Final Report: HRSA-R40-MC- 06636-03: Maternal Sexual Infections and Adverse Child Outcomes

I. Introduction

A. Nature of the Research Problem: The overall goal of this project was to answer the research question: Do sexually associated infections during pregnancy result in an increased risk for mental retardation (MR), developmental delay (DD) and cerebral palsy (CP)? Sexually associated diseases included were: sexually transmitted diseases and infections associated with intercourse (including UTI, bacterial vaginosis and candidiasis). A major strength of this study was the large sample size available for analysis. Another notable strength was our ability to link mother and child files that incorporate medical diagnoses and prescription information as well as early childhood data. We also excluded children with known causes of MR/DD since we have diagnosis and treatment codes. By excluding these children, we were able to focus on the role of sexually associated diseases in otherwise unexplained cases of MR/DD and CP; further, we will avoid the dilution of measurable effects that would likely occur if known causes were kept in the analysis. Our use of prospectively collected data alleviates the potential problem of bias in reporting sexually associated infections in relation to childhood outcomes. The benefit of this research is to provide information about the impact of treated and untreated sexually associated conditions on fetal and infant outcomes. There is potential for prevention if sexually associated conditions are associated with adverse outcomes. Medicaid program recipients (including minority women and families with low incomes) will directly benefit from this project since the findings can be used to inform prevention of lifelong disabilities.

B. Purpose, scope and methods of the Investigation: The purpose of the study was to identify the association of genitourinary infections in pregnant women and the outcomes of MR and CP in their liveborn children. We examined the associations between maternal sexually associated illnesses and treatments during the prenatal period, and their association with MR and CP. This study was a secondary data analysis using prospectively collected data, although the study design was a retrospective cohort.

C. Nature of the findings: The findings of the study were the identification of maternal genitourinary infections as a potential risk factor for both MR and CP. This study is observational and a causal association could not be specified. The results are important to direct both basic science and clinical studies which would allow for testing for microbial infection during pregnancy, identification of pathways of exposure for infants, and testing of outcomes. Thus this study is primarily hypothesis generating. The epidemiologic findings are compelling and important and numerous publications have resulted. These publications and our presentation at a national meeting should contribute to the development of other studies.

II. Review of the Literature

Sexually Associated Infection and Neurologic Impairment: Aside from the well-known impact of congenital syphilis and TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) infections on cognitive function, there is a paucity of evidence regarding the potential role of maternal reproductive tract infection and MR/DD. The lack of knowledge was the primary rationale for this research proposal. However, there has been significant research investigating the role of infection and inflammation as risk factors for cerebral palsy. It is well established that preterm birth is a significant predictor

of CP and the risk of prematurity. There is also accumulating evidence that intrauterine infection and inflammation are independent predictors of CP. Generally, two approaches have been used to establish the link, one focusing on the documented presence of organisms in the amniotic fluid or chorioamnion and the other on the presence of inflammatory mediators. Both approaches support the premise that infection is a significant cause of CP.

An association between intrauterine infection/inflammation has been demonstrated for both term and pre-term (Grether & Nelson 1997; Wu & Colford 2000; Wu 2002, Schendel 2001; Nelson 2002) infants, though not necessarily for very preterm infants (<32 weeks of gestation) (Grether, Nelson, Walsh, Willloughby, & Redline 2003; Nelson, Grether, Dambrosia, et al 2003), implying that gestational age remains an important consideration when examining the impact of maternal infection on neurological morbidity in children.

Given the evidence that intrauterine infection/inflammation is a significant cause of CP, it seems reasonable to believe that a similar relationship may be present for MR/DD. This is especially plausible since approximately 30% of children with CP also have MR/DD (Evans, Evans & Alberman 1990; Rumeau-Rouquette, du Mazaubrun, Mlika, Dequae 1992).

