, alp1 (epsilon)*, *alp2/alp3*, and *rib* are encoding the proteins alpha c, beta c, alp1 (epsilon), alp2, alp3, and R4 (rib), respectively. A serovariant is the combination of serotype and surface protein, or the gene that encodes the protein. Animal studies have shown that antibodies to the proteins confer protection against GBS [20]. Increasing evidence suggests that surface proteins contribute to virulence and thus will be of relevance for vaccine development [21].

The aims of this study were to survey the incidence of invasive GBS disease in infants and adults and detect possible trends in characteristics of invasive GBS strains in Norway during the period 1996 to 2006.

Patients and methods

Data were obtained from The Norwegian Surveillance system for Communicable Diseases (MSIS) provided by The Norwegian Institute of Public Health (NIPH). MSIS is the official monitoring system for infectious diseases in Norway. Laboratory confirmed cases of invasive GBS disease are compulsorily notifiable in Norway and have been reported to the MSIS database consecutively by all medical microbiological laboratories since 1985. Statistics on population in different age groups, births, and mortality are from Statistics Norway (www.ssb.no).

Characterization of GBS strains

The Department of Medical Microbiology, St. Olavs Hospital, Trondheim is the national reference laboratory for GBS in Norway. The laboratory receives strains from microbiological laboratories for capsular typing, subtyping, and in certain cases genotyping (pulsed-field gel electrophoresis [PFGE] and multilocus sequence typing [MLST]). Unlike the MSIS report system, forwarding strains to the reference laboratory is not compulsory. In the period 1996–2005, GBS strains from 56% of the cases reported to MSIS were characterized. However, in 2006, the reference laboratory received GBS strains from 84% of all cases reported to MSIS and from 100% of the infant cases.

Capsular polysaccharide (CPS) antigen typing was done by an indirect fluorescent antibody test (FAT) [22]. From January 2006, this method was replaced by a PCR method to detect capsular polysaccharide synthesis gene clusters [23, 24].

From 1996–2005 antibody-based detection of surface proteins (sero-subtyping) was performed using murine monoclonal antibodies against alpha c protein, beta c protein, and R4 in an indirect whole cell-based fluorescent antibody test (FAT) [25]. From January 2006, this method was replaced by molecular methods detecting the genes *bca, bac, alp1 (epsilon)*, *alp2/alp3*, and *rib* [26, 27]. The genes *alp2* and *alp3* were not tested for separately.

Since 2003, all GBS isolates were tested for susceptibility to erythromycin and clindamycin by agar diffusion and analysed according to interpretational criteria recommended by the Norwegian AFA Group (www.antibiotikaresistens.no). Erythromycin resistant, clindamycin sensitive strains were tested with erythromycin and clindamycin tabs or discs, with inner edges 25 mm apart. Strains with D-shaped clindamycin zones (inducible clindamycin resistance) were classified as resistant to clindamycin (www.srga.org).

Statistics

Data were collected and analysed using Windows Office Excel and SPSS software (SPSS Inc., Chicago, IL). Minitab and Pearson's chi-square test were used for comparison of proportions of serotypes and incidences of invasive GBS disease.

Results

There were 4,681,100 inhabitants in Norway as of January 1, 2007. From 1996 to 2006, there were 1,403 cases of invasive GBS disease in infants, children, and adults reported to MSIS.

GBS disease in infants

From 1996 to 2006 there were 638,452 live births (range, 55,434–60,927 per year) in Norway. In this period 422 infants with GBS disease younger than 90 days old were

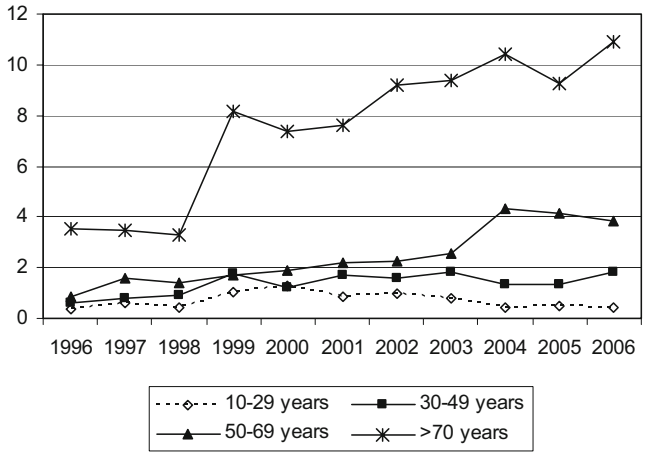

Fig. 1 Incidence rates of invasive GBS disease per 100,000 persons by age groups in Norway 1996–2006

