Appendix A: Methods

Three policies to decrease mother-to-child transmission of HSV are compared from a societal viewpoint to assess net costs versus consequences (1): 1) no specific management, 2) following current American College of Obstetricians and Gynaecologists (ACOG) guidelines and 3) identifying discordant HSV infection in pregnant women and their partners with subsequent aciclovir therapy for men. To achieve this comparison we first construct a theoretical decision analysis model, including the three policies, which estimates the incidence rate of vertical transmission from pregnant women over the course of the year 2000, in California. We then estimate costs and consequences of each programme to calculate the saving/cost ratios and cost per case averted for the interventions compared with the ‘no management’ alternative. California was chosen because of the availability of costs data.

The first programme (P1) is ‘no management’ which has no costs above those of a normal pregnancy, but has consequences in the care of subsequent neonatal herpes. P1 was considered to allow comparison with ACOG guidelines, and the proposed intervention. The second programme (P2) recommends caesarean section for women presenting with genital lesions at delivery. (2) The ACOG also recommends the use of aciclovir for primary HSV in pregnancy, but primary or non-primary first episode infection is difficult to diagnose without the use of diagnostic tests. (3)

Lastly programme 3 (P3), treating partners with aciclovir, would counsel and screen all pregnant women in the last trimester of pregnancy. Partners of women at risk would be counselled, screened and, if necessary, receive aciclovir to reduce transmission of HSV. Importantly, serodiscordant couples would be counselled regarding condom usage and risks of
oral sex. Caesarean delivery would be recommended for women with herpetic lesions at the time of delivery.

**Epidemiological Model – Decision Analysis**
A theoretical transmission model is used to calculate the number of neonatal infections as a result of primary or non-primary first-episode HSV infection among women late in pregnancy (Figure 1). The calculation was limited to first episode infections as the proposed programme targeted them, but it should be recognised that this group does not constitute the sole target of the ACOG guidelines.

The model used the number of births and the prevalence of HSV-1 and HSV-2 in men and women from the NHANES study to estimate the number of births where the mothers would be at risk of incident infection. The rate of transmission from partner to mother and then to the child is used to estimate the number of neonatal infections. The overall risk for vertical HSV transmission was estimated to be 44% among women with incident HSV infection. When following ACOG guidelines (P2), the likelihood of caesarean delivery is assumed to increase from 23% to 85% when genital lesions are present. Caesarean section was assumed to decrease vertical HSV transmission by 50%. The use of counselling and suppressive therapy (P3) is assumed to reduce the risk of partner to mother transmission by 80%, which was varied in the uncertainty analysis.

For example, looking at Figure 1, it was estimated that 8.4% of couples consist of HSV-1 positive and HSV-2 negative women with HSV-2 positive male partners. We assume that 1.7% (95% CI 1.1%-2.3%) of these women will seroconvert during pregnancy, but only 40% of those seroconversions will occur in the third trimester. Of
those who acquire HSV-2 it was estimated that 28% shed HSV asymptotically at the
time of delivery. Without intervention, 77% of those women will have vaginal deliveries
(8), and 45% of their infants would become infected. Long term, 56% of HSV positive
infants would be normal, 19% would die and 25% would have long-term neurological
disability.(10),(11) Based on studies not associated with neonatal infection we would
expect fewer women with prior HSV-1 infection to present with lesions than HSV
negative women. This does not appear to be the case with the 1997 Brown study used to
estimate our parameters. This is probably a function of the small sample size rather than
a real increase in lesions in those with prior HSV-1 infection.(12)

Because of the limited amount of information available we had to make several
assumptions which maximise the benefits of P3, which has the effect of generating a
dichotomy between the most effective, affordable version of screening and treatment and
‘no management’. The assumptions below are summarised in Table 1:

- Couples were assumed to be monogamous in the third trimester of pregnancy. This
  assumption would increase screening (P3) effectiveness and therefore increase the
  savings associated with it.

- Partnerships were independent of HSV serostatus increasing the number of cases of
  neonatal herpes and therefore increasing the benefits seen with P3. It is likely that the
  serostatus of partners is correlated due to the obvious prior risk of transmission.
  However, the assumed 26% of susceptible women compared favourably with the 22%
  of susceptible women in HSV serodiscordant couples found by Gardella and
  colleagues.(13)
- It was assumed that participation of pregnant women and their partners would be 100%, favouring P3. While prenatal care is well established for pregnant women, participation of their partners is not, and health education would have to promote partner participation. Participation was varied in the sensitivity analysis.
- Diagnostic sensitivity and specificity was assumed to be >99% favouring P3.
- Acyclovir therapy reduced the frequency of detectable HSV DNA by a median of 80% (range 34-91%). The model assumes that reduction in HSV DNA detection translates to decreased viral shedding and hence decreases HSV transmission (80%) an assumed impact of aciclovir suppression. An earlier study showed that the reduction in asymptomatic shedding associated with aciclovir was similar to the reduction in clinical recurrences. For HSV-negative women with HSV-1 positive, HSV-2 negative partners there is no published data to support aciclovir suppression efficacy in men and the counselling component of P3 (avoiding oral sex in the last 4 weeks of pregnancy) was estimated to reduce the transmission risk by 80% and the uncertainty considered in the uncertainty analysis.
- A scaled up version of current guidelines with education and surveillance (more costs) was assumed.

