High Rates of *Streptococcus Agalactiae* Clindamycin and Erythromycin Resistance in Vietnamese Pregnant Women

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Abstract

Background

Group B *streptococcus* (GBS) is a leading cause of morbidity and mortality in newborns. Maternal GBS colonization rates vary depending on geographic area, ethnic and social conditions worldwide. Many studies suggested the continuous surveillance of GBS to provide data to guide decision-making and planning prevention and control strategies. Here, we report the rate and the antimicrobial susceptibility pattern of GBS from Vietnamese pregnant women over 5 year period.

Methods

We worked with 3863 Vietnamese pregnant women at < 37 weeks of gestation at the National Hospital of Obstetrics and Gynecology, Hanoi, Vietnam from Jan 2016 to Dec 2020. The data were recorded and retrieved from the computerized laboratory database. GBS was identified according to the American Society for Microbiology's guidelines. Antimicrobial susceptibility was tested by the VITEK 2 system or E-test strips. The results were calculated according to the MIC breakpoints recommended by the Clinical and Laboratory Standards Institute.

Results

The positivity for GBS was 8.02% (310/3863) and the highest resistance rate was to tetracycline 89.66% (234/261), followed by 76.23% (202/265) for erythromycin, 58.21% (156/268) for clindamycin. The multidrug-resistance rate was 59.19% (161/272), and 8.46% (23/272) of isolates were resistant to 6 to 7 of the 12 antibiotics. Resistance to clindamycin in the absence of erythromycin resistance was found in 6/272 (2.2%) samples. The resistance rate to clindamycin was significantly increased ($p < 0.01$) over the time study period. Nevertheless, all isolates were sensitive to penicillin, ampicillin, ceftriaxone, cefotaxime, quinupristin/dalfopristin, and vancomycin.

Conclusion

Our results indicate that penicillin and ampicillin are currently the drugs of choice for the prevention and treatment of GBS-related diseases for Vietnamese pregnant women. However, antibiotic resistance to erythromycin and clindamycin was high. Thus, it reinforces the need for continuous surveillance of GBS to provide data to guide planning prevention and control strategies.

Background

Streptococcus agalactiae (also called group B *Streptococcus*; GBS) is one of the leading causes of neonatal infections. GBS is a major cause of meningitis, sepsis, and pneumonia in newborns, and is

responsible for high mortality and morbidity in neonates (1). Maternal transmission of GBS to neonate occurs mostly during the peripartum period (2). Newborns infected with GBS intrapartum from the genital tract of their mothers (3). The maternal infection with GBS during pregnancy is associated with preterm delivery and pregnancy loss (4), as well as causes third-trimester stillbirths (5). The prevalence of GBS in pregnant women varied significantly among different populations (6). The continuous surveillance of GBS in pregnant women and antibiotic susceptibility globally is needed (7).

Penicillin and ampicillin are the drugs of choice for the prevention and/or treatment of maternal and neonates GBS infections. Clindamycin and erythromycin have been used as an alternative for patients who have an allergy to β-lactams (8). The rate of resistance to clindamycin and erythromycin has increased in several past years (9). The frequency of vaginal-rectal colonization and antibiotic-resistant varies widely worldwide, depending on the geographical location (10). Thus, epidemiological surveillance of GBS provides useful information for the control of GBS infection in Vietnam. The Center for Disease Prevention and Control (CDC) has recommended testing for GBS colonization in vaginal and anorectal of all pregnant women to prevent neonatal infection (11). Many studies suggested the continuous surveillance of GBS to provide data to guide decision-making and planning prevention and control strategies (7, 10, 12). However, the prevalence and susceptibility of GBS disease in the Vietnamese population have not been concerned. In this context, to contribute to the regional data, this report is to determine the actual colonization and the susceptibility patterns of the isolates to a variety of antibiotics of GBS in Vietnamese pregnant women in the Hanoi metropolitan area, Vietnam to support decision-making in infection control programs.

Materials And Methods

Study setting

The data were recorded and retrieved from the computerized laboratory database at the National Hospital of Obstetrics and Gynecology (NHOG) in Hanoi, Vietnam. NHOG is an approximately 1500-bed public academic hospital, which is the largest referral hospital for Northern Vietnam, serving about 55 million Vietnamese people. The hospital provides primary and tertiary care for pregnant women and treats patients with related diseases.

Identification and antimicrobial susceptibility testing

Between January 2016 and December 2020, vaginal swabs were obtained from 3863 pregnant women at < 37 weeks of gestation who agreed to participate in this study. During the study period, no protocol for the prevention of GBS disease, such as routine testing of pregnant women, had been established in the Hospital. Vietnamese pregnant women did not receive antimicrobials days before and during the sampling.