reported to MSIS. The cumulative incidence of infants <90 days old was 0.66 per 1,000 live births (annual range, 0.38–1.0/1000), and the cumulative incidence of EOD was 0.46 per 1,000 live births (range, 0.28–0.83/1000). The incidence of invasive GBS in infants showed no significant trend throughout the study period (p=0.2). However, the proportion of LOD increased during the last two years of the period of observation, from 28% (range, 16.9–33.3%) of invasive disease in 1996–2004 to 42.7% (42.5–42.9%) in 2005 and 2006 (p=0.006). Meningitis was reported in 25 infants (6%). Reported case fatality of newborns and infants with GBS disease was 6.5% (range, 1–5 deaths per year) from 1996–2005. In 2006 the case fatality increased to 20% (p=0.02) with ten deaths caused by GBS.

GBS disease in adults and children >1 year old

During the period 1996–2006, 969 cases of invasive GBS disease in adults and children >1 year were reported to MSIS. The annual numbers increased during the period. The increasing incidence was most obvious in the elderly >70 years since 1999, and from 2004 also in the age groups 50–69 years (Fig. 1). The overall mean incidence of GBS disease in adults (>19 years) increased from 1.34 cases per 100,000 in 1996–1998 to 3.1 cases per 100,000 in 1999–2006 (p<0.001). The mean incidence in the elderly (>70 years) increased from 3.9 per 100,000 in 1996–1998 to 9.15 in 1999–2006 (p<0.001) (Fig. 1).

Characterization of invasive GBS strains

From 1996 to 2006 capsular type III was predominant in strains from newborns and infants, while capsular type V was predominant in the elderly (Fig. 2). The other capsular types were evenly distributed in different age groups (Fig. 2). There was no significant change in the frequency of any of the serotypes throughout the period (results not shown). The most common surface proteins observed were rib (30% in infants and 15.1% in adults) and alpha c (20.2% in infants and 25.2% in adults) (Table 1). The distribution of surface proteins and serovariants did not change significantly in the period from 1996 to 2005 (results not shown).

From infants <1 year the reference laboratory received 218 GBS strains (58% of MSIS reported cases) from cases of invasive disease during the period 1996–2005. Of these 218 strains, 141 were from neonates with EOD and 68 from LOD. In addition, nine strains were from infants <1 year, but without information of onset of the disease. Most of these strains (n=209) were isolated from blood cultures—eight from CSF and one from synovia. Serotype III was the most common serotype (53%) followed by serotype Ia (12.8%), V (11.9%), and Ib (10.1%) (Table 1). Serotype III was more frequent in LOD than in EOD (63.2% vs. 48.2%, respectively) (p=0.04) (Fig. 2). Seven of eight strains recovered from cerebrospinal fluid were serotype III. Surface proteins were detected in the majority of type Ia, Ib, II, and IV strains, fewer in type III (48%), and in only 27% of type V (Table 1).

In 2006, invasive strains from 55 infants (110% of MSIS reported cases) were received and analyzed by the reference laboratory, including 47 strains from blood cultures and eight

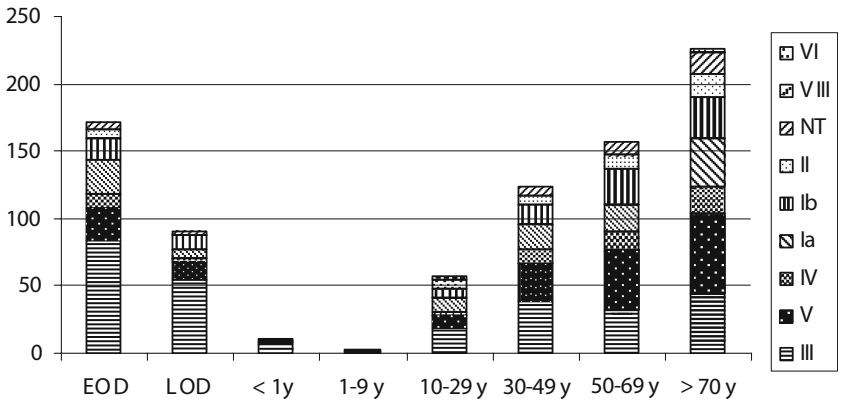

Fig. 2 Number of invasive GBS strains and distribution of serotypes in different age groups, 1996–2006. *EOD* early onset disease, *LOD* late onset disease, *NT* non typable<1 y = infants < 1 year, with onset of disease unknown

