16
Infectious diseases in preconceptional care

Dean V. Coonrod

Consensus is developing that acting prior to pregnancy for a number of disease states could improve reproductive outcomes; infectious diseases are no exception. The means by which infections have an impact on reproductive outcomes are almost as varied as the diseases themselves. For example, infections in the preconceptional period can affect both male and female fertility factors, leading to decreased fecundity or actual infertility. They can also affect early pregnancy in an 'all or nothing' fashion if they cause spontaneous abortion. Congenital infection of varying degrees of severity also can occur, in many cases with minimal maternal illness. Infections can affect the mother, leading to either maternal or obstetric complications with eventual preterm delivery or maternal death followed by death of the fetus.

Infections may be acquired either prior to or during pregnancy; both can affect neonatal outcomes. An additional possibility is that the fetus may be free of disease owing to the barrier imposed by the placenta, but acquire infection at birth through vertical transmission. Infections can affect the vulnerable infant especially in the early neonatal period due to an immature immune system. Preconceptional interventions to reduce the impact of infections include preventing infection through immunization, safer sex initiatives and needle exchange programs; reducing the quantity and location of an infectious agent, such as prevention of diarrheal disease through improved sanitation; and, finally, reducing the effects of an infection on the host, especially in chronic infections and/or repeated episodes of acute infections leading to immunocompromise in the host.

Considering that any infection is the result of interactions between the host, the agent and the environment, preconceptional interventions can occur in any of these areas to reduce the impact of an infectious disease on reproductive outcomes. Initiatives such as changing the environment through interventions aimed at reducing poverty or promotion of breastfeeding can have a positive impact on infectious disease outcomes. Finally, infectious diseases are diverse in their impacts and in the manner in which interventions can occur, all types of infectious agents with preconceptional implications have been identified including viruses, bacteria and parasites; however, prion-caused infectious diseases have yet to be investigated fully.

METHODS

Burden of disease was used to prioritize those diseases selected for review. Diseases were divided into those affecting women of reproductive age, pregnant women and infants. For women of reproductive age, infectious conditions including HIV/AIDS, tuberculosis and maternal sepsis are significant contributors[1]. In Africa, in particular, HIV/AIDS, TB and malaria along with 'other infectious and parasitic diseases' make up about one-third

of the disease burden[1]. Meanwhile, for childhood deaths, those occurring in the neonatal period (days 0–28 of life) comprise 37% of all deaths for children aged 0–5 years; 25% of these neonatal deaths are a result of neonatal infections, 3.4% neonatal tetanus and 2.6% diarrheal disease. Other causes of neonatal deaths are those due to prematurity and low birth weight (31%) and congenital anomalies (6.7%) which can have an infectious etiology component[1]. Finally, many of the remaining deaths before age 5 (postneonatal) are communicable including acute respiratory infection (17%), diarrheal disease (16%), malaria (7%), measles (4%), HIV/AIDS (2%) and other infections and parasitic diseases (9%). Together, these infectious diseases account for about 55% of deaths in 0–5 year olds[1]. Under these circumstances, the prime focus of this chapter includes HIV/AIDS (see also Chapter 15), tuberculosis (see also Chapter 14), malaria, neonatal acute respiratory infection, neonatal diarrheal disease, measles, neonatal tetanus, neonatal infections (sepsis and meningitis), infection-related preterm birth, low birth weight and congenital anomalies/infections. Finally, Chlamydia, gonorrhea and hepatitis (B and C) receive specific attention in the category of 'other infectious disease'. Each is considered separately.

HIV/AIDS

HIV/AIDS is the leading cause of infectious complications and deaths worldwide. In 2008, 33.4 million people were living with HIV, including 2.1 million children (most secondary to maternal–child transmission), with 480,000 incident cases in children. Also in 2008, there were 2 million deaths, with 280,000 deaths occurring in children[2]. HIV/AIDS is a significant causal factor in maternal and infant deaths[2,3]. In well resourced countries, however, neither consequence needs to be frequent[4], as effective antiretroviral treatment is available for some women and for all during pregnancy[5]. There are specific recommendations to screen preconceptionally those with risk factors and, in countries where many incident cases have no risk factors, to offer screening to those with no risk factors[6,7].

Screening may be initiated voluntarily or via provider initiated testing with an opt-out approach being recommended (*a patient be must given the opportunity to specifically request that an HIV test is <u>not</u> performed*)[7,8]. Knowing a potential mother's HIV status in the preconceptional period is important since treatment ideally should begin early in pregnancy. (Current WHO recommendations are to begin antiretroviral therapy at around 14 weeks (in the second trimester), as transplacental transmission to the fetus can occur this early (recommended for women who are HIV positive and early in the disease process – normal CD4 count and no HIV associated illness)[5].) Furthermore, for women who are symptomatic or with low CD4 counts, antiretroviral therapy is recommended throughout pregnancy[5].

Other components of preconceptional care include primary prevention of the disease, such as public health campaigns to decrease transmission including condom use, male circumcision, needle exchange programs or any combination of these initiatives[9,10]. For couples where one partner is HIV positive, a reproductive life plan should be developed[11]. One recommended question for this is, 'What are your thoughts about having children now that you are HIV-infected?'[11] Information provided to the patient and her partner (if available) should include the fact that pregnancy does not alter the course of HIV infection for an infected woman and the distinct and clear risk of maternal–child transmission; information on the availability of antiretroviral therapy during pregnancy and at the time of delivery; and the possible recommendation for cesarean delivery to prevent transmission[11]. For couples wishing to defer childbearing, appropriate contraception must be offered.