Vaginal samples were processed for the detection of GBS according to the American Society for Microbiology’s guidelines (13). Briefly, vaginal samples were inoculated in 1–2 mL of Todd-Hewitt broth

supplemented with colistin 10 µg/mL and nalidixic acid 15 µg/ mL and incubator at 35°C for 18-24h. After incubation, each sample was seed on Columbia Agar with 5% sheep blood (Oxoid, Singapore), culture plates were incubated at 37ºC with 5% CO_2 for 24 hours. All suspected GBS, e.g. β or γ hemolytic colonies were taken from the plates and the bacterial identification was performed by conventional biochemical tests.

All suspected GBS colonies were selected to perform antimicrobial susceptibility testing by the VITEK 2 system (BioMérieux, France) or antimicrobial E-test strips (BioMérieux, France). The isolates were considered either susceptible or resistant according to the MIC breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) (14).

Statistical analyses

The Chi-square test for trend was used to examine trends across the study period using R 4.0.2. A *p*-value below 0.05 was considered statistically significant.

Results

Baseline characteristics of enrolled participants

The detailed baseline characteristics of all participants are listed in Table 1. Of the 3683 enrolled participants, 310 were GBS positive (8.02%). Of the 310 individuals, the age ranged between 18 and 54 years, with an average age of 30.49 ± 6.43 years. The gestational age ranged between 8 and 41.2 weeks, with an average gestational age of 31.32 ± 7.89 weeks. The preterm birth and stillbirth rates were 1.94 and 3.87%, respectively. The rate of primiparous, 2nd -, 3rd -, 4th -, and 5th parity was 41.61%, 20%, 9.68%, 3.23%, and 0.32%, respectively (Table 1).

Table 1
Baseline characteristics of enrolled participants for this study

Demographic and clinical Characteristics	n (%)
Total number of enrolled participants	3863
Total number of positive isolates	310 (8.02)
Age in years (Range)	18–54 years
Mean age (Years)	30.49 ± 6.43
Median gestational age in weeks (range)	34 (8–41.2)
Mean gestational age (weeks)	31.32 ± 7.89
Preterm birth	6 (1.94)
Stillbirth	12 (3.87)
Primiparous	129 (41.61)
2nd Parity	62 (20)
3rd Parity	30 (9.68)
4th Parity	10 (3.23)
5th Parity	1 (0.32)
Parity (not available)	78 (25.16)
In vitro fertilisation (IVF)	55 (17.74)
Occupation	
Self-employed	103 (33.23)
Teacher	62 (20)
Office worker	77 (24.84)
Farmer	24 (7.74)
Student	5 (1.6)
Healthcare worker	4 (1.29)
Engineer	2 (0.65)
Housewife	2 (0.65)
Factory worker	31 (10)

Identification and antimicrobial susceptibility testing

We observed that 310 of 3,863 (8.02%, 95%CI: 7.20–8.94%) women tested positive for GBS. Of the 310 (87.74%, 95%CI 83.44–91.08%), 272 samples had susceptibility testing and the results are summarized in Table 2.

Table 2
Antibiotics susceptibility profiles of GBS isolated from pregnant women in Vietnam

Group	Antibiotics tested		Susceptibility results (%)		
	Antibiotics	n	Susceptible	Intermediate	Resistant
Penicillins	Ampicillin	245	100	0	0
	Penicillin	243	100	0	0
Cephems	Cefotaxime	36	100	0	0
	Ceftriaxone	33	100	0	0
Glycopeptides	Vancomycin	244	100	0	0
Macrolides	Erythromycin	265	11.7	12.08	76.23
Tetracyclines	Tetracycline	261	10.34	0	89.66
Fluoroquinolones	Levofloxacin	260	70.38	1.15	28.46
Nitrofurantoins	Nitrofurantoin	199	89.95	8.04	2.01
Phenicols	Chloramphenicol	42	40.48	7.14	52.38
Lincosamides	Clindamycin	268	40.67	1.12	58.21
Streptogramins	Quinupristin/dalfopristin	207	100	0	0
* Clindamycin (n = 102), erythromycin (n = 101)					

Among those samples positive for GBS, 100% were sensitive to penicillin, ampicillin, ceftriaxone, cefotaxime, quinupristin/dalfopristin, and vancomycin, 89.95% (179/199) were sensitive nitrofurantoin. The resistance to tetracycline was highest with 89.66% (234/261), followed by erythromycin with 76.23% (202/265), clindamycin with 58.21% (156/268), chloramphenicol with 52.38% (22/42), ciprofloxacin with 30.83 (37/120), moxifloxacin with 28.51% (71/249), levofloxacin with 28.46% (74/260), trimethoprim/sulfamethoxazole with 14.55% (8/55), nitrofurantoin with 2.01% (4/199), ampicillin with 0.41% (1/245), benzylpenicillin with nearly 0.41% (1/243). None of the isolates was resistant to cefotaxime, ceftriaxone, vancomycin, quinupristin/dalfopristin. The multidrug-resistance rate was 59.19% (161/272), and 8.46% (23/272) isolates tested were resistant to 6 to 7 of the 12 antibiotics tested. Resistance to clindamycin in the absence of erythromycin resistance was found in 2.2% (6/272).

