HUG
Hôpitaux Universitaires de Genève

PREVENTION OF NEONATAL INFECTIONS

Catalin Stan
Unité de Développement en Obstétrique, H U G

NEONATAL SEPTICAEMIA

- Early-onset: first week
- Late-onset: 7-28 days
- Perinatal septicaemia: first 24-36 hours

Epidemiology

- 1 to 5 cases/1000 live births
- 1970-1980s: E. Coli, K. Pneumoniae, P. Mirabilis
- 1990s: Group B Streptococcus, E. Coli, Enterobacter
- Differences depending on countries/continents

Pathogenesis

- Maternal infection
- Amniotic fluid infection (frequent)

Prevention

- Prevention of hematogeneous spread: maternal fever
- Prevention of ascending infection:
  - Risk factors:
    - Vaginal examinations ≥ 6 *(Seaward 1997)*
    - Duration of active labour ≥ 12h *(Seaward 1997)*
    - Rupture of membranes before labour ≥ 24h *(Gunn 1970)*
    - Group B Streptococcal colonisation *(CDC 1996)*

Prevention

- Mother:
  - vaginal disinfection during labour *(Taha 1997)*
  - induction of labour *(Hannah 1996)*
  - antibiotic prophylaxis (see GBS) *(Smaill 1994)*
  - antibiotic treatment if suspected chorioamnionitis
- Neonate:
  - surveillance (CBC, CRP) if risk factors
  - antibiotic prophylaxis

Problems

- Low incidence, but high mortality and morbidity
  - surveillance of many pregnancies to prevent one infection
  - surveillance of many neonates to prevent one infection
- Costs
  - diagnostic test
  - antibiotic treatment
  - hospitalisation and care
  - future costs because of sequelae
- Limitations:
  - women's access to health services
  - anaphylaxis, bacterial resistance

EARLY-ONSET GROUP B STREPTOCOCCAL SEPSIS

- USA, Australia (before adoption of preventive strategies)
  - incidence of the neonatal GBS sepsis: 1.4-3.0 ‰
  - prevalence of maternal colonisation: 18-35%
- Europe:
  - incidence of the neonatal GBS sepsis: 0.2-1.0 ‰
  - prevalence of maternal colonisation: 7-15%

EPIDEMIOLOGY

Prevalence of maternal colonisation: 2 - 35%

⇩

Vertical transmission to the neonate: 40 - 70%

⇩

Early-onset GBS sepsis: 1 - 2% of the colonised neonates

Mortality: 6 - 20%

Sequelae: 10 - 20%

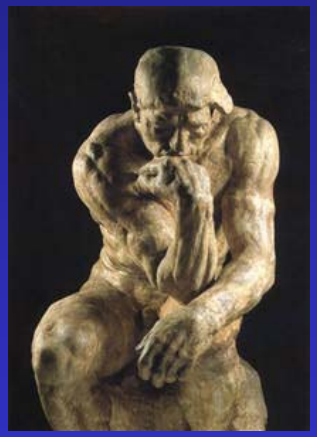
EARLY-ONSET GBS SEPSIS

- < 5 - 7 days
- 90% during the first 12 hours
- 1 - 2% of the colonised neonates
- rapid evolution
  - ↳ ARDS/septic shock

PREVENTION OF THE EARLY-ONSET GBS SEPSIS

- After delivery ? ➡ TOO LATE, the fetus is generally infected before delivery
- Treatment of GBS colonised women?
  - during pregnancy: inefficient (recolonisation)
  - during labour: appropriate *(Smaill 1994)*
- Culture during labour? ➡ Results after > 36h
- Rapid tests? ➡ Low sensitivity *(Yancey 1992)*
- Treat all women during labour? ➡ Inacceptable