Barrier contraception should be recommended for all couples – even those in which both are HIV infected, as transmission of different HIV types/subtypes is possible[11]. An antiretroviral containing microbiocide vaginal gel may prevent the primary acquisition of HIV, a recent advance which should be of benefit for discordant couples[12,13].

For those wishing to pursue pregnancy, on the other hand, prevention of transmission at conception through sperm washing (male infected and female uninfected) or donor insemination (male uninfected and female infected) is recommended[14]. Timing of conception is best done in the setting of a maximally suppressed[15] or undetectable[11] viral load. Medications taken by HIV infected women considering pregnancy should be reviewed and altered as required[11]. For example, efavirenz is contraindicated in the first trimester owing to the risk of neural tube defects[11,15].

Other issues to be discussed include the importance of prenatal care, that pregnancy does not appear to alter the course of the HIV disease[11], and the increased risk of maternal death (much of the maternal mortality due to HIV/AIDS is considered to be as a result of obstetric causes[16,17]). Of interest, fertility may be impaired in HIV infected women, due to tubal factor[14,18], such that advanced reproductive therapy may be needed, and is available in certain settings[14]. Other recommendations for preconceptional care include being in good health, folic acid supplementation as recommended in other sections of this text as well as other general considerations for preconceptional health; this dictum is applicable to all conditions considered in this chapter[15].

TUBERCULOSIS

A total of 700,000 women die each year globally as a result of tuberculosis (TB)[19]. In areas with a high prevalence of TB, women of reproductive age bear the highest burden of suffering[19]. If the woman does not have TB induced infertility and if she is able to become pregnant, the consequences of TB in pregnancy include fetal death, low birth weight, growth restriction, premature birth and, rarely, congenital tuberculosis[19,20]. These outcomes are more likely in women co-infected with HIV[19].

The current worldwide strategy for TB prevention aims to detect TB and provide treatment using DOTS (directly observed therapy, short course)[21]. Other important components of the 'DOTS' strategy include political/community commitment to addressing TB; quality diagnostic procedures (positive sputum smears being the most broadly applied diagnostic technique, with other forms also being detected, i.e. extrapulmonary, smear negative and resistant TB); widespread availability of medications; and assessment of program outcomes[21]. In some developed countries, strategies include the detection of TB in the latent form to prevent progression to active TB[22]. Finally, the Bacille Calmette-Guérin (BCG) vaccine is also available and used, in many countries with a high burden of TB, soon after birth to prevent early childhood TB; this is most effective in infants who are HIV negative[23]. That HIV positive infants receiving the BCG vaccine can develop disseminated BCG has led to recommendations that the vaccine be avoided in HIV positive children[24]. This poses a challenge in areas with high rates of HIV and poor availability of the special diagnostic tests needed to diagnose HIV in newborns[24,25]. The vaccine is not effective for the prevention of adult pulmonary disease[24] and is also contraindicated in pregnancy[23]. Currently, WHO recommends the vaccine for adults exposed to multidrug resistant TB[23].

Diagnosis and treatment of TB prior to pregnancy would have the advantage of potentially avoiding risks of treatment with drugs which could be harmful to the fetus such as streptomycin, fluoroquinolones, or those with few safety data in pregnancy such as pyrazinamide, although most first-line drugs are considered

safe in pregnancy[20]. Finally, if latent tuberculosis infection (LTBI) is to be the target of treatment, as treatment is often withheld during pregnancy based on reasonable concerns of a higher risk of isoniazid induced hepatotoxicity, it may be reasonable to treat in the preconceptional period[6].

MALARIA

Malaria is very common globally, with about 50 million pregnancies occurring annually in malaria endemic areas[26]. Malaria is a mosquito-borne infectious disease caused by a eukaryotic protist of the genus *Plasmodium*. Five species of the *Plasmodium* parasite infect humans; the most serious forms of the disease are caused by *Plasmodium falciparum*. Malaria caused by *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* results in milder disease in humans and are not generally fatal.

Malaria is naturally transmitted by the bite of a female *Anopheles* mosquito. When a mosquito bites an infected person, a small amount of blood is taken, which contains malaria parasites. These develop within the mosquito, and about 1 week later, when the mosquito takes its next blood meal, the parasites are injected with the mosquito's saliva into the person being bitten. After a period of between 2 weeks and several months (occasionally years) spent in the liver, the malaria parasites start to multiply within red blood cells, causing symptoms that include fever and headache. In severe cases the disease worsens leading to hallucinations, coma and death.

Direct complications of malarial infection in pregnancy include miscarriage, growth restriction, low birth weight, premature delivery and maternal anemia[27]. Malarial deaths (2.7 million per year) are concentrated in sub-Saharan Africa where children under 5 account for 75% of global deaths[27]. Pregnancy poses some increased risk of infection, as there is some evidence of pregnancy representing increased attractiveness to the mosquito carrier[28], as well as the pregnant woman being infected by the parasite[27].

Women at highest risk of infection are those with a first pregnancy, in the second trimester, HIV infected or those with no immunity to the infection[27]. While many pregnant women are asymptomatic, there is also a higher risk in pregnancy of anemia, cerebral edema, pulmonary edema and hypoglycemia[29]. Congenital malaria is defined as infection of the fetus or newborn. Risks of congenital malaria depend on the immune status of the mother – risk is highest in those with low levels of immunity[27]. Immunity waxes and wanes in pregnancy depending on antibody levels which may in turn be mediated by continued exposure to the parasite (for example, women from endemic areas moving to non-endemic areas may be at higher risk due to reduced exposure to the parasite)[27].