A significant increase in the proportion of isolates resistant to clindamycin was observed from January 2016 to December 2019 (41.3% in 2016 versus 65.69% in 2019, $p < 0.01$). A slight decrease in the

proportion of isolates resistant to erythromycin was also observed (84.78% in 2016 versus 82.18% in 2019, $p > 0.05$) (Fig. 1).

Discussion

Group B *Streptococcus* (GBS) is an important cause of infection in maternal and neonatal in many countries in the world (15, 16). The most important risk factor of the infectious disease in the neonatal in developing countries was maternal GBS colonization (17). The strategy of prevention and control of GBS related diseases is data collection in different populations, but there are still little data from Vietnam.

The rate of the carriage in the present study was 8.02% which was lower than that of other reported from Vietnam, e.g. 9.2% (18), and much lower than that of other reports from previous studies, e.g. 15.6% (19), 26.1% (20), 17.2% (21), and higher than that in other reported 3.65% (22). The difference in the carriage rate of GBS may be explained by the differences in the population, social-economic status, and geographical in each study (6, 10).

Penicillin and ampicillin are both the antimicrobial of choice for the prevention or treatment of GBS infections, clindamycin, erythromycin (8), and vancomycin are the recommended alternatives antimicrobial for patients with a high risk of anaphylaxis to β-lactam antibiotics. However, the resistance rate to erythromycin and clindamycin has increased in recent years (9). Similar to other reports (21, 23), none of the isolates resistant to penicillin, ampicillin, and vancomycin was found in this study. Although the GBS resistance to ampicillin, penicillin, and vancomycin has been documented (22, 24, 25), penicillin and ampicillin remain the drugs of choice for intrapartum antibiotic prophylaxis for GBS colonization in Vietnamese pregnant women.

Resistance to lincosamides without resistance to erythromycin (L phenotype) is rare in GBS but has been previously reported in clinical isolates. The frequency of these phenotypes among GBS isolates has increased in recent years (1). In this context, the rate in this study was 2.2% which was higher than that in other studies (0.31%) (1). To the best of our knowledge, this is the first time this phenotype has been reported among GBS isolates from Vietnamese pregnant women.

Clindamycin and erythromycin are the antimicrobial of choice for maternal GBS colonization who are serious allergy to penicillin (8). An increase in resistance of GBS to erythromycin and clindamycin has been reported (26). In this study, 76.23% and 58.21% of the isolates were resistant to erythromycin and clindamycin, respectively. This rate was significantly higher than that from previous studies, e.g., 26.7% and 22.1% (19), 52.21%, and 48% (22), 36.8%, and 7.7% (20), 50.7%, and 38.4% (27) indicating that more Vietnamese pregnant women are at risk. It also threatens the progress to protect patients in healthcare, limits the treatment option for maternal and neonatal GBS colonization. Therefore, more action is needed to fully protect maternal and neonatal.

Clindamycin resistance rate was increased over time ($p < 0.01$), which is in line with a previous study (28). The selection of an alternative prophylactic antibiotic for penicillin-allergic patients should base on the

antibiotic resistance patterns in each region. The clindamycin and erythromycin resistance rate in this study strongly suggests that antibiotic susceptibility testing should be performed before using these antibiotics as a method to prevent neonatal GBS infection. The high resistance rate of GBS to clindamycin and erythromycin requires the restriction in use for penicillin-allergic women who are at high risk for anaphylaxis.

In this study, all isolates sensitive to penicillin, ampicillin, ceftriaxone, cefotaxime, quinupristin/dalfopristin, and vancomycin, suggest that these four antibiotics could be a good option for the treatment of both asymptomatic and symptomatic bacteriuria caused by GBS. Our results could contribute to further understand GBS epidemiology and surveillance targets. The high rates of multidrug resistance (59.19%) and 8.46% resistance to 6–7 of the 12 antimicrobial agents tested suggest that antibiotic susceptibility should be determined. A limitation of this study is that we did not determine the serotypes and virulence factors of these isolates. Therefore, the data on the serotype distribution of GBS from low to middle-income countries like Vietnam remain lacking for vaccine development (29).

Conclusion

This study results reveal that the total colonization and the antibiotic resistance rate to tetracycline, erythromycin, clindamycin were high. Penicillin and ampicillin are currently the drugs of choice for the prevention and treatment of GBS-related diseases for Vietnamese pregnant women. Further studies are needed in the future to investigate GBS serotype and continuous surveillance of GBS epidemiology.