PREVENTIVE STRATEGIES

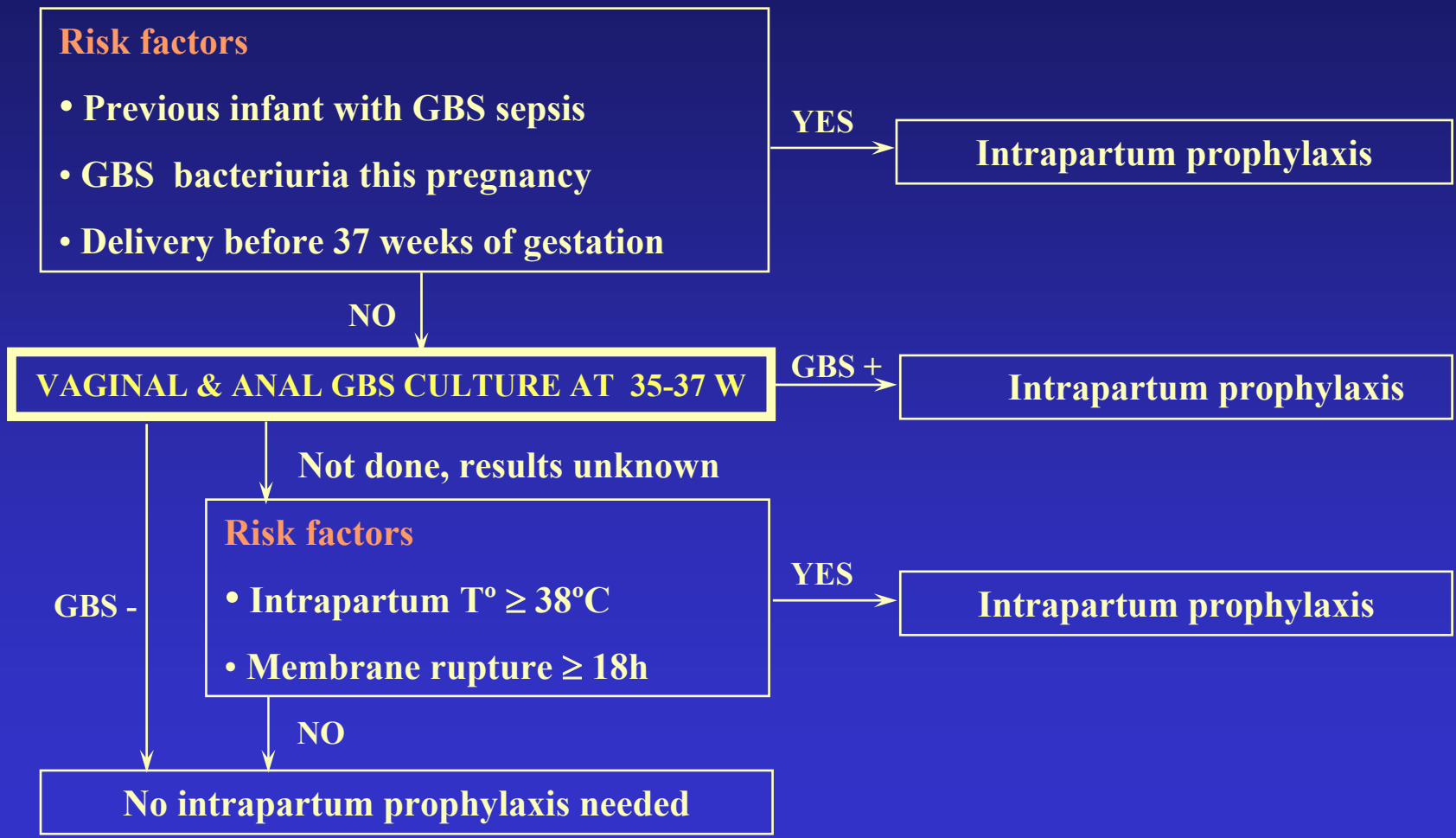


Consensus CDC & AAP & ACOG (1996)