Acquisition by the fetus occurs through transplacental spread in most cases, although up to 40–50% of newborn cases involve either a different genotype or no evidence of placental infection in some studies[27]. *Plasmodium falciparum* is the protozoa which poses the greatest risk for the mother and fetus, and is the only species involved in placental infection[27]. Chloroquine administered on a weekly basis has been used as a preventive mechanism (with evidence that it prevents anemia and low birth weight) and is especially effective if given early in pregnancy (first and second trimester)[27]. However, resistance and compliance with the regimen are problematic, and its use is limited[27]. Intermittent preventive treatment in pregnancy (IPTp) has been recommended more recently for areas of high transmission – two courses of treatment 1 month apart in the second trimester with sulfadoxine-pyrimethamine[30], with evidence that this treatment improves hemoglobin levels and birth weight[27]. Insecticide-treated bed nets are another preventive strategy along with recommendations for IPTp[30].

Finally, effective case management is recommended in areas of low and high transmission[30]. In women with co-existing HIV infection, the risks of malaria infection for the mother and fetus are more severe in part probably as a result of immune dysfunction[27,29]. More frequent IPTp may be recommended in these women as well as preventive measures to avoid exposure to the mosquito[27]. Trimethoprim-sulfa (cotrimoxazole), which is used for prevention/treatment of opportunistic infections in HIV, is efficacious against malaria and there is some evidence that the protease inhibitors may also inhibit malaria parasites[27].

For pregnant travelers who are non-immune (or usually reside in non-endemic areas), travel to endemic areas should be avoided. If travel is necessary, prevention strategies (bed nets and *N*,*N*-diethyl-*meta*-toluamide (DEET) containing insecticides which are safe in pregnancy) and chemoprophylaxis are recommended. In these circumstances, chloroquine only should be administered in areas were resistance is not documented or combination treatment with various regimens depending on resistance and the presence/absence of *P. falciparum* in the area (see the CDC's 'Yellow Book' for the most current recommendations http://wwwnc.cdc.gov/travel/content/yellowbook/home-2010.aspx)[31].

Prophylaxis with IPTp prevents complications in pregnancy; however, this has not been recommended in the first trimester, and there are no recommendations for prophylaxis in the preconceptional period other than for those traveling from non-endemic to endemic areas[30].

ACUTE RESPIRATORY INFECTIONS

Acute respiratory conditions including pneumonia and pertussis, led to an estimated 1.8 million deaths of children 0–5 years old in 2008[32]. Pneumonia is the leading cause of death from acute respiratory conditions, accounting for 1.5 million of the 1.8 million fatalities (with 386,000 occurring in neonates)[32]. Most recommendations to deal with this disease target children directly, and include early recognition and treatment, promotion of exclusive breastfeeding (itself an interconception intervention[33]) and vaccination against pneumococcal pneumonia, measles, *Haemophilus influenza* type b (Hib) and pertussis[34]. Vaccinations are promoted since pneumonia can be caused either directly by the organism targeted by the vaccine (the pneumococcal or Hib vaccines) or by a complication of vaccine preventable conditions such pertussis, measles (the latter is considered in a separate section) and influenza (although this particular vaccine is not a recommendation of the UNICEF strategy for pneumonia). Accordingly, vaccination of women for these conditions in the preconceptional period might prevent some of the deaths arising from the conditions through passive immunization or decreasing household transmission, especially to neonates.

In one study, administration of pneumococcal vaccine in pregnancy increased maternal, breast milk and infant antibody levels[35]. However, another study demonstrated only modest increases in antibody levels in mothers when the vaccine was administered in the preconceptional period and no significant increases in neonatal antibody levels[36]. This same study did provide data, however, to suggest that the *Haemophilus influenza* type b vaccine, when administered to women before pregnancy, led to protective antibody levels at birth, and in the immediate postnatal period to higher antibody levels in the neonate[36]. Unfortunately, these studies[35,36] are limited in that they did not examine whether vaccination in pregnancy or in the preconceptional period prevented subsequent disease in infants.

Pertussis is a condition which leads to chronic cough. Between 300,000 and 600,000 cases are estimated to occur in the US each year (in adults); worldwide in 2003 there were 17.6 million recorded cases[37,38]. As the number

of recorded cases invariably underestimates the total number because of underreporting, it is likely that the prevalence of this condition is even higher than the numbers provided suggest. More than 90% of the annually estimated 279,000 deaths occur in developing countries[38]. Because infants under 12 months are especially susceptible, a strategy of early immunization and passive immunization of the newborn has been proposed[39]. Currently CDC recommends giving the vaccine to the mother in the immediate postpartum period to avoid early onset disease in the newborn[40]. As the vaccine is not a live vaccine, it can be administered during pregnancy; this practice is often avoided because of limited safety data. A strategy of giving the vaccine during the preconceptional period has the advantage of avoiding these concerns and ensuring that the mother has fully developed an immune response before delivery[41].

Influenza is estimated to cause 250,000–500,000 deaths a year worldwide in its seasonal form[42]. In the US, a pandemic form H1N1 virus was estimated to have affected 61 million individuals and caused 12,000 deaths between April 2009 and April 2010[43]. H1N1 was in a pandemic form during its worldwide circulation in 2009 and 2010; it was recently declared to be postpandemic by WHO, although is it predicted to remain in circulation as one of the seasonal forms of the virus[44]. Vaccination against the influenza virus, including H1N1, is an effective prevention strategy; however, revaccination is required on an annual basis due to changes in the virus each year[45]. In the US, annual flu vaccination is recommended for all individuals over 6 months of age[45]. The inactivated form (not the live virus form) is recommended for women during pregnancy as it is documented to be safe[45]. Vaccination prior to pregnancy with either form of the vaccine is recommended for women who may be pregnant during the flu season[46]. These recommendations are put forward to prevent maternal complications during pregnancy and newborn illness, both of which can be severe[45].