- The dissemination of ACOG guidelines (P2) was assumed to increase recognition of lesions by obstetricians (100%) and increase caesarean sections indicated by genital lesions (85%). While ACOG guidelines are implemented in California, its effectiveness in decreasing neonatal herpes has not yet been estimated and there is no active disease surveillance. This theoretical decision analysis model estimates neonatal herpes cases if an education and surveillance programme was in place.
The effectiveness of elective caesarean section was assumed to be 50%, but the evidence for caesarean section efficacy is limited. Among 56 women with asymptomatic shedding at delivery, as a result of both first-episode and recurrent HSV infection, 14% (6/43) of neonates delivered vaginally became infected compared to 8% (1/13) delivered by caesar ean section.(6) The efficacy of Caesarean section was varied in the uncertainty analysis.

**Costs**

Costs are calculated from a societal perspective (to include all the costs to patients and providers) using the human capital approach for maternal mortality and long-term neurological sequelae in infants.(1) The human capital approach uses estimates of lost wages to evaluate morbidity and mortality. Our analysis fails to take account of neonatal deaths, which would normally be assessed in a cost utility analysis or using a willingness to pay approach.

To bring past estimates of costs up to year 2000 values we used the consumer price index (CPI), and, in calculating the value of future costs we used a 3% discount rate.(1) Hospital and personnel costs were obtained from the Californian department of health (15), and the United States Department of Labour’s Occupational Outlook Handbook for 1997.(16) Economic indicators were obtained from the Californian Department of Finance.(17) The itemised cost of consequence menu is found in Table A1.

In the literature the cost for acute neonatal herpes varied from US$1 584 (8) to US$37 309 (18) dependent on clinical presentation and study perspective. We felt the most realistic estimate to use was US$26 196 per case from birth to age one year, a
weighted average of the costs of the three types of neonatal HSV infection, as determined at the University of Alabama based on 93 treated cases from 1974 to 1989.(18) However, this value was varied through a sensitivity analysis (see article text). Using discounted potential earnings at time of delivery the estimated cost of maternal mortality was US$443 858 per death.(17) California’s low unemployment rate of 4% was thought to justify calculating the cost of maternal mortality, because employees would not necessarily be replaced.(17)

The costs of long-term disability were assumed equivalent to other cases of cerebral palsy and, including medical services, long term care, education and development services, care giver costs and productivity losses, were estimated to be US$782 035 per case until age 15 years.(19) The neurological effects of neonatal herpes include mental disability and seizures as seen with cerebral palsy, and while not specific for neonatal herpes, the long-term costs for cerebral palsy are thought to be a fair representation of the long-term costs of neonatal herpes sequelae. The cost benefit ratio is termed the saving/cost ratio and was calculated as the benefit for every US$1 spent in each programme.

The itemised costs menus for P2 and P3 and the itemised costs menu of the consequences are tabulated in Table A2 and A3. To implement ACOG guidelines for P2, an obstetrician would disseminate written information and two nurses would perform follow-up visits to ensure compliance. This intervention design was used because a study looking at vaccine protocol implementation found that 75-79% of physicians followed the protocols after pamphlet distribution and a follow-up visit.(20) Costs were included for the additional caesarean sections indicated by genital lesions (surgical complications,
longer hospital stay and increased maternal mortality rate). An epidemiologist and data clerk would be responsible for monitoring and feedback.

To implement screening and aciclovir prophylaxis (P3), two full time obstetricians would run seminars for Californian obstetricians covering type specific HSV diagnostics and the risk factors for neonatal herpes. Two nurses would provide follow-up and an epidemiologist, assisted by a data clerk, would co-ordinate monitoring and feedback. The cost of a point of care, HSV type specific diagnostic test was estimated to be US$70 per couple per pregnancy. Type specific tests have recently been developed and the CDC estimated that the cost of test materials would range from US$8 to US$40 per assay.(21) The POCKit test, type specific for HSV-2, currently retails for US$38.

The impact of different costs was considered in univariate sensitivity analysis (Table 1). In addition multivariate ‘uncertainty’ analysis was performed to take account of the combined uncertainty of parameters (detailed in Table 1). A distribution was defined for each parameter and the model was run 10 000 times, each time choosing a random sample of parameter values (Latin hypercube sampling) and reporting a 95% credibility interval around the estimated results. In a regression analysis of the outcome variable against the input value, it is possible to look at which variables have the largest influence on the outcome.