Health Economic Evaluation of CDC’s Recommendation (1996 and 2002) for Prevention of Early Onset Group B Streptococcal Disease in Thailand

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ABSTRACT : Background : Group B streptococcus (GBS) infection is one of the leading causes of morbidity and mortality in the neonatal period in the USA. The Centers for Disease Control and Prevention (CDC) issued a recommendation to prevent early-onset GBS infection in 1996 and a revised recommendation in 2002. Objectives : To perform a health economic analysis of the CDC recommendation using clinical data currently available in Thailand. Study design : Health economic analysis. Materials and Methods : After reviewing the literature regarding clinical data in Thailand, a decision analysis was performed to evaluate the outcomes of 3 strategies : universal culture screening, intrapartum risk factors assessment, and no prevention. Outcomes : The medical care cost for each strategy and incremental medical care cost for the prevention of one GBS case were analyzed. Results : Under the present conditions in Thailand and using the cost estimated from Siriraj Hospital’s charge in the year 2005, the no prevention strategy was the most cost-effective strategy. The incremental medical care cost to prevent one GBS case for the universal culture screening and the intrapartum risk assessment were 594,754.17 Baht and 83,677.78 Baht, respectively. Conclusion : Although neither of the preventive strategies recommended by the CDC was cost-effective in general clinical practice in the present situation in Thailand, the intrapartum risk assessment strategy may be reasonable because the incremental cost to prevent one GBS case was less than 100,000 Baht.

Key words : health economics, group B streptococcal infection

Group B streptococcus (GBS) infection is one of the leading causes of morbidity and mortality in the neonatal period. The mortality rate of patients with neonatal GBS in the USA used to be as high as 50% in the 1970s but it has been dramatically reduced to 4% in the 1990s due to improvement in neonatal care. The majority of infections in newborns occur within the first week of life and are designated as early onset diseases. Late onset disease usually occurs in infants aged 1 week to 3 months. The common manifestations of invasive GBS disease include sepsis and pneumonia; whereas meningitis, osteomyelitis, and septic arthritis are occasionally found.

An infant may be infected intrauterinely by the bacteria ascending from the vagina, or extraterinely by the bacteria residing in the birth canal. The natural reservoir for GBS is the gastrointestinal tract which is the likely source of vaginal colonization. Approximately 10% to 30% of asymptomatic pregnant women in developed countries are colonized with GBS in the vagina or rectum. GBS colonization can be transient, chronic, or intermittent. Maternal intrapartum GBS colonization is a major risk factor for early-onset diseases in infants. Vertical transmission of GBS from a mother to a fetus primarily occurs after the onset of labor or rupture of membranes. However, colonization early in pregnancy is not predictive of neonatal sepsis. Culture screening of both the vagina and rectum for GBS late in gestation can detect those who are likely to be colonized with GBS at the time of delivery and are thus at higher risk of perinatal transmission of the organism.

Epidemiologic studies conducted during the 1980s revealed that women with prenatal GBS colonization were >25 times more likely than women with negative prenatal cultures to deliver infants with an early-onset GBS disease. Researchers used prenatal cultures as a basis for identifying candidates for intrapartum antimicrobial chemoprophylaxis because clinical trials demonstrated reduction in vertical transmission of the organism as measured by infant colonization or by protection against early-onset diseases.

Before the widespread use of intrapartum antibiotics, the incidence of invasive neonatal GBS diseases ranged from 2 to 3 cases per 1,000 live births. After active prevention efforts with intrapartum antibiotics in the 1990s, the incidence of early-onset GBS diseases declined by 70%, to 0.5 cases per 1,000 live births in 1999. In contrast, the rate of late-onset GBS disease remained fairly constant throughout the 1990s suggesting that this intervention is not effective against the late-onset disease.

In 1996 the Centers for Disease Control and Prevention (CDC) issued a guideline for the prevention of perinatal GBS infection. The guideline recommended two prevention strategies: a risk-based approach and a culture-based approach. The risk-based approach recommended identifying factors associated with early-onset diseases. The culture-based approach recommended screening of all pregnant women. The pregnant women with either the presence of a risk factor or the colonization of GBS were then offered prophylaxis intrapartum antibiotics at the time of labor. There was evidence suggesting that each strategy was able to reduce the incidence of early-onset GBS diseases. Later, it was demonstrated that the culture-based approach was >50% more effective than the risk-based approach in preventing perinatal GBD disease. Therefore the CDC’s guideline was revised and reissued in August 2002. This latest guideline recommended only a universal prenatal GBS screening strategy, ignoring the risk-base approach.