Diphtheria is another preventable (by vaccination) acute respiratory infection[46]. It is distinct from other respiratory conditions in that its classic manifestations occur in the upper airway (pharynx, nasal mucosa and palate) in the formation of a gray membrane[46], a rare but potentially fatal circumstance in which death occurs via airway obstruction[46]. Routine vaccination in childhood prevents this condition; however, it is unknown whether vaccination of women of childbearing age would result in lower rates of neonatal disease before routine vaccination of children can be accomplished. Diphtheria is part of the Tdap vaccine recommended for adults as a preconceptional strategy to prevent pertussis in the US, and is part of the Td vaccine recommended as a booster dose in adults to maintain lifelong immunity[47].

DIARRHEAL DISEASE

It is estimated that 1.5 million deaths occur in children from some form of diarrhea each year; many of these are concentrated in South Asia and Africa[48]. Of the many recommended prevention strategies, one intervention, that is, face-to-face counseling to promote exclusive breastfeeding, is part of the worldwide strategy to prevent the disease[48]. Breastfeeding is particularly recommended because it is associated with a 6-fold decreased risk of death from diarrheal disease in the first months of life[49]. Also included in the global strategy are the promotion of the administration of measles (see section below) and rotavirus vaccines in children. Because the rotavirus vaccine currently has a maximum age limit for administration of 32 months, its use as a provider of passive immunity in mothers preconceptionally has not been tested. Although not part of the global diarrheal disease strategy, a cholera vaccine exists for endemic areas, and pregnant women have been prioritized for vaccination[47].

Childhood undernutrition is another contributor to mortality in diarrheal disease, as there is growing evidence that at least some underweight may have its origin in preterm birth and growth restriction (see below). Under these circumstances, preconceptional interventions may assist indirectly in preventing diarrheal disease[50]. Interestingly, diarrhea in women of childbearing age has been shown in one study to be a risk factor for neural tube defects, most likely due to decreased absorption of folic acid[51]. Here also, prevention efforts that secondarily benefit adults may have preconceptional health benefits.

MEASLES

Measles is a common disease worldwide and is most easily recognized by a maculopapular rash preceded by a high fever, coryza, cough and conjunctivitis[52]. Complications include pneumonia and diarrhea, both of which are implicated in mortality associated with this condition. Those most vulnerable live in developing countries and are young children with undernutrition, vitamin A deficiency and immune dysfunction such as HIV[52]. Other complications include otitis media and post-measles encephalitis[52]. Onset in pregnancy has been associated with miscarriage, low birth weight and preterm birth[52].

Measles containing vaccines (MCVs) most commonly used are either MMR (mumps, measles, rubella) or MMRV (mumps, measles, rubella, varicella); all are live virus vaccines which should be avoided in pregnancy[53]. Use of these combined vaccines is recommended in countries which can achieve high levels (>80%) of population vaccine coverage[47]. Measles containing vaccines are part of childhood recommended vaccine programs, and long-term immunity has been demonstrated[53]. Adults traveling to areas with a measles outbreak and health care workers have been prioritized to obtain booster doses[52]. The contribution of a similar program for women preconceptionally has not been assessed as a strategy to prevent pregnancy complications or for protection of the newborn (although the latter is possible given that IgG antibody, which crosses the placenta, is produced as a result of vaccination; however, in titers that are lower than natural infection[54]). It should be noted, however, that adults who cannot demonstrate evidence of previous vaccination are recommended to receive a two dose series[52].

TETANUS

Tetanus is an infection of wounds caused by the inoculation with *Clostridium tetani* spores which are ubiquitous in the soil[55]. When such wounds are oxygen poor, this leads to the production of a neurotoxin and tetanus symptoms: lockjaw (trismus) and muscle rigidity, including rigidity of the musculature required for respiratory function[55]. Neonatal tetanus is caused by acquisition of the spores through the umbilical stump; when disease develops, the fatality rate is very high[55,56]. Such cases are associated with insufficient or total absence of cleanliness at delivery and are more likely to occur in areas with low coverage of tetanus toxoid[55,56].

The 59,000 infants estimated to have died worldwide of neonatal tetanus in the last reported year represent a substantial reduction (92%) from the late 1980s[56]. Major contributors to this decline have been efforts to improve the cleanliness of instruments to cut the umbilical cord at birth and improved tetanus toxoid coverage[57]. A recent meta-analysis estimated that a strategy of two injections of tetanus toxoid in reproductive age women, including pregnant women, would reduce neonatal tetanus mortality by 94%[58]. Protection from tetanus is best achieved through immunization in childhood followed by periodic booster dosing in adolescence and adulthood[47]. Areas with high rates of maternal/neonatal

tetanus are recommended to undertake special efforts to ensure coverage of women of childbearing age and who are pregnant[57].

NEONATAL INFECTIONS

Neonatal infections, aside from those mentioned above, include neonatal sepsis and neonatal meningitis. Many of the efforts aimed at reducing the neonatal sepsis disease burden are postnatal interventions and early detection and treatment[59]. In certain settings, this incorporates home-based treatment[60]. No specific preconceptional interventions for this condition are available, but some diseases causing sepsis might benefit from preconceptional healthcare.

One cause of neonatal sepsis, group B streptococcus infection, is best prevented with specific treatment in pregnancy and not in the preconceptional period[2]. Higher risk of mortality and morbidity from sepsis is present when births are preterm, following preterm rupture of membranes, maternal chorioamnionitis and low birth weight[61]. Preconceptional interventions which prevent these conditions would therefore have indirect effects to prevent neonatal sepsis.