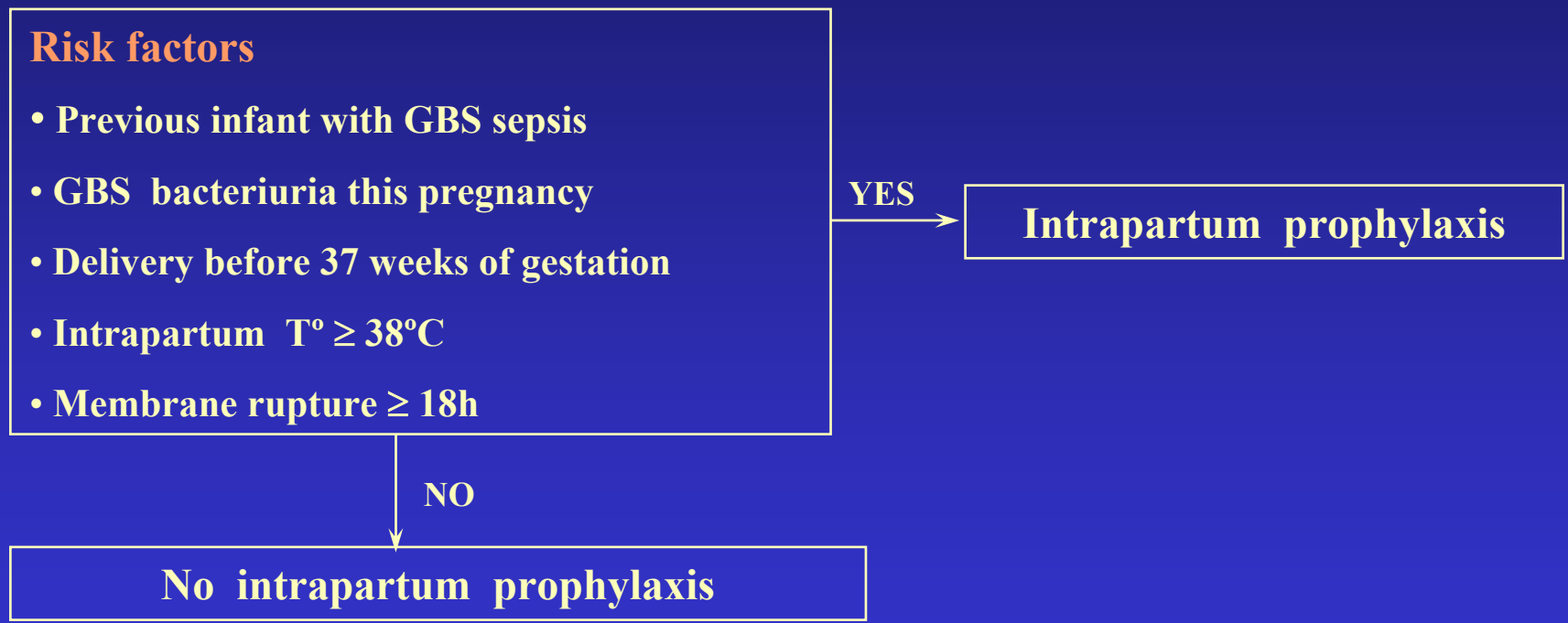
Two equivalent strategies are accepted:

1. **Strategy based on vaginal and anal culture screening at 35 - 37 weeks**
2. **Strategy based on risk factors**