Exposure to microbial toxins has the potential to impair fetal brain development apart from the impact of inflammation. Gram negative bacteria, such as *Neisseria gonorrheae*, are known to produce endotoxins (lipopolysaccharide) (Morse 1978; Gregg, Melly et al. 1980; Gregg, Melly et al. 1981), and women with bacterial vaginosis have been noted to have increased endotoxin levels in vaginal fluid (Sjoberg & Hakansson 1991). Lipopolysaccharide from *Chlamydia trachomatis* also has endotoxic activity (Heine, Wiesenfeld et al. 1998). Endotoxin exposure also appears to sensitize the developing brain, making it more susceptible to injury from future hypoxia (Redline, Wilson-Costello, Borawski, Fanaroff, Hack 2000). Many bacteria and other infectious agents produce exotoxins that act locally to achieve pathogenicity. One such organism is *Trichomonas vaginalis*, a protozoal parasite believed to produce hydrolytic enzymes with cytotoxic effects (Savoia & Matinotti 1989). *In vitro* evidence indicates that certain microbial exotoxins may have the potential to disrupt placental-fetal blood flow by inciting vasospasm (Hyde, Smotherman et al. 1989). It is logical that some SADs may produce toxins that are neurotoxic to the fetus, by interrupting placental perfusion or direct neuronal effects.

<u>Epidemiology of one suspect organism: Trichomonas vaginalis:</u> *Trichomonas vaginalis* is a protozoan that causes genital infections in humans. It is almost exclusively sexually transmitted, and is the most common non-viral sexually transmitted infection in the United States, causing over 7 million new infections in Americans each year (35). Two large epidemiologic studies have investigated the prevalence of *Trichomonas vaginalis* in pregnant American women. The Vaginal Infections and Prematurity study cultured almost 14,000 pregnant women for *T. vaginalis* and found that the infection was present in 12.6% participants (37). Again, the prevalence was substantially higher in African American women (22.8%) than white women (6.1%). The prevalence was also substantially elevated in women who were unmarried (16.9% versus 6.7%), those who had not attended college (13.3% versus 9.8% of college students), and those with low income (15.4% in women with income < $5,000 versus 5.6% in women with income <u>≥</u> $20,000). The Preterm Prediction Study was conducted in almost 3,000 pregnant women, and tested for *T. vaginalis* infection using the less sensitive wet mount method (rather than culture). Not surprisingly, it revealed a lower prevalence of *T. vaginalis*

infection (approximately 5% at either 24 or 28 weeks), but the prevalence was again higher in African American women (6.7%) than in women of other races (1.9%) (38).

T. vaginalis infection is asymptomatic or subclinical in 50% to 70% of cases (39) and it has traditionally received less public health emphasis than other prevalent sexually transmitted infections. For example, it is not on the CDC's list of nationally notifiable diseases (gonorrhea, Chlamydia, and syphilis), and screening for asymptomatic infection is not recommended. However, research in the past two decades has pointed to the potential for significant repercussions of trichomoniasis. Trichomoniasis has also been linked to adverse pregnancy outcomes. In the Vaginal Infections and Prematurity study, *T. vaginalis* infection was associated with a 30% relative increase in the odds of preterm birth and a similar increase in the risk of low birth weight (37). Minkoff et al found that women with trichomoniasis were significantly more likely to experience premature rupture of membranes (58). Paradoxically, a randomized trial of metronidazole treatment for asymptomatic *T. vaginalis* infection in pregnant women detected an increased risk of infection in treated women (60); the biologic mechanism behind the adverse treatment effect is not known.

The Role of Infection Timing: Since fetal development occurs in stages, it is expected that the timing of the insult will influence the risk, nature, and extent of the outcome. In the case of infectious diseases, it is difficult to ascertain what the critical gestational ages are, since asymptomatic infection and even clinical symptoms may precede diagnosis by days, weeks or even months (Cornette 2004). Previous research by the PI of this proposal identified the third trimester of diagnosis of UTI was significantly associated with MR/DD (McDermott et al. 2001). Intrauterine inflammation is associated with CP in both term and preterm infants, but not in very preterm infants. Fetal death is a common event very early in pregnancy and becomes quite rare as full term approaches (Kiely 1991).