Most cases of neonatal meningitis are caused by similar organisms to those that cause neonatal sepsis; these include Gram negative bacteria such as *Escherichia coli* and *Klebsiella* sp, and group B streptococcus (with Gram negative bacteria being a more common etiology in developing countries)[63]. In the US, the rate of bacterial meningitis is 0.3 per 1000 live births and 0.02–0.5 per 1000 herpes simplex meningitis (see Congenital infections section below)[62].

Listeria monocytogenes is the third most common pathogen identified in cases of neonatal meningitis in the US. Current preconception recommendations include the avoidance of foods prone to develop listeria, including unpasteurized dairy products and to cook certain foods to steaming levels[6]. Its inclusion as a preconception recommendation is due to its association with early pregnancy loss and severe maternal illness early in pregnancy based primarily on expert opinion[6]. This pathogen is also association with preterm labor, chorioamnionitis, stillbirth and neonatal sepsis of early onset[63].

Neisseria meningitides (meningococcus) causes most meningitis, with infants aged 3–12 months being the most vulnerable in endemic areas[64]. The greatest number of cases occur as epidemic or endemic forms in sub-Saharan Africa[64]. Passive immunization of neonates occurs from maternal antibodies[64]. Furthermore, IgA in the breast milk of vaccinated mothers may be protective[65]. As a consequence, some authors suggest that maternal immunization be 'considered'[65], although it is not known whether a strategy of preconceptional immunization would be beneficial.

PRETERM BIRTH/LOW BIRTH WEIGHT

This section discusses infection-related preterm birth/low birth weight. As much low birth weight is related to preterm delivery, discussion does not consider term low birth weight due to growth restriction related to maternal smoking, multiple births, chronic medical conditions or hypertensive disorders, all of which are beyond the scope of this chapter.

A small number of those with term low birth weight that might be infection related are owing to congenital infection and are considered below. It has long been recognized that a proportion of preterm births are infection related, as they are preceded by clinical chorioamnionitis, occurring in association with either preterm labor or preterm premature rupture of membranes[66]. Further reinforcing this concept are studies which have shown that a significant proportion of these births are as a result of subclinical infection[67]. Finally, a

number of observational studies show associations between preterm births and a variety of infectious conditions such as asymptomatic bacteriuria, bacterial vaginosis, periorodontal disease and chlamydial infection (see below).

Asymptomatic bacteriuria in pregnancy is associated with significant maternal morbidity, as it leads to acute pyelonephritis. Based on a number of randomized trials, screening and treatment of this condition has been recommended as a means of preventing both maternal illness in pregnancy and low birth weight[68]. However, to date, no evidence supports screening in the pre-pregnancy period, and it is not currently recommended[2]. Similarly, following observational studies which demonstrated associations, randomized trials have been conducted of treatment in pregnancy for infections, such as bacterial vaginosis, trichomoniasis and periodontal disease. Results of these trials have been disappointing, yielding no improvement of preterm birth rates in most cases when comparing treated versus untreated women[68]. This circumstance then sparked debate about the sufficiency of the treatments, choice of antibiotics and also led to hypotheses that treatment undertaken in pregnancy may be 'too late', as the etiology of the preterm birth is postulated to be as a result of chronic inflammation caused by these diseases[69,70]. In order to address this potential deficiency, a limited number of investigations of treatment prior to pregnancy, in both observational studies and randomized trials[69,71,72], were initiated. To date, these efforts have not yielded results that have led to recommendations to screen and treat these conditions in the preconceptional period[72]. It should be noted, however, that detection and treatment may be made on other grounds[73]. Given the body of evidence showing the link between infection and preterm birth, and the significant burden of disease imposed by this association, a need clearly exists to test with properly conducted randomized trials the hypothesis that screening and treating conditions associated with preterm birth in the preconceptional period is of benefit.

Another etiology of preterm birth and second trimester loss is cervical incompetence which, in certain instances, is less directly a complication of infectious disease. This condition may result from prior surgery on the cervix such as conization or loop electrosurgical excision procedure (LEEP)[68] performed to treat cervical dysplasia which itself is due to infection with the human papilloma virus (HPV). Currently two vaccines[47] protect against the HPV types which cause most cervical cancers. To the extent that the vaccine can protect against the development of cervical dysplasia and lead to fewer cervical ablative procedures, the HPV vaccine has been considered a preconceptional intervention[41].

CONGENITAL INFECTIONS

Congenital infections can cause disease in both the mother and, by definition, in the fetus through transplacental transmission if they occur in pregnancy. These make up the so called TORCH (toxoplasmosis; others including syphilis and parvovirus; rubella; cytomegalovirus (CMV); and herpes virus infections (herpes simplex and varicella)) infections. All but toxoplasmosis and syphilis are viral infections. The primary area of concern for perinatal medicine is their transplacental spread and subsequent disease for the fetus. This type of spread also occurs with other infections mentioned above, such as HIV and influenza, but in these instances it is quite rare and not the primary consideration. Although herpes simplex is of more concern due to vertical transmission at birth, congenital infection also occurs. Finally, in a number of cases maternal disease is mild, asymptomatic or with nonspecific symptoms; this is true for toxoplasmosis, parvovirus, rubella and cytomegalovirus. The others may be asymptomatic in some instances but are better known for their well

described clinical syndromes, i.e. herpes simplex infection, varicella and syphilis.