Although intrapartum antibiotic prophylaxis has been proven to be very effective in preventing early-onset GBS in neonates in developed countries, it has never been studied systematically in Thailand. The CDC’s recommendation may be cost-effective in the USA but its value in Thailand has never been evaluated. The objectives of this study were (i) to estimate the cost-effectiveness of 2 strategies for prevention of early-onset GBS disease in neonates compared to the no prevention strategy, and (ii) to generalize the results by performing a sensitivity analysis of 3 main variables, including the prevalence rate of GBS.
colonization in pregnant women, the infectivity rate, and the direct medical care cost in Thailand.

MATERIALS AND METHODS

Study design

In order to perform health economic evaluation, a clinical decision analysis model was developed to project all possible clinical outcomes of the infants whose mothers received one of the two GBS preventive strategies or no prevention. The analysis was performed according to standard procedure. Briefly, four basic steps were followed: (i) constructing a decision tree which is a flow diagram that specifies alternative courses of treatment or prevention strategies, and possible outcomes of these strategies; (ii) applying an associated probability to each chance node, the branch point in the decision tree, the probability of which was estimated from medical literature; (iii) assigning a relative value such as cost to each outcome; and (iv) calculating scores for each decision alternative by multiplying the relative value for each outcome by the probability of its occurrence, and then adding the scores across all branches of the decision tree.

The outcomes of the decision analysis included (i) the probability of early-onset GBS in each strategy, (ii) the total medical care cost of each strategy (expressed in bath/gravida), and (iii) the incremental medical care cost to prevent one case of early-onset GBS (expressed in bath per case prevention) compared to no prevention practice.

The present health economic analysis was performed from a hospital/health care provider point of view.

Prevention strategies

Strategies for the prevention of early onset GBS diseases consist of two methods: (i) the universal screening culture, and (ii) the intrapartum risk assessment.

The universal screening culture referred to a GBS screening culture from the lower vagina and rectum in pregnant women at 35-37 weeks gestation using a selective enrichment broth for maximal isolation of GBS.

The intrapartum risk assessment referred to maternal risk factors identified during the intrapartum period. The risk factors included one of the following: (i) preterm delivery at <37 weeks gestation, (ii) duration of membrane rupture >18 hours, or (iii) intrapartum temperature ≥100.4°F or >38.0°C.

Cost-effectiveness analysis

The net medical costs for each strategy were calculated from its probability and the cost of each event. To determine the cost-effectiveness of each strategy, the incremental cost, risk reduction of GBS infection and incremental ratio were calculated using the following formulas:

\[
\text{Incremental cost} = C_p - C_n
\]
\[
\text{Risk reduction} = P_p - P_n
\]
\[
\text{Incremental ratio} = \frac{\text{Incremental cost}}{\text{Risk reduction}}
\]

Cost reduction

Where \( C_p \) = net cost of a preventive strategy, \( C_n \) = net cost of no prevention practice; \( P_p \) = probability of GBS infection in a preventive strategy, and \( P_n \) = probability of GBS infection in no prevention practice.

These formulae allowed estimation of the net

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**Table 1.** Estimated values for calculation in clinical decision analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Percentage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of GBS colonization in Thai pregnant women</td>
<td>6</td>
<td>Werawatakul et al, 2001</td>
</tr>
<tr>
<td>Negative predictive value of screening culture</td>
<td>96</td>
<td>Yancey et al, 1996</td>
</tr>
<tr>
<td>Prevalence of mothers with intrapartum risk factors</td>
<td>15</td>
<td>Data from statistics of year 2002, Department of Pediatric, Phramongkutklao Hospital</td>
</tr>
<tr>
<td>Prevalence of Penicillin anaphylaxis</td>
<td>0.01</td>
<td>Mendell</td>
</tr>
<tr>
<td>Pediatric evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of early-onset GBS in infants of untreated colonized mothers</td>
<td>6</td>
<td>Boyer et al, 1986</td>
</tr>
<tr>
<td>Infectivity of early-onset GBS in infants of untreated colonized mothers</td>
<td>40</td>
<td>Yossuck et al 2002</td>
</tr>
<tr>
<td>Mortality</td>
<td>5</td>
<td>Zagwell et al 1992</td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Fig 1.** Decision tree and net medical care cost per gravida of each strategy (Cost = government hospital’s charge, Prevalence of GBS colonization in mother = 6%, infectivity rate of GBS exposure = 6%)
medical cost for each strategy and incremental medical care cost to prevent one case of early onset GBS infection when compared to no prevention strategy.

**Sensitivity analysis**

The medical care cost per gravida and the incremental medical care cost per case prevention were generalized by performing sensitivity analyses in which the prevalence of GBS colonization in mothers, the infectivity of GBS in exposed neonates, and the medical care costs were varied.