Summary of Literature Reviewed:
The literature demonstrates that the fetus or infant may be at risk due to maternal GU infection in the following ways:

- Maternal GU infection can result in amniotic infection and inflammation;
- Maternal GU infection can result in fetal exposure to microbial toxins; and
- Maternal infection can be transmitted to the fetus or infant prior to or during birth.

These exposures may lead to the outcomes of MR, DD, or CP via the following mechanisms:

- An increased risk of premature rupture of membranes, prematurity, and low birth weight, which are themselves risk factors for the adverse outcomes of interest;
- An inflammatory response in the fetus that is associated with brain injury;
- Potential endotoxin and exotoxin effects on perfusion of the fetal brain that may lead to neurologic insults; and
- Possible other mediating effects that have not yet been elucidated.

To date the likely connection between maternal SAD and MR in children has not been established, though relationships with UTI have been identified. The evidence regarding associations with CP is better than for MR but still does not adequately answer the question of how SAD impact the risk of these outcomes. Studies of the association between SAD (including sexually transmitted infections as well as other GU infections) and MR and CP are needed. A recent review of the literature dealing with maternal infections and cognitive limitations in preterm children came to a similar conclusion: "We conclude that the relationship between antenatal infection and cognitive limitations

deserves much further attention by researchers interested in the prevention of this undesirable outcome [cognitive limitation] of prematurity" (Dammann, Kuban, Leviton 2002). The same reviewers proposed a conceptual model passing mainly from maternal infection through inflammation, then to direct neuronal injury or preterm birth. A recent article stresses the interplay between the direct effects of inflammation and the direct and sensitizing effects of microbial toxins via alterations of fetal-placental perfusion (Cornette 2004).

III. Study Design and Methods

A. Study Design: We used Medicaid maternal and child health and birth certificate data from 1996-2002 for over 152,000 maternal-child pairs in a retrospective cohort design.

B. Population Studied: We obtained de-identified South Carolina Medicaid billing records for pregnancies and deliveries that occurred from 1996 through 2002. Gestational age was obtained from birth certificate data. Births from 1996 through 2002 were studied, and children diagnosed with other conditions likely to cause MR or CP, were excluded.

C. Sample Selection: The infections evaluated were: trichomoniasis, Chlamydia/non-gonococcal urethritis, gonorrhea, vulvovaginal candidiasis, urinary tract infection, vaginitis, cervicitis, ascending reproductive tract infection (pelvic inflammatory disease or chorioamnionitis), and unspecified genitourinary infection. The genitourinary infections were identified on the basis of ICD-9 codes. Cases of cerebral palsy were identified on the basis of ICD-9 code 343 in the child's Medicaid files. Cases of mental retardation were identified based on ICD-9 codes 317, 318, or 319 in the Medicaid file, in addition to receipt of special education in South Carolina Department of Education records and receipt of services related to mental retardation from the South Carolina Department of Disabilities and Special Needs. We initially modeled diagnosis with mental retardation in any of the above data sources. Then we conducted additional analyses, limiting mental retardation cases to children with one of the following: diagnosis of 'trainable mentally handicapped' (TMH) or 'profoundly mentally disabled' (PMD) in Department of Education records receipt of services for mental retardation by the South Carolina Department of Disabilities and Special Needs (DDSN). Children identified in one or both of these sources comprise children with moderate to profound mental retardation, which has been definitively evaluated. Therefore, we consider this outcome to be 'definite, severe mental retardation,' in contrast to the 'any mental retardation' group that includes children with mild mental retardation and children diagnosed with MR in Medicaid data but not confirmed in school or DDSN records.

Multiple pregnancies in the same mother cannot be considered independent. To avoid problems with correlated observations, we limited the analysis to one pregnancy (the first) for each woman in the cohort.