STRATEGY BASED ON CULTURE SCREENING AT 35 - 37 WEEKS



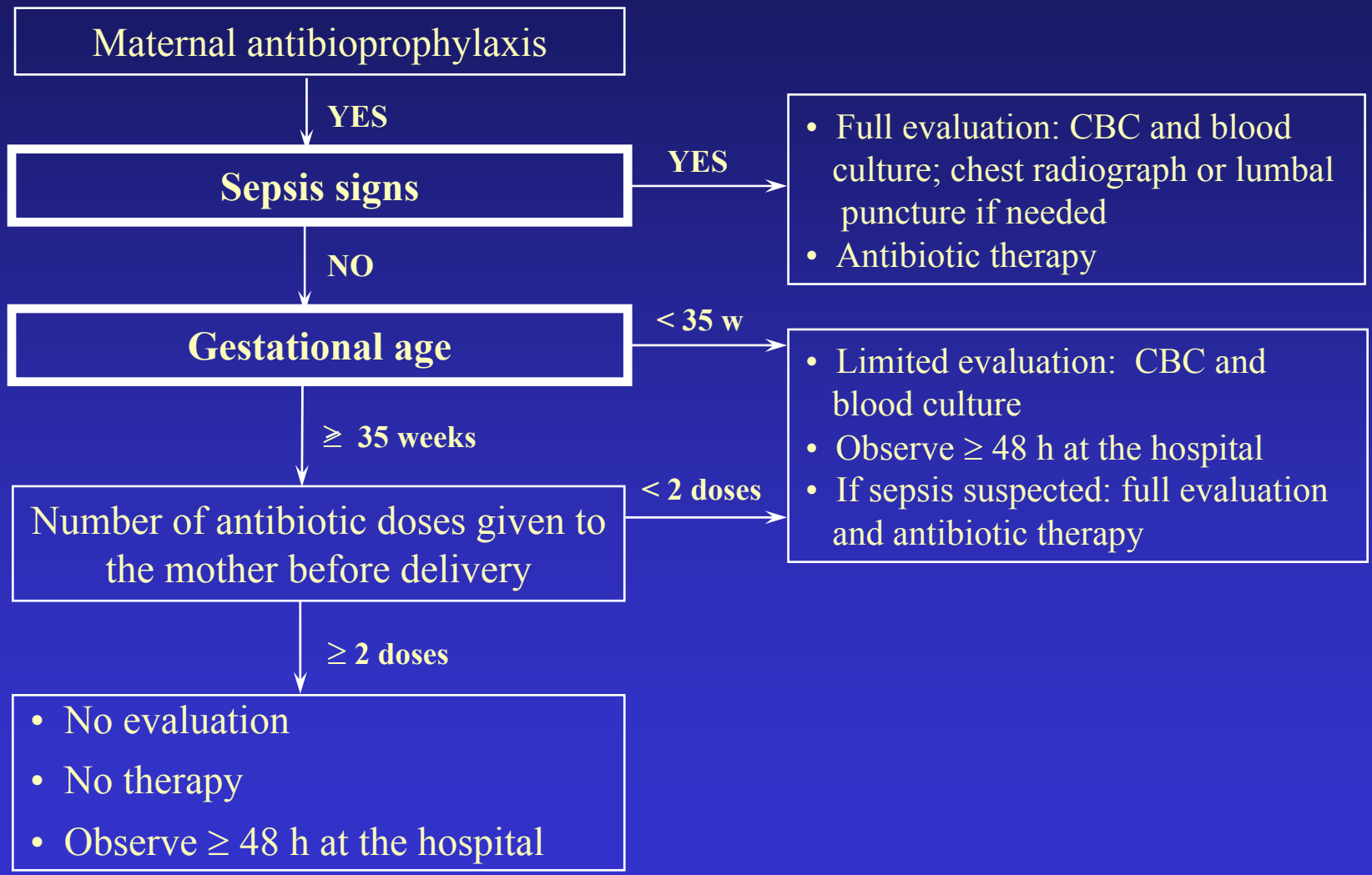
STRATEGY BASED ON RISK FACTORS



ANTIBIOTICS

- IV antibiotics during labour: decrease the risk of vertical transmission by 90% *(Smaill 1994)*
- Administration *(De Cueto 1998)*:
  - < 1h before delivery: vertical transmission 40%
  - 1-2h: transmission 28%
  - 2-4h: transmission 2.9%
  - > 4h (≥ 2 **doses**): transmission < 1%
- Proposed antibiotics:
  - penicillin G *or* ampicillin
  - allergy: clindamicin *or* erythromycin