List Of Abbreviations

CDC
The Center for Disease Prevention and Control
CI
Confidence Interval
CLSI
Clinical and Laboratory Standards Institute
GBS
Group B *Streptococcus*
MIC
Minimum Inhibitory Concentration
NHOG
National Hospital of Obstetrics and Gynecology

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants before sampling. The study was approved by the institutional review board of the National Hospital of Obstetrics and Gynecology, Hanoi, Vietnam. All methods and protocols were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The data sets compiled and analyzed for the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Not applicable.

Authors' contributions

NTV and HVT carried out the statistical analyses, interpreted results, and wrote the manuscript. VVD, PTD, NLT, CVM, NTB and HAS collected the data, carried out the statistical analyses, and interpreted results. All authors agreed with the results and conclusions.

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Authors' information

Not applicable

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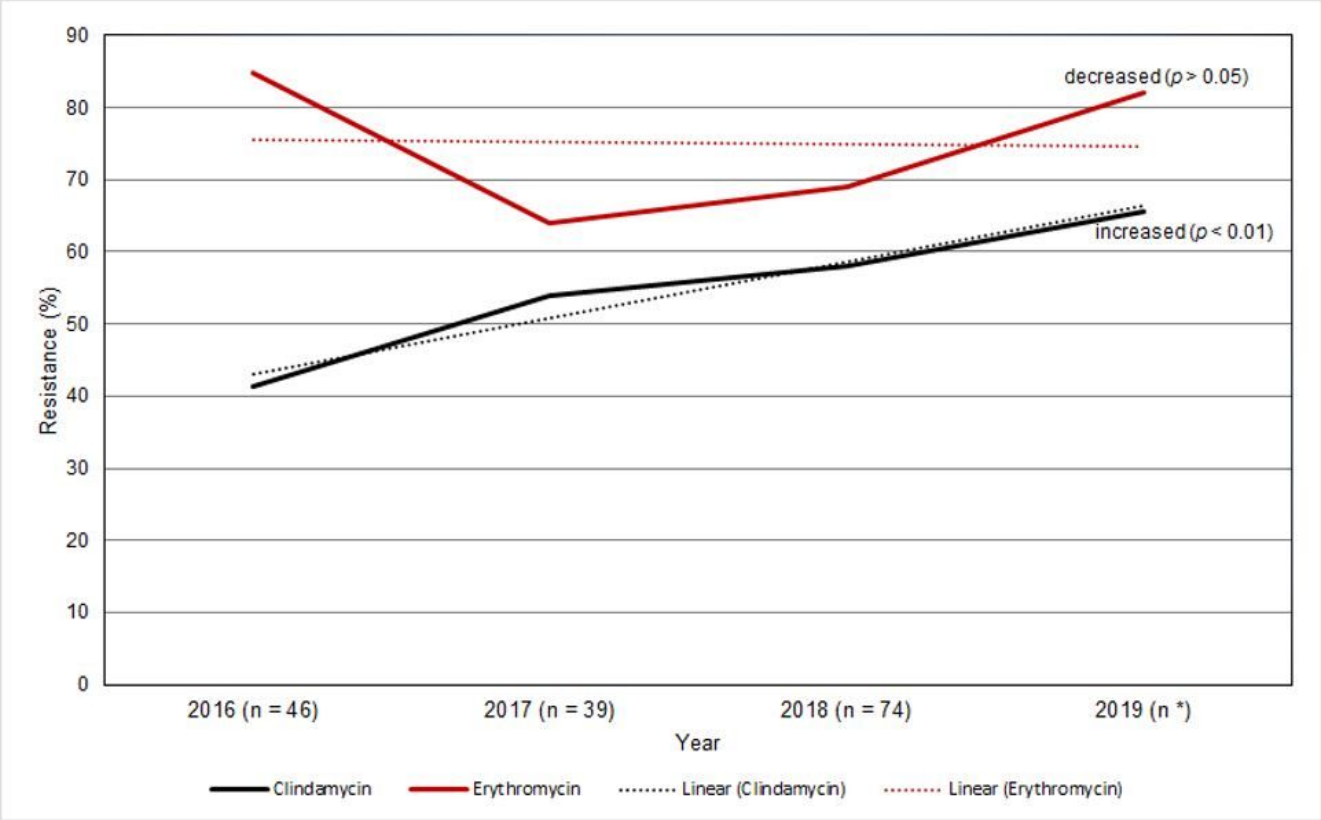
Figures



* Clindamycin (n = 102), erythromycin (n = 101)

Figure 1

Clindamycin and erythromycin resistance rate among group B Streptococci isolates by year.