The prevalence of GBS colonization in Thai women was 6%. However, this number may be underestimated because other studies reported that the prevalence varied from 10 to 30%. Therefore, in the sensitivity analysis this variable would be varied from 5 to 35%.

The infectivity of GBS in exposed neonates was reported to be 6%. From the prevalence of GBS colonization in Thai women (6%), the expected prevalence of early-onset GBS in Thai neonates should be 3.6 cases in 1,000 births. However, the reported prevalence of early-onset GBS in the Thai neonates was 0.1 in 1,000 live births. Therefore, the infectivity rate of GBS in Thai population must be approximately 0.2% which was much lower than that reported in the western countries. This variable would be varied from 1% to 7%.

The cost was estimated from a government hospital’s (Siriraj Hospital) charge as shown in Table 2.

This cost was used to determine medical care cost for each strategy and incremental medical care cost of each strategy to prevent one case of early-onset GBS disease compared to no prevention practice. In one-way sensitivity analysis, the medical care cost for each strategy was calculated from either the varied value of prevalence and fixed infectivity or vise versa. In two-way sensitivity analysis of the incremental medical care cost, the medical care cost was the second variable to be varied in addition to the prevalence or the infectivity. Due to the lack of data about long-term disability in the early-onset GBS survival, the pediatric cost would be varied from 2 to 20 times the pediatric based-cost.

**Assumptions**

The analysis was performed under the following assumptions: (i) prenatal GBS screening could be done on all pregnant women, (ii) the laboratory process and technique of GBS culture were standardized, (iii) the efficacy of intrapartum antibiotic prophylaxis for early onset GBS disease was 100%, (iv) maternal antibiotic anaphylaxis required only one-day treatment in an intensive care unit, and there was no maternal death from this complication, (v) the length of hospitalization for early-onset GBS infection in an infant was 7-14 days, and (vi) the presence of intrapartum risks did not alter clinical course in a neonate.

**RESULTS**

The decision tree used in this analysis is shown in Figure 1. Estimated values for calculating the analysis derived from published data are summarized in Table 1.

**Medical-Care Cost**

Table 3 demonstrates the medical care cost per gravida for each strategy. At 6 percent prevalence of GBS colonization in pregnant women, or at 6 percent infectivity of GBS in exposed neonates, and medical care cost based on a government hospital’s charge, the strategy that yielded the low est cost was the no prevention followed by the intrapartum risk assessment and the universal culture screening. Similar results were also obtained after increasing the cost to the level of middle class private hospital’s charge, which was approximately equal to 2 times the government hospital’s charge.

**TABLE 2. Estimated costs in a government hospital (Siriraj Hospital)**

<table>
<thead>
<tr>
<th>Events</th>
<th>LOS (day)</th>
<th>Probability</th>
<th>Cost/ event (Baht)</th>
<th>Total cost (Baht)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal or rectal culture</td>
<td>NA</td>
<td>NA</td>
<td>350</td>
<td>NA</td>
</tr>
<tr>
<td>Pelvic examination</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>NA</td>
<td>NA</td>
<td>360</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment for anaphylaxis</td>
<td>1</td>
<td>NA</td>
<td>10,000</td>
<td>10,000</td>
</tr>
<tr>
<td>Pediatric costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death case</td>
<td>&lt; 7</td>
<td>0.4</td>
<td>NA</td>
<td>10,000</td>
</tr>
<tr>
<td>Survival case</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m Uncomplicated</td>
<td>7</td>
<td>0.5</td>
<td>2,000</td>
<td>14,000</td>
</tr>
<tr>
<td>m Complicated</td>
<td>14</td>
<td>0.1</td>
<td>4,000</td>
<td>56,000</td>
</tr>
</tbody>
</table>

**Cost-Effectiveness**

The medical care cost for each strategy in Table 3 was used to calculate incremental medical care cost to prevent one case of early onset GBS disease compared to no prevention practice. The results are demonstrated in Table 4 showing that the universal culture screening strategy cost was 594,754.17 Baht whereas the intrapartum risk assessment strategy was 83,677.78 Baht in order to prevent 1 case of early onset GBS disease. These costs were 36 and 5 times the average cost (16,600 Baht) for treating one case of early onset GBS infection.