D. Instruments Used: Since this was a retrospective cohort study using secondary data no instruments were used. Instead maternal genitourinary infections (the exposure) and MR and CP (the outcomes) were identified using ICD-9 codes in the Medicaid billing data.

E. Statistical Techniques Employed: We modeled the outcomes initially using logistic regression (with MR and CP as a dichotomous outcome) and infection any time during pregnancy as the primary independent variable. In each model, we controlled for maternal age and race, tobacco and alcohol use as reported on birth certificates,

maternal education (dichotomized as < 12 years or 12 or more years), year of birth, and child's sex birthweight, gestational age at delivery and whether the child was born small for gestational age (defined as weight less than the 10th percentile for gestational age at birth). Initially, we also controlled for a maternal diagnosis of hypertension or pre-eclampsia/eclampsia during pregnancy and for whether the pregnancy resulted in a singleton birth. We then tested the effect of excluding women with hypertension, pre-eclampsia /eclampsia, or multiple gestation. We examined the role of any genitourinary infection, and of specific infections (trichomoniasis, Chlamydia, gonorrhea, urinary tract infection, and candidiasis).

IV. Detailed Findings

Thirty-eight percent of the women were diagnosed with at least one GU infection. Three percent of the total cohort (5% of African American women) were diagnosed with trichomoniasis. Children of women with a genitourinary infection were 21% more likely to be diagnosed with mental retardation in at least one data source ($p < .001$). The association was slightly stronger (OR = 1.29, $p < .001$) when limiting the model to cases of 'definite, severe mental retardation' (TMH, PMD, or DDSN). The association between maternal infection and cerebral palsy was similar (OR = 1.27, $p = .007$). The association between infection and mental retardation and cerebral palsy was stronger for infections diagnosed in the first two trimesters ('early infection'). Early infection was associated with a 47% increase in the odds of definite severe mental retardation and a 45% increase in the odds of cerebral palsy. Infection was a significant risk factor for MR in both preterm and term infants, while the association between infection and cerebral palsy was significant only in preterm infants.

When specific infections were analyzed separately, urinary tract infection, Chlamydia, and trichomoniasis were all significantly associated with one or more outcome. Trichomoniasis was the only infection significantly associated with all three outcomes: any diagnosis of mental retardation, definite severe mental retardation and cerebral palsy.

Table 1: Risk of Genitourinary Infection and Mental Retardation and Cerebral Palsy

		Any MR Diagnosis		**Definite Severe MR**		**Cerebral Palsy**	
Model Specifics	**Infection Measure**	**OR**	**P**	**OR**	**P**	**OR**	**P**
All births	Any Infection	**1.21**	**<.001**	**1.29**	**<.001**	**1.27**	**.007**
All Births	First Two Trimesters	**1.29**	**<.001**	**1.47**	**< .001**	**1.45**	**<.001**
All Births, Controlling for SGA, GA, BW	First Two Trimesters	**1.22**	**<.001**	**1.38**	**<.001**	**1.28**	**.007**
All Births, Controlling for SGA, GA, BW	Third Trimester	1.05	.193	1.06	.534	1.14	.208
GA > 37; BW > 2500	Any Infection	**1.19**	**<.001**	**1.29**	**.006**	1.11	.336
GA > 37; BW > 2500	First two trimesters	**1.24**	**<.001**	**1.45**	**<.001**	1.16	.229
GA < 37 or BW < 2500	Any Infection	**1.20**	**<.001**	1.17	.248	**1.36**	**.016**
GA < 37 or BW < 2500	First Two	**1.35**	**<.001**	**1.37**	**.026**	**1.62**	**.0002**

	Trimesters						
All Pregnancies	**Trichomoniasis**	**1.30**	**<.001**	**1.96**	**<.001**	**1.74**	**.003**
	Chlamydia	1.18	.300	**2.72**	**<.001**	**2.07**	**.045**
	Urinary tract infection	**1.21**	**<.001**	1.18	.072	**1.25**	**.026**
	Gonorrhea	1.19	.205	0.59	.262	0.75	.560
	Candidiasis	0.99	.833	1.19	.348	0.91	.675

*Each model adjusts for maternal race, education, and age and for child's gender and year of birth.