Table 1 Capsular (CPS) type and surface expressed proteins in GBS strains from infants <1 year and from adults and children >1 year, Norway, 1996–2005 (FAT method)

Age	CPS type	alpha c	beta c	alpha c and beta c	rib (R4)	c protein and rib not detected	Total
<1 y	Ia	22	0	2	1	3	28
	Ib	8	1	12	0	1	22
	II	4	0	1	2	4	11
	III	0	1	1	56	58	116
	IV	8	0	0	0	1	9
	V	0	0	1	6	19	26
	VIII	-	-	-	-	-	0
	NT	2	0	0	0	4	6
Total <1 y		44	2	17	65	90	218
>1 y	Ia	50	0	6	3	9	68
	Ib	35	3	29	2	1	70
	II	4	2	4	5	11	26
	III	0	0	2	46	66	114
	IV	21	0	0	0	16	37
	V	2	6	5	8	91	112
	VIII	0	0	0	0	2	2
	NT	5	0	1	6	24	36
Total >1 y		117	11	47	70	220	465

from CSF. The distribution of serotypes was similar to the period from 1996 to 2005 (Table 2). Genes encoding surface proteins were detected in all but two strains (Table 2).

From adults and children >1 year, isolates recovered from 465 cases of invasive GBS (55% of MSIS reported cases) were analyzed in the period 1996–2005. Serotypes III (24.5%) and V (24.1%) were the most frequent serotypes (Table 1). The rank order of serotype frequency among people >70 years did not change significantly after 1998 when the incidence of GBS increased; neither did it change in the age group 50–69 years after 2003 when a similar increase in incidence was observed (Fig. 1). Surface proteins were detected in the majority of types Ia, Ib, II, and IV strains, fewer in type III (40.3%), and 19% of type V (Table 1).

In 2006, 101 invasive GBS strains from adults and children >1 year (78% of MSIS reported cases) were analyzed. Serotypes were distributed similarly as in the period from 1996 to 2005 (Table 2). Genes for surface proteins were detected in 97 of 101 strains (Table 2).

Table 2 Capsular (CPS) type and genes for surface proteins in GBS strains from infants <1 year, and adults and children >1 year in Norway 2006

Age	CPS type	*bca*	*bca* and *bac*	*alp1* (*epsilon*)	*alp2 /alp3*	*rib*	Gene not detected	Total
<1 y	Ia	1	1	3	0	0	0	5
	Ib	1	1	0	0	0	2	4
	II	-	-	-	-	-	-	0
	III	0	0	0	0	29	0	29
	IV	0	0	3	0	0	0	3
	V	0	0	0	13	0	0	13
	VI	1	0	0	0	0	0	1
Total <1 y		3	2	6	13	29	2	55
>1 y	Ia	2	2	12	0	1	1	18
	Ib	0	7	0	0	0	0	7
	II	2	7	5	0	2	0	16
	III	1	0	0	0	18	1	20
	IV	0	0	11	0	0	1	12
	V	0	0	0	26	1	1	28
	VI	-	-	-	-	-	-	0
Total >1 y		5	16	28	26	22	4	101

Resistance to clindamycin and erythromycin

From 2003 to 2005, 4% of 75 strains from infants were resistant to clindamycin and erythromycin. In adults, 1.4% of 208 isolates were resistant to clindamycin, and 3.4% were resistant to erythromycin in the same period. Only one case of inducible clindamycin resistance was observed. In 2006, however, 14 of 55 strains (25.4%) from infants were resistant to erythromycin and clindamycin, of which ten showed inducible clindamycin resistance. Seven of ten strains with inducible clindamycin resistance in infants were serotype V of which five were identical or closely related as analysed by pulsed-field gel electrophoresis (PFGE) (result not shown). The last three strains with inducible clindamycin resistance were serotype III. Inducible clindamycin resistance was observed in four of the ten strains from fatal cases in infants in 2006, all of which were all type V. In 2006, 11.9% of 101 strains from adults were resistant to erythromycin and 10.9% to clindamycin. Nine of the twelve resistant strains showed inducible clindamycin resistance.