Toxoplasmosis is a zoonosis caused by the protozoa *Toxoplasma gondii*[74]. Sources of this parasite include raw meat, soil and the feces of cats[74]. Infection in pregnancy can cause mild or severe disease including chorioretinitis, blindness, hearing loss (sensorineural), mental retardation and seizures[74]. In the US the birth prevalence is estimated to be about 1 per 1000[74]. Neither the American College of Obstetricians and Gynecologists (ACOG) or the UK National Institute for Health and Clinical Excellence (NICE) recommend screening for antibodies to the condition but rather recommend measures to prevent acquisition, such as cooking meat to a safe temperature, washing fruits and vegetables, hand washing prior to handling food, wearing gloves during and washing hands after gardening or working with soil and avoiding handling of cat feces[75,76]. Screening for antibodies has been advocated in France prior to pregnancy to identify those at risk with the purpose of targeting education on modes of prevention[74] especially since congenital infection has been documented to occur with periconceptional infection[77]. In addition, preconceptional testing has been advocated as an aid to the diagnosis of congenital infection[78]. Nevertheless, given the controversy about testing in pregnancy, it may be premature to advocate widespread testing in the prepregnancy period. Education regarding modes of transmission has been recommended as one strategy to decrease the incidence of this congenital infection[79,80]. There are as yet, however, no data supporting the role of this education prior to pregnancy, and the amount of emphasis to be given to these educational interventions might be limited[81,82]. This could also apply to other conditions in which education is promoted as an intervention such as listeriosis and CMV.

Syphilis, a sexually transmitted infection caused by the spirochete, *Treponema pallidum*, which causes significant disease in the mother and infant[83]. Initial stages are often asymptomatic and lead to latent syphilis in the mother[83]. When passed to the fetus, a possibility in up to 80% of pregnancies[84], infection can lead to prematurity and perinatal death[83]. The condition can be treated and its complications prevented through screening and treatment with penicillin[83]. In the US, screening has been advocated during pregnancy and prior to pregnancy for those at high risk[85]. It is estimated that worldwide 2 million cases of congenital syphilis occur each year, with 25% ending in pregnancy loss (stillbirth or miscarriage) and 25% with serious infection or low birth weight[84]. The current global strategy calls for testing and treatment in pregnancy of women and their partners, as well as screening those at high risk, such as patients in sexually transmitted infection clinics some of whom might not be pregnant but are of reproductive age[83].

Parvovirus or fifth disease is associated with a rash, erythema infectiosum and non-specific symptoms of a viral syndrome[75]. About 50% of adults are immune to the disease in the US[86]; however, few data are available from low and middle income nations[87]. Among individuals with acute infection in pregnancy, only 4% are affected with fetal loss and hydrops fetalis as a consequence of fetal anemia; most cases have healthy outcomes[88]. Parvovirus infection has not been associated with mental retardation or congenital anomalies[86]. Antibody levels for parvovirus are recommended for the evaluation of stillbirth[89], as these have been reported in up to 7–15% of stillbirths in some European-based series[87]. There are no specific recommendations for testing for antibody status prior to pregnancy or for counseling for prevention other than recommending routine hand hygiene[6].

Rubella, German measles, is the quintessential and historical preconceptional intervention. Vaccination for this condition has as its primary aim the prevention of congenital rubella syndrome (CRS). The infection causes mild disease in children and adults, whereas

in affected fetuses it can cause CRS characterized by deafness, cataracts, microcephaly, mental retardation, cardiac defects, liver and spleen damage, and bone lesions[90]. Since the introduction of the vaccine in the US in 1969, the incidence of the syndrome has declined by 99%[91]. WHO currently recommends two strategies for the incorporation of rubella vaccine in national immunization programs, as either a targeted approach for women of reproductive age or, where good vaccine coverage (>80%) can be assured, universal childhood vaccination, with the aim of eliminating rubella and congenital rubella[47]. (If rubella vaccination is performed on a wide scale, it is most typically in a combination vaccine with mumps, which does not cause congenital infection but is associated with spontaneous abortion.) Since rubella vaccination coverage is not always universal, one recommended preconceptional test is to check the rubella status especially in groups emigrating from countries with low rates of rubella vaccination[41].

Cytomegalovirus infection in pregnancy can cause a variety of symptoms in the affected fetus including hearing loss, mental retardation, cerebral palsy, chorioretinitis, growth restriction, hepatosplenomegaly, thrombocytopenia, jaundice and anemia[75]. More severe disease is more likely with primary infection but can occur in cases of secondary infection[92,93] and has been reported following infection occurring either before or shortly after conception[94]. Some authors recommend testing in the preconceptional period to focus prevention efforts on those at risk for primary disease[95], although others question the value of any screening program[96]. The prevention efforts recommended are those to prevent transmission from young children to adults through avoidance of personal contact and hygiene efforts to prevent contact with saliva and urine[97]. Examples include hand washing, especially after changing diapers or feeding young children, not sharing eating utensils or toothbrushes with young children and avoiding saliva when kissing young children[97]. Although some evidence supports education in seronegative pregnant women[98–100], at least one study suggested this intervention was not as effective among non-pregnant women[100] as those who were pregnant. Showing more promise, however, is a vaccine for CMV which has demonstrated efficacy in phase two randomized trials[101].