MANAGEMENT OF THE NEONATE



PREVENTIVE STRATEGIES

- The incidence of the early-onset GBS sepsis decreased from 1.4-2.0‰ to 0.2-0.8‰ in the USA and Australia *(Schuchat 1999, Jeffery 1998, Isaacs 1999)*
- Compliance: 50-90% *(Cheon-Lee 1998, Lieu 1998)*
- Side effects:
  - risk of anaphylaxis *(Towers 1998)*
  - risk of bacterial resistance *(Morales 1999)*
  - ⬆ incidence of E. Coli sepsis *(Towers 1998)*

CURRENT POLICY IN OUR OBSTETRIC CLINIC

- No routine GBS culture during pregnancy
- Cervico-vaginal cultures, including GBS if:
  - preterm labour
  - preterm premature rupture of membranes
  - leucorrhea
- Antibiotic treatment during labour if:
  - maternal fever (≥ 38°C)
  - positive GBS culture during pregnancy (urine or cervix)
  - preterm premature rupture of membranes before 34 weeks

GENEVA STUDY - OBJECTIVES

- To estimate the prevalence of maternal GBS colonisation, of risk factors, the predictive value of the GBS culture at 35-37 weeks of pregnancy
- To analyse the impact of preventive strategies compared with the current policy in our clinic.

MATERIEL AND METHODES

- Prospective cohort study
- Rectovaginal GBS culture at 35-37 weeks (n = 264) and during labour (n = 334). Both cultures in 208 women.
- Decision and economic analyses.

RESULTS

Geneva epidemiological data concerning GBS:

- Incidence of the early-onset GBS sepsis: 0.4‰
- Maternal colonisation (labour): 7.8% (95% CI: 5-11)
- Recto-vaginal culture at 35-37 weeks
  - sensitivity 33% (95% CI: 14-59)
  - specificity 95% (95% CI: 90-97)
- Prevalence of risk factors: 17.7% (95% CI: 14-21)

RESULTS

Prevalence of risk factors: **17.7%**

- Premature delivery: 7.4%
- Rupture of membranes ≥ 18h: 8.8%
- Fever during labour: 1.6%
- GBS bacteriuria during pregnancy: 1.6%
- Previous infant with invasive GBS disease: 0.5%

Predictive value of the antenatal culture

GBS 35-37w 10.6%	GBS - Labour 7.8% +	-	TOTAL
+	6	10*	16
-	12	177	189
TOTAL	18	187	205

* 3 cases excluded for antibiotherapy because of antenatal culture +

Sensitivity	*33%*	*95% CI : 14 - 59%*
Specificity	*95%*	*95% CI : 90 - 97%*
PPV	38%	95% CI: 16 - 64%
NPV	94%	95% CI: 89 - 97%