Discussion

The incidence of EOD in Norway was 0.3 per 1,000 in the period 1986 to 1992, but increased to 0.47 per 1,000 between 1992 and 1994 [28]. After 1994, the incidence of GBS disease in newborns and infants has remained unchanged. The mean incidence of EOD in 1996–2006 (0.46/1000) was lower than reported in Finland (0.62/1000) but higher than reported in Germany (0.28/1000) and the USA (0.37/1000) [3, 29, 30]. However, the incidence of GBS disease in newborns and infants is probably underestimated worldwide due to a significant number of culture-negative sepsis-like syndromes in neonates. Studies have estimated a total incidence of EOD three to four times higher than the incidence of confirmed disease [31]. Therefore, it is difficult to interpret and compare incidences between countries and from one period to another.

The increasing rates of GBS disease in adults may be attributed in part to an expanding population of elderly who are living longer with significant underlying medical conditions. However, this does not explain the apparent rapid change occurring in Norway after 1998. There has been no change of diagnostic methods or routines for surveillance in recent decades. A higher prevalence of more virulent GBS strains in the population might explain the increased incidence.

In general, the serotype distribution was similar to what has been found in other countries [15, 32, 33]. Serotype V strains with identical or similar PFGE patterns were found in four of the ten deaths in infants in 2006 and were also predominant among the observed resistant GBS strains the same year. This may indicate circulation or introduction of a more virulent GBS type V strain in Norway. However, these findings were based on small numbers and in 2006 only. Thus, further observation of incidences, lethality, and characterization of invasive strains is required in the future.

Identification of certain surface proteins or genes encoding surface proteins in invasive GBS strains from Norway might have indicated candidate components of a GBS vaccine. However, no single surface protein or gene was sufficiently common to fulfil this purpose, and further, the detection rate of surface proteins in type III and V strains was low. The low detection rate of surface proteins in type V is probably due to the fact that type V often carries R1 surface protein [34] which was not tested for in this study. In type III strains with no detected surface proteins, the cause might be expression of no or very low levels of R4 proteins as shown by Maeland et al. [34]. Genes encoding surface proteins were detected in nearly all strains (Table 2). All genes (Table 2), except *alp1(epsilon)* which was more common in strains from adults in Norway in 2006, were similarly distributed as in strains from western Sweden [35].

The change of typing method as of January 1, 2006 was an administrative decision and not influenced by the later observed increased lethality in infants, but might represent a bias in our study. However, we consider the distribution of serotypes in 2006 comparable to the period from 1996 to 2005 as former studies have shown a good correlation between conventional serotyping and typing with molecular methods [23, 36]. Antibody-based methods for serotyping and subtyping require large laboratory resources. In addition, the molecular methods for typing of GBS strains provide a better typability than conventional methods and are therefore more suitable for epidemiological studies of GBS.

In the period 1996–2005 the reference laboratory characterized strains from 56% of MSIS reported cases while in 2006 the reference laboratory characterized strains from all MSIS reported cases in infants and 78% of MSIS reported cases in adults. This increase was due to a decree issued by the health authorities in 2006, requesting medical microbiological laboratories to forward invasive GBS strains to the reference laboratory. Although this increased number and proportion of strains received in 2006 might represent a bias in our material, the characterization of a nearly complete nationwide collection of invasive GBS strains gives a more comprehensive picture of GBS in Norway.

In conclusion, the overall incidence of invasive GBS disease in Norway increased significantly from 1996 to 2006. This was entirely due to an increase among the elderly.

After 1998 more than two thirds of all invasive GBS disease in Norway occurred in adults. The data demonstrate a stable incidence of early-onset GBS disease in Norway (0.46/1000 live births), but the increased incidence in the elderly, the increased lethality in infants in 2006, and the increased resistance to erythromycin and clindamycin the same year, might indicate changing characteristics of GBS strains. Although based on small numbers, these indications of change underline the need for continuous surveillance.

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