In subsequent analyses, we limited the modeling to specific diagnoses of trichomoniasis, urinary tract infection, gonorrhea, or Chlamydia that occurred in the first two trimesters (before 27 weeks), since it was apparent that infections in the first two trimester were more important risk factors for mental retardation and cerebral palsy than third trimester infections. Early trichomoniasis and early urinary tract infection were the only two conditions associated with increased risk of all three outcomes. Infants of women with early trichomoniasis were more than one-third more likely to have any mental retardation diagnosis, and were approximately twice as likely to have severe mental retardation or cerebral palsy (Table 2). We further tested the effect of limiting the analysis to infants born preterm or with low birth weight (because these infants are at higher risk of MR and CP), and found that the impact of early trichomoniasis was even stronger in this group. The odds of definite severe MR and of CP were more than doubled in preterm/low birth weight children of women with trichomoniasis in the first two trimesters.

Table 2. Specific Infections in the First Two Trimesters and Mental Retardation or Cerebral Palsy

	Any Gestational Age or Birth Weight						**GA < 37 or BW < 2500**					
	Any MR		**Severe MR**		**Any CP**		**Any MR**		**Severe MR**		**Any CP**	
	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P
Early Trichomoniasis	**1.36**	**.0004**	**2.06**	**.0002**	**1.91**	**.004**	**1.58**	**.001**	**2.46**	**.003**	**2.26**	**.004**
Early Chlamydia	1.01	.97	2.18	.09	2.26	.11	0.61	.24	1.47	.60	1.56	.54
Early Gonorrhea	1.21	.29	0.47	.029	0.00	.96	1.41	.24	0.58	.59	0.00	.97
Early UTI	**1.24**	**<.0001**	**1.28**	**.02**	**1.29**	**.04**	**1.19**	**.02**	1.40	.06	**1.42**	**.03**

*Controlling for maternal age, race, education, alcohol and tobacco use, child's gender, and year of birth.

V. Discussion and Interpretation of Findings

A. Conclusions:

a. Trichomoniasis and Mental Retardation: We believe this is the first study to report an association between maternal trichomoniasis and mental retardation in children. This association was robust and strongly statistically significant. It was particularly strong for more severe/definitive classifications of MR. We believe this pattern makes the results even more compelling.

Children with TMH/PMH, by definition, have moderate to severe MR (IQ < 55). All children with confirmed MR are eligible for DDSN services, but those who are

enrolled in these services tend to be those with more severe disabilities. Both school based services for TMH or PMH and receipt of services from DDSN require a complete battery of individual testing, and therefore represent rigorous case definitions of MR. The fact that trichomoniasis was associated with a two-fold increase in the odds of these outcomes is strong evidence of a true association. The other characteristics associated with increased risk of MR (increasing maternal age, minority race, male gender, low maternal education, small for gestational age, and lower gestational age and birth weight) are consistent with known risk factors for MR, which lends further credence to the study's key findings.

b. Maternal Genitourinary Infections and Cerebral Palsy: Genitourinary infections in pregnant women were significantly associated with increased risk of CP in children. The association was especially strong for infections occurring in the first two trimesters of pregnancy, and in preterm/low birth weight children. Adjusting for birth weight, gestational age, and small for gestational age reduced but did not eliminate the association between infection and CP. The findings also remained when limiting 'cases' of CP to children who were diagnosed by more than one health care provider. Trichomoniasis, Chlamydia and UTI appeared to be associated with CP while gonorrhea and candidiasis did not. The odds ratios for trichomoniasis and Chlamydia ranged from 1.55 to 2.65; however, the associations were not always statistically significant, likely because of the relatively small number of women diagnosed with each infection. We believe this is the first study to identify trichomoniasis and Chlamydia as potential risk factors for CP.