Predictive value of the risk factors

GBS - Labour 7.8%

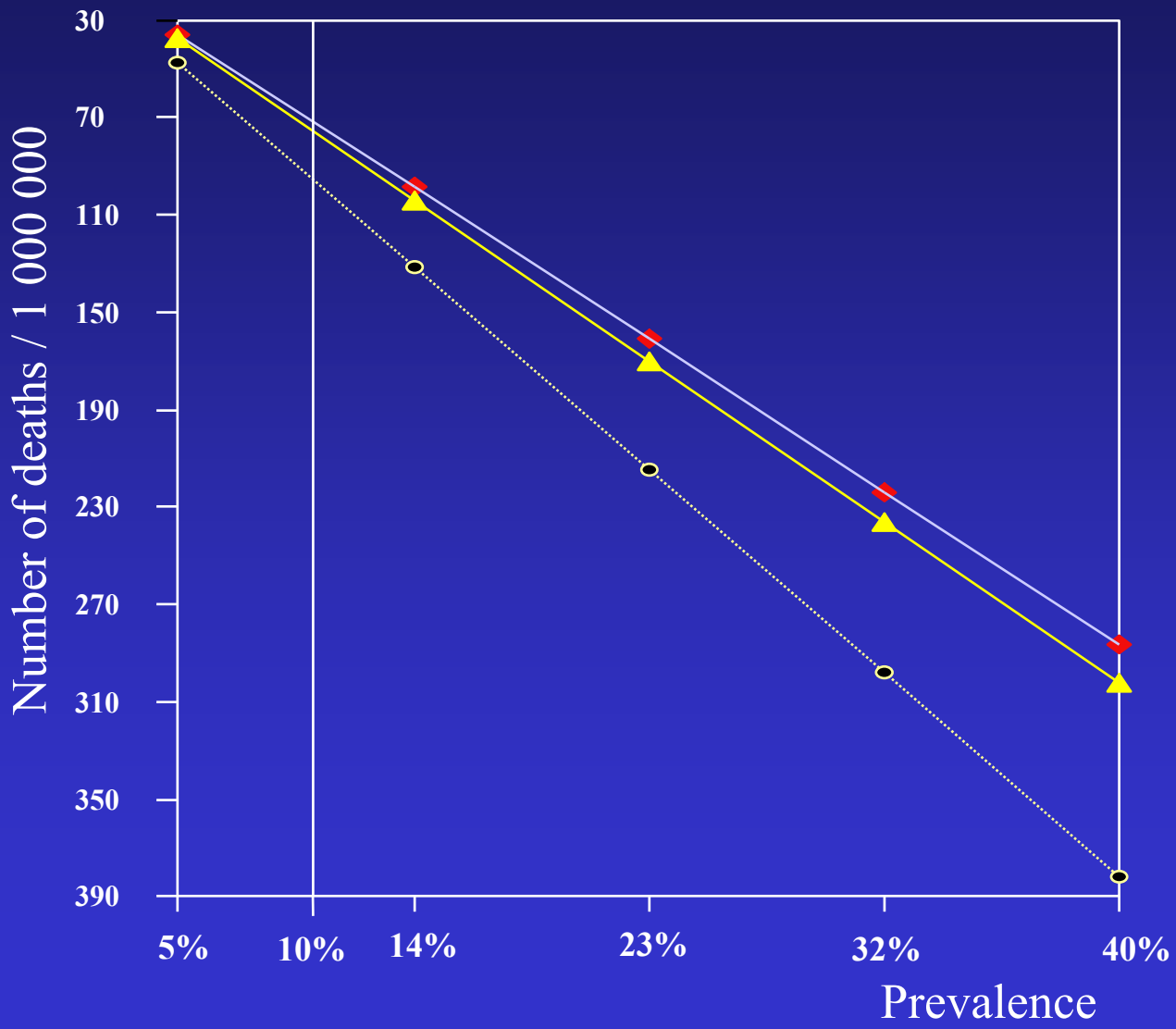
RF 17.7%	+	-	TOTAL
+	8	49	57
-	18	259	277
TOTAL	26	308	334

Sensitivity	*31%*	*95% CI: 13 - 49%*
Specificity	84%	95% CI: 80 - 88%
PPV	14%	95% CI: 5 - 23%
NPV	94%	95% CI: 91 - 96%