Two other herpes infections besides CMV can affect the fetus. Genital herpes simplex infection rarely causes congenital infection but when transmitted vertically during childbirth it can lead to herpes, a devastating CNS infection or disseminated disease[102]. Thus, vertical transmission is the subject of most prevention efforts[102]. Like CMV, primary infection in pregnancy is associated with worse outcomes than secondary infection[102]. In patients with genital herpes, if known to exist in pregnancy, strategies are undertaken to reduce transmission including prophylaxis in the last month of pregnancy and cesarean delivery in the presence of active genital lesions at delivery[102]. To date there are no recommendations to universally screen for herpes simplex virus (HSV) sero status in asymptomatic women either during or prior to pregnancy[102]. In contrast, recommendations suggest testing women whose partners have genital herpes with type specific antibodies and using measures to reduce the acquisition of HSV through daily antiviral therapy[103] and condom use[104].

Herpes zoster virus or varicella zoster virus (VZV), causes both varicella and zoster infection. Primary infection can lead to congenital infection[105]. Unlike herpes simplex, however, only primary infection is of concern, and a vaccine is available[105]. A high risk of severity exists for the mother if infection occurs during pregnancy including the development of varicella pneumonia[41]. Screening prior to pregnancy and in adults can be performed via a reliable history or, in the face of a negative history, with screening for VZV antibodies[105]. As the vaccine is a live attenuated virus, it

must be avoided in pregnancy, but its use in the preconceptional period has been recommended[41]. Currently the vaccine is not recommended for routine use by WHO[47], or in the UK as a routine in childhood or reproductive aged adults, where it is recommended in high risk individuals[106]. In the US, the vaccine is recommended in childhood. Adults, including women with no documented immunization, no prior infection or seronegative, if tested, are recommended to be vaccinated[107]. Women documented to be negative during pregnancy are recommended to be vaccinated in the postpartum period[107].

CHLAMYDIAL AND GONORRHEAL INFECTIONS

Infection by *Chlamydia trachomatis* is the most common bacterial sexually transmitted infection worldwide, with an estimated 92 million cases worldwide in one 1999 estimate[108,109]. Gonorrheal infection was estimated to have 62 million incident cases in the same year[109]. Both cause cervical infection which can lead to pelvic inflammatory disease (PID), chronic pelvic pain and infertility[108,110]. Outcomes of pregnancy include ectopic pregnancy and, in neonates, eye infection and specific to Chlamydia, pneumonia, and to gonorrhea, disseminated gonococcal infection (sepsis, arthritis, meningitis) or scalp abscess (if a fetal scalp electrode is used in the setting of maternal gonorrhea)[108,111]. It is estimated that 1000–4000 newborns worldwide are left blind owing to untreated ophthalmia neonaturum as a consequence of Chlamydia or gonorrhea[112]. Some of these cases are preventable, especially those due to gonorrhea, with the use of silver nitrate or antibiotic ointment eye prophylaxis; in contrast, those due Chlamydia are not[111].

Chlamydia is largely asymptomatic in men, considered carriers of the disease[108], and often asymptomatic in women (70–90%); screening those at high risk for infection has been recommended to decrease the burden of disease[113]. Many recommendations rest on the findings of randomized trials which demonstrated a decrease in PID in screened versus unscreened populations[114,115]. However, issues regarding trial design and results from observational studies have led to questions about the magnitude of benefit of screening programs[116]. Those at high risk in developed countries with access to highly sensitive testing (women less than age 25 and women over that age with multiple sex partners or a new sex partner or those with a history of sexually transmitted disease) are recommended to be screened[111,117]. Women in pregnancy at high risk also deserve screening[76,111,117], in part because the prevalence of neonatal infection (conjunctivitis and pneumonia) has decreased with widespread screening[111]. Direct randomized trial data supporting this recommendation are lacking[118].

Gonorrhea, unlike Chlamydia, is largely symptomatic in men but similar to Chlamydia is frequently asymptomatic in women[111]. In the UK, asymptomatic individuals are not screened in part because the disease is less prevalent and complications are less common; targeted interventions may have a role in groups at an especially high risk such as inner city residents, those attending clinics for sexually transmitted infections, and men who have sex with men and others[119]. In the US, the US Preventive Health Task Force cites fair evidence to screen asymptomatic pregnant and non-pregnant women at high risk, including women under age 25 and those with new or multiple sex partners[120]. The task force also cites the potential for prevention of preterm labor and chorioamnionitis as a rationale for screening in pregnancy[120].

Studies in Africa have shown a high prevalence of Chlamydia infection in pregnancy ranging from 9 to 13%, and in Asia rates vary from 6 to 27%[109]. Gonorrheal prevalence in pregnancy in Africa varies widely from less than 1% to 8%[109]. In areas where access to

testing is limited, a syndromic approach to screening pregnant women for these infections is recommended[118]. Efforts to control Chlamydia and gonorrhea globally involve screening women who are commercial sex workers and their partners[121]. Some evidence suggests that screening and treating Chlamydia and gonorrhea may help prevent the acquisition of HIV[121]. Women in the preconceptional period at high risk who are screened and who have these infections may benefit from a reduction of their sequelae for themselves, their pregnancy and their newborns.

HEPATITIS B AND C

Hepatitis B and C are caused by viruses and can lead to chronic liver inflammation[122,123]. Both are transmitted from infected blood – from receiving a transfusion with the virus present (uncommon where testing of blood is performed), intravenous drug use/unsafe injection practices, vertical transmission at birth and as a sexually transmitted infection[122,123]. In developing countries sources of infection for hepatitis B also include early childhood infections through close contact with infected household contacts where, along with vertical transmission, these account for a majority of cases[122,124]. Because acute infection with viruses is often either asymptomatic or associated with non-specific symptoms, many individuals are unaware they are infected unless tested[122,123].