B. Explanation of Study Limitations: The most significant limitation of this study is our reliance upon billing data to identify maternal infections. We cannot be certain that all the women diagnosed with a genitourinary infection were diagnosed accurately. It is also likely that some women without diagnosed GU infection actually had an infection, since many GU infections are asymptomatic or subclinical in approximately 50% of infected women. We do not know whether the association between diagnosed infections and the outcomes of MR and CP extends to women with undiagnosed/subclinical infections.

Another limitation is that unmeasured confounders could have affected the results; that is, women with infections may have been more likely to have other, unmeasured risk factors that increase the risk of MR or CP. It seems unlikely, though, that unmeasured confounding could account for the very strong association detected in this study.

Finally our cohort was limited to women who were enrolled in the South Carolina Medicaid program. Medicaid primarily insures low income women, with an income eligibility limit of 185% of poverty for pregnant women in South Carolina. Approximately 4% of children in the cohort were diagnosed with MR, which is higher than expected for the general population (1 to 2%) (McDermott et al, 2007), but it is not surprising for the prevalence to be greater in a low income population (Durkin et al, 2008; Andrews et al 1995). Though low income children are more likely to be diagnosed with MR, we do not believe there is reason to doubt that the association between MR and GU infections would be generalizable to higher income children as well. However, additional study with a wider range of socioeconomic status is probably warranted.

Comparison with findings of other studies: It is established that mild MR typically does not have a known biological cause, and is much more common in children whose parents have low income and/or little education; therefore mild MR is believed to include a substantial proportion of children with poor cognitive performance due to social deprivation, or to being at the "low end of the bell curve" of intelligence (Durkin et al, 2008; Stromme and Magnus, 2000). Inclusion of these children in the analysis would be expected to result in non-differential outcome misclassification and a reduction in the observed association with infections. More severe cases of MR, on the other hand, are frequently due to biologic insults, and are relatively evenly distributed by social class. Misclassification of this outcome is unlikely, which permits more accurate measurement of the effect of GU infections. We are only aware of one published study linking trichomoniasis with neurological outcomes. Stelmach et al (2004) found that hypoxic-ischemic encephalopathy occurred in 4 of 18 (22.2%) of women with trichomoniasis, compared to 23 of 372 (6.2%) of women without trichomoniasis; however, trichomoniasis was not independently associated with "developmental disorders" (including CP) at two years of age. We have identified no studies demonstrating an association between *Chlamydia trachomatis* infection and CP.

C. Possible application to MCH health care delivery situations: With respect to possible mechanisms for an association between maternal infections and MR, it is noteworthy that the association was independent of birth weight, gestational age, and small for gestational age. We believe the most likely mechanism is neurological insult to the developing brain due to inflammation. Trichomoniasis has been shown to produce a significant intra-vaginal and systemic immune response (Simhan et al, 2007; Anderson et al 2007) and though *Trichomonas vaginalis* is not generally thought to invade the placenta, amniotic fluid, or fetus, it has been linked to clinical pelvic inflammatory disease and histologic endometritis in non-pregnant women (Moodley et al, 2002; Paisarntantiwong et al, 1995; Cherpees et al, 2006). It is unknown whether *T. vaginalis* may cause PID directly, or facilitates ascending infection by other microbes (for example, by decreasing the integrity of the cervical mucus plug)(Moodley et al, 2002). Additional research investigating the effects of trichomonal infection on the intrauterine environment are needed to illuminate possible mechanisms whereby trichomoniasis may impact fetal brain development.