PREVENTIVE STRATEGIES

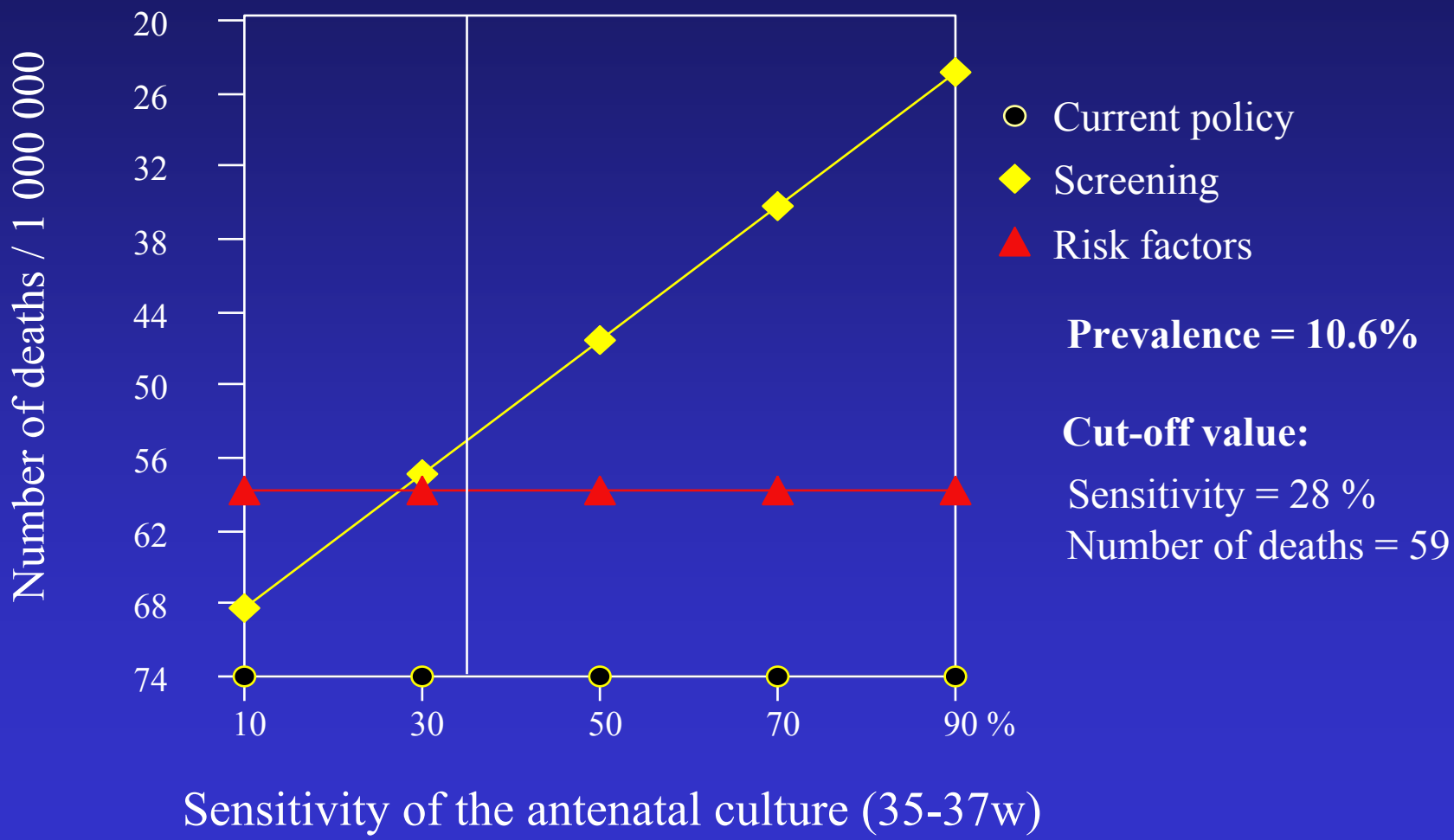
	Expected sepsis/ 10^6 births	Prevented sepsis/ 10^6 births	Cost / 10^6 births	Marginal cost effectiveness ratio
Current policy	378	--	$ 4 970 000	--
Risk factors	309	69	$ 11 146 000	$ 89 500
Screening	276	102	$ 29 933 000	$ 698 200

SENSITIVITY ANALYSIS: prevalence of maternal colonisation



Sensitivity of antenatal culture screening = 33%

SENSITIVITY ANALYSIS: Sensitivity of the antenatal GBS culture for predicting colonisation at delivery