**Sensitivity Analyses**

One-way sensitivity analyses of the medical care cost of each strategy are demonstrated in Figure 2. At the

**TABLE 3. Medical-care costs per gravida for each preventive strategy**

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Probability of EOGBS</th>
<th>Net cost (Baht)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal screening culture</td>
<td>0.00226</td>
<td>859.11</td>
</tr>
<tr>
<td>Intrapartum risk assessment</td>
<td>0.00360</td>
<td>104.95</td>
</tr>
<tr>
<td>No prevention</td>
<td>0.00360</td>
<td>59.76</td>
</tr>
</tbody>
</table>

**Fig. 2. Government hospital charge per gravida for each strategy:** (a) at 6% prevalence of GBS colonization in mother; (b) at 6% infectivity of GBS; culture = universal culture screening strategy; risk = intrapartum risk assessment strategy; no = no prevention practice.
6% fixed prevalence of GBS colonization in women and the varied infectivity rate of GBS in exposed infants, the no prevention practice yielded the lowest cost, followed by intrapartum risk assessment, and universal culture screening strategies (Figure 2a). Similarly, at the 6% fixed infectivity rate and the varied prevalence, both preventive strategies yielded a higher cost than the no prevention practice (Figure 2b). However, a break-even point between the no prevention practice and the intrapartum risk assessment was found at the 35% prevalence of GBS colonization in women.

Two-way sensitivity analyses of incremental medical care cost per gravida are demonstrated in Figure 3. Figures 3(a) and 3(c) show the incremental cost of the preventive screening strategy over the no prevention practice; Figures 3(b) and 3(d) show that of risk assessment strategy over that of no prevention practice. In Figures (a) and (b) the prevalence of GBS colonization was fixed at 6% and the infectivity rate was varied, and vice versa in Figures (c) and (d). The second variable was the cost, varying pediatric cost to 20 times the base-cost. Both preventive strategies would yield benefits over the no prevention only when the pediatric cost component was much higher than that in the base-cost (up to 10-20 times), and the prevalence of GBS colonization and/or the infectivity rate of GBS in the neonate was higher than those estimated in the Thai population. However, the intrapartum risk assessment strategy provided more benefit by preventing a case at a lower cost than the universal culture screening strategy did.

**DISCUSSION**

The use of decision analysis together with the sensitivity analysis enabled us to compare the two preventive strategies to the no prevention practice. Considering medical costs based on Siriraj Hospital’s charges, neither of the preventive strategies was cost-saving compared to the no prevention practice at any prevalence of GBS colonization in women, or at any infectivity of GBS in exposed neonates. Because the government hospital’s charges were likely to be underestimated, increasing the costs to two times, which reached a range of private hospitals’ charges, generally provided a more realistic approach. However, with this based-cost, the two preventive strategies still cost much more than no prevention practice. This CDC’s recommendation for prevention of early-onset GBS is cost-effective in the USA but it is not in Thailand.

The obvious difference between the USA and Thailand was the prevalence of GBS colonization in pregnant women. The recent surveillance for GBS colonization in pregnant women in Khon kaen Province reported a prevalence rate of 6.2 percent$^{16}$, which was much lower than the 30% in the USA.

If the prevalence of GBS colonization in Thailand was as high as that in the USA, even with lower costs in Thailand, the intrapartum risk assessment followed by prophylactic antibiotic would become cost-effective, as shown in Figure 2(b).

The second different factor was the infectivity of GBS in the exposed infant. Boyer in 1986 reported an infectivity rate of 6% estimated from the incidence of early-onset GBS disease cases in infants exposed to untreated colonized mothers.$^5$ Such data in Thailand was not available. However, calculation from a prevalence rate of GBS colonized pregnant Thai women$^{20}$ and a prevalence of early-onset GBS disease cases$^3$ suggested the infectivity rate in Thailand to be as low as 0.2%.

Although the medical care cost in the USA was much higher than that in Thailand, it might not be an important factor for an economic analysis because costs for both the prevention and the treatment in the USA increased at the same scale. However, in this study the authors varied the cost in the two-way sensitivity analysis because the pediatric cost in the survival cases might largely vary due to various long-term disabilities.

Obviously, the threshold prevalence of GBS colonization was lower when the medical care cost was higher. Similarly, considering the incremental cost necessary to prevent one early-onset GBS case, both preventive strategies were cost-effective only when the pediatric costs were increased to 5-20 times of the based-cost as shown in Figure 3.

From the epidemiologic evidence in Thailand, i.e., the prevalence of GBS colonization in pregnant women (6%) and infectivity of GBS in exposed neonates (<1%) which were much lower than the estimated values used in the CDC’s recommendation, none of the preventive strategies were cost-effective for the Thai population.