We did not identify significant differences in the risk of MR based on treatment for trichomoniasis. This analysis utilized outpatient pharmacy billing data to identify women who were treated within 14 days of a diagnosis of trichomoniasis. It is possible that some "untreated" women may have received metronidazole purchased out of pocket or by another payer. Additional research using more inclusive data sources is needed to evaluate the effects of treatment with oral metronidazole on the risk of MR. A recent randomized controlled trial found that women treated with oral metronidazole for asymptomatic trichomoniasis had increased risk of preterm delivery (Klebanoff et al, 2001). To our knowledge the impact of treatment on long term child outcomes has not been investigated. Even if metronidazole treatment during pregnancy does not reduce the risk of MR, this study has important public health implications. Because trichomoniasis has traditionally considered a benign, self limited condition, public health efforts to combat the infection have generally been lacking. More recently, trichomoniasis has emerged as a risk factor for HIV transmission, particularly in low income nations where HIV is highly prevalent.[21] Despite this development, there continues to be less emphasis on trichomoniasis

prevention than on other sexually transmitted infections such as syphilis, gonorrhea, and chlamydia.[15] Behavioral interventions (promotion of abstinence, monogamy, and/or condom use) and routine screening of the reproductive age population have the potential to reduce the prevalence of trichomoniasis in pregnant women. If trichomoniasis is in fact a risk factor for adverse child outcomes, such public health efforts may be warranted.

D. Policy Implications: In spite of the limitations, this study provides substantial evidence that maternal GU infection is associated with increased risk of MR and CP in children. These finding has particular clinical relevance if antimicrobial treatment is found to mitigate the effects of infection. A recent randomized trial found that treatment of asymptomatic trichomoniasis during pregnancy was paradoxically associated with an increased risk of preterm birth, but did not evaluate long term child outcomes like CP.[26] Our preliminary analysis did not find a significant protective or harmful effect of treatment for trichomoniasis or UTI within 30 days of the initial diagnosis. However, these findings must be viewed with caution since the effect of filling a prescription for appropriate antimicrobial therapy may be confounded by a number of issues including the severity of symptoms, method and precision of the diagnosis (presumptive versus confirmed diagnosis), direct provision of treatment in a hospital, emergency room, or physician's, length of time between the initial infection and the diagnosis, and the woman's general level of self-care and adherence to medical advice.
Even if treatment of pregnant women does not ameliorate the effects of infection on the fetal brain, efforts to reduce the prevalence of GU infections in the general population may indirectly reduce rates of CP by reducing the number of pregnant women who acquire infections. Public health approaches like screening for and treating asymptomatic sexually transmitted infections and risk behavior modification may have the potential to substantially reduce rates of mental retardation and cerebral palsy over time.

E. Suggestions for Further Research: Additional research using clinical records rather than billing data may provide further insight into the effects of antimicrobial treatment on the long term outcome of child MR and CP. In addition, basic science research in humans and animals is indicated to identify the mechanism for these adverse outcomes.

VI. List of Products

Refereed Papers

1. Mann JR, McDermott S, Bao H, Bersabe A. (2009) Maternal genitourinary infection and risk of cerebral palsy. Developmental Medicine and Child Neurology, 51: 282- 288.

2. Mann, JR, McDermott S, Gregg A, Gill TJ. (2009). Maternal genitourinary infection and small for gestational age. American Journal of Perinatology. In press.

3. Mann, J., McDermott, S., Zhou, L., Barnes, T., Hardin, J.(2009). Treatment of trichomoniasis in pregnancy and preterm birth: an observational study. Journal of Women's Health and Gender-based Medicine. In press.

In Review

Mann, J., Zhou, L., McDermott, S., Barnes, T. 2008. Trichomoniasis in Pregnancy and Mental Retardation in Children. American Journal of Epidemiology, In review.

Presentation at National Meeting

Mann JR, McDermott S, Hardin J, Bao H. *Maternal Trichomoniasis is Associated with Increased Risk of Mental Retardation.* Presented at the Gatlinburg Conference on Reseach & Theory in Intellectual & Developmental Disabilities. New Orleans, LA. March 21, 2009.