PREVENTIVE STRATEGIES

	Proportion of treated women	Anaphylaxis/ 10^6 births	NNT*
Current policy	6%	6	--
Risk factors	13.5%	13.5	1087
Screening	16.5%	16.5	1029

*Number of women needed to treat to avoid one neonatal GBS sepsis

EFFECTIVENESS AND COST EFFECTIVENESS RATIO: sensitivity analysis

		Prevalence of maternal GBS colonisation		
		7.8%	20%	30%
Risk factors	CE*	89 500	43 000	33 000
	E†	69	171	257
Screening				
Sensitivity 33%	CE*	698 300	295 000	207 000
	E†	102	255	382
Sensitivity 87%	CE*	155 000	79 000	62 000
	E†	234	584	876

* Marginal cost effectiveness ratio in $/prevented sepsis

† Effectiveness of a preventive strategy compared to the current policy (prevented sepsis/10^6 births)

CONCLUSIONS

- **Effectiveness:** strategies based on risk factors and screening are more effective than the current policy
- **Cost:** preventive strategies have important costs; the screening strategy has the highest cost in our context
- **Cost effectiveness:** important increase of the cost per averted sepsis if adoption of a screening strategy

CONCLUSIONS

Prevention decreases the incidence of the early-onset GBS sepsis

Problems:

- detection of high-risk mothers and neonates: incomplete
- high costs for the screening strategy and for the antibioprophylaxis
- is it reasonable to give antibiotics to 20-40% of women in labour?
- could we afford a cost to prevent a GBS sepsis case between $33 000 and $700 000 ?
- probably a good option in countries with high incidence of GBS sepsis and with important health ressources

CHOICE OF A PREVENTIVE STRATEGY

- low incidence of the early-onset GBS sepsis in Geneva
- high cost of the preventive strategies
- significant increase of the proportion of women receiving antibiotics during labour

Implementation of a preventive strategy does not seem justified in our clinic

CONCLUSIONS

Search for alternative attitudes:

- Antibioprophylaxis limited to women with positive GBS screening presenting with risk factors *(Jakobi 1996)*
- Vaginal disinfection with chlorhexidine: efficient *(Burman 1992, Adriaanse 1995, Taha 1997)*
- PCR rapid test *(Bergeron 2000)*
- Vaccine: not yet available *(Harrison 1998)*

DISINFECTION OF THE BIRTH CANAL

(Taha TE et al. BMJ 1997;315:216-20)

- **Objective:** Does disinfection of the birth canal during labour reduce infections in mothers and babies postnatally ?
- **Design:** Alternate periods of intervention (chlorhexidine 0.25%) and no intervention in a tertiary centre in Malawi
- **Participants:** 6965 women giving birth over a 6 month period to 7160 babies

RESULTS

	Intervention		No intervention		Relative Risk (95% CI)
	No	Rate*	No	Rate*	
Infants	(n=3743)		(n=3417)		
• Admissions due to sepsis	29	7.8	61	17.9	0.43 (0.28-0.67)
• Mortality due to sepsis	9	2.4	25	7.3	0.33 (0.15-0.70)
Mothers	(n=3635)		(n=3330)		
• Admissions due to sepsis	6	1.7	17	5.1	0.37 (0.13-0.82)
• Admissions overall	107	29.4	134	40.2	0.73 (0.57-0.94)

* Rates are per 1000 live births (infants) and per 1000 deliveries (mothers)

Influence of prevalence on the decision to implement an intervention

	Malawi	Geneva
• Prevalence	18‰	1‰
• RR	0.43	0.43
• DR	10‰	0.6‰
• NNT	100	1600

Prevalence of a disease influences the absolute effectiveness and the decision to implement an intervention

CONCLUSIONS

- Cleansing the birth canal with chlorhexidine reduced early neonatal and maternal postpartum infections
- The simplicity and the low cost of the procedure suggest that it should be considered as standard care to lower infant and maternal morbidity and mortality
- Other studies showed similar results: *Burman 1992, Adriaanse 1995*