Nevertheless, if the medical care cost was equal to Siriraj Hospital’s charge, the incremental medical care cost to prevent one case of early-onset GBS disease would be only 83,677.78 Baht for the intrapartum risk assessment strategy, and 594,754.17 Baht for the universal culture screening strategy. Although the costs of prevention were 5 and 36 times the cost of treatment for early-onset GBS disease, the prevention may be cost-beneficial because it would prevent death and long-term disabilities; the costs of which were unable to calculate as direct medical care cost and they were expected to be very

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*Fig 3. Sensitivity analyses of incremental medical care cost per gravida for 2 preventive strategies comparing to no treatment practice: (a) and (b) vary medical care cost and infectivity, (c) and (d) vary medical care cost and prevalence; 1x = base cost = government hospital’s medical care cost; 2x = 2 times of pediatric base cost and other costs = base cost; 5x = 5 times of pediatric base cost and other costs = base cost; 10x = 10 times of pediatric base cost and other costs = base cost; 20x = 20 times of pediatric base cost and other costs = base cost.*
high. In general, a government hospital’s charge was likely to be lower than a real medical care cost. The real cost would be somewhere in between a government hospital’s and a private hospital’s charge. Calculating the cost using a charge of middle class private hospital increased the incremental medical care cost per case prevention to two times.

From the above, the intrapartum risk assessment strategy may be the reasonable preventive strategy in Thailand. However, the cost for this strategy is largely affected by the prevalence of intrapartum risk factors. Such prevalence is not really known. In this study the authors used a prevalence of 15%, the data of which was derived from medical record review during a short period in the Pediatric Department at Phramongkutkla Hospital. At Siriraj Hospital, the annual statistical report for the years 2000 to 2002 of the Department of Obstetrics and Gynaecology demonstrated an average incidence of low birth weight newborns to be 11% of all deliveries.21-23 The incidence included incidence of preterm babies but it also included other causes which might not be risk factors for GBS infection. Moreover, incidences of two other risk factors, i.e., prolong rupture of membrane and intrapartum fever, were not included. Even though the exact incidence was not available, the incidence varying from 10 to 20% still provided the same incremental cost per case prevention.

The present study had some limitations, including the following: (i) indirect medical care cost and intangible cost were not included in the analysis; (ii) the medical cost of long-term care for neurological deficits in the GBS survivors was not available for analysis; (iii) the data of probability in the decision tree were taken from different studies and populations. Furthermore, the present study was designed to aid in the decision for only early-onset GBS infection; therefore no attempt should be made to estimate the prevalence and medical costs of late-onset GBS infection. The applications of this analysis to general practice require caution for interpretation.

CONCLUSION

Given the present situation in Thailand, neither of the preventive strategies recommended by CDC is cost-effective in general clinical practice. This analysis includes neither the direct and indirect medical care costs for long-term sequelae of disabled survivors nor the intangible invaluable cost of death. Considering these indirect costs, the intrapartum risk assessment strategy may be reasonable in Thailand because the incremental cost to prevent one case was less than 100,000 Baht.

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ประกาศเรยูมวิธีการปฏิบัติต่อ CDC (ปี พ.ศ. 2539 และ 2545) เพื่อป้องกันการติดเชื้อ Group B Streptococcus แบบ Early-Onset ในประเทศไทย

เนื่องจาก Group B streptococcus (GBS) เป็นสาเหตุของการเกิดปัญหาทางการแพทย์ในหลายๆ ประเทศทั่วโลก ซึ่งมีการรับรู้การติดเชื้อที่กล่าวถึงในปี พ.ศ. 2539 และ 2545 จึงมีการตีความและอนุมัติให้ใช้ในประเทศไทย โดยมีการดำเนินการคัดกรองซ้ำจุดประสงค์เพื่อการประเมินตนเอง (self-assessment) ที่มีการวิเคราะห์ผลการติดเชื้อที่กล่าวถึงในปี พ.ศ. 2539 และ 2545 แล้วตรวจสอบผลการวิเคราะห์ที่กล่าวถึงในประเทศไทยโดยมีการวิเคราะห์ในด้านการวิเคราะห์ปัจจัยที่ขึ้นอยู่กับผลการวิเคราะห์ที่กล่าวถึงในประเทศไทย เพื่อให้ได้ผลการติดเชื้อที่มีความมั่นใจและเป็นไปตามที่คาดหวังได้มากที่สุด

ผลการวิเคราะห์ที่กล่าวถึงในประเทศไทยโดยมีการวิเคราะห์ที่มีความมั่นใจและเป็นไปตามที่คาดหวังได้มากที่สุด

ผลการวิเคราะห์ที่กล่าวถึงในประเทศไทยโดยมีการวิเคราะห์ที่มีความมั่นใจและเป็นไปตามที่คาดหวังได้มากที่สุด

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