Hepatitis B is very common; worldwide estimates count 2 billion as infected, 350 million living with chronic infection and 600,000 dying from complications of hepatitis[125]. Death occurs from either cirrhosis or liver cancer[125]. The risk of chronic disease is age dependent – 90% of those who contract it in infancy (0–1 year), 30–50% of children and 10% of adults progress to develop chronic disease[125]. If chronic disease develops as a child, the risk of complications is high, with about 25% eventually developing cirrhosis or liver cancer[125]. The primary focus of hepatitis B in preconceptional care involves vaccination to prevent vertical transmission, which can occur at variable rates from as low as less than 10% to as high as 70–90% in the absence of any prevention measures, depending on the pattern of the chronic infection[126]. Currently hepatitis B vaccine is recommended in childhood shortly after birth and in adults previously vaccinated who are at high risk[47]. Other recommendations for preconceptional care include testing those at high risk for hepatitis B carrier status, instructing them on avoidance of transmission to uninfected individuals including information on the prevention of vertical transmission[41]. Some patients with hepatitis B may undergo treatment of long duration[127] in which case their reproductive life plan and adequate contraception should be considered before embarking on therapy.

Hepatitis C is also common, with an estimated 123 million people worldwide being infected[128]. Major modes of transmission in developed nations are injection drug use and in undeveloped nations unsafe therapeutic injections and transfusions[128]. Unlike hepatitis B, infection through sexual contact and perinatal transmission is much less efficient and thus represents a smaller source of hepatitis C infection[128]. HIV infection along with alcohol use are also important co-factors in the global burden of disease associated with hepatitis C[128]. As the risk of vertical transmission is low (4%, although it is 2–3 times higher in those with HIV) and most children are asymptomatic and have no sequelae, there are no recommendations to screen pregnant women or to perform cesarean delivery or other specific interventions to prevent such infection[123,129]. Current preconceptional recommendations include screening those at high risk of the

disease to inform them of the risks of transmission and the disease course[6]. Similar to hepatitis B, treatment for hepatitis C is long term and includes ribavarin[130] which is contraindicated in pregnancy. A woman undergoing treatment should have her reproductive life plan reviewed and have appropriate contraception[6].

CONCLUSION

Infections comprise a significant burden of disease for women of reproductive age and their neonates. A great many can be prevented through immunization, with many vaccinations being recommended in childhood. For others, early detection and treatment, if indicated, in the preconceptional period may benefit not only the mother, but also her children as well. These interventions and strategies represent a doubling of effect since at least two individuals are frequently the beneficiaries of preconceptional care.

REFERENCES

1. WHO. *The global burden of disease: 2004 update*. http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html
2. WHO. HIV/AIDS: *Global epidemic data and statistics*. http://www.who.int/hiv/data/global_data/en/index.html
3. Abdool-Karim Q, Abouzahr C, Dehne K, *et al*. HIV and maternal mortality: turning the tide. *Lancet* 2010;375:1948–9
4. Burr CK, Lampe MA, Corle S, Margolin FS, Abresh C, Clark J. An end to perinatal HIV: success in the US requires ongoing and innovative efforts that should expand globally. *J Public Health Policy* 2007;28:249–60
5. WHO. *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access*. Geneva: World Health Organization, 2010
6. Coonrod DV, Jack BW, Stubblefield PG, *et al*. The clinical content of preconception care: infectious diseases in preconception care. *Am J Obstet Gynecol* 2008;199:S296–309
7. Branson BM, Handsfield HH, Lampe MA, *et al*. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep* 2006;55:1–17; quiz CE1–4
8. WHO. *Guidance on provider-initiated HIV testing and counselling in health facilities*. Geneva: World Health Organization, 2007
9. Padian NS, Buve A, Balkus J, Serwadda D, Cates W Jr. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. *Lancet* 2008;372:585–99
10. Strathdee SA, Hallett TB, Bobrova N, *et al*. HIV and risk environment for injecting drug users: the past, present, and future. *Lancet* 2010;376:268–84
11. New York State Department of Health AIDS Institute. *Preconception Care for HIV-Infected Women*. New York: New York State Department of Health AIDS Institute, 2010
12. Cates W Jr. After CAPRISA 004: time to re-evaluate the HIV lexicon. *Lancet* 2010;376:495–6
13. Karim QA, Karim SS, Frohlich JA, *et al*. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 2010;329:1168–74
14. Gilling-Smith C, Nicopoullos JD, Semprini AE, Frodsham LC. HIV and reproductive care--a review of current practice. *BJOG* 2006;113:869–78
15. Aaron EZ, Criniti SM. Preconception health care for HIV-infected women. *Top HIV Med* 2007;15:137–41
16. McIntyre J. Mothers infected with HIV. *Br Med Bull* 2003;67:127–35
17. Louis J, Landon MB, Gersnoviez RJ, *et al*. Perioperative morbidity and mortality among human immunodeficiency virus infected women undergoing cesarean delivery. *Obstet Gynecol* 2007;110:385–90
18. Coll O, Lopez M, Vidal R, *et al*. Fertility assessment in non-infertile HIV-infected women and their partners. *Reprod Biomed Online* 2007;14:488–94

19. Marais BJ, Gupta A, Starke JR, El Sony A. Tuberculosis in women and children. *Lancet* 2010;375:2057–9
20. CDC. Treatment of tuberculosis. *MMWR Recomm Rep* 2003;52:1–77
21. WHO. *The Stop TB Strategy.* http://www.who.int/tb/publications/2010/strategy_en.pdf
22. CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep* 2000;49:1–51
23. WHO. BCG vaccine. WHO position paper. *Wkly Epidemiol Rec* 2004;79:27–38
24. Kaufmann SH, Hussey G, Lambert PH. New vaccines for tuberculosis. *Lancet* 2010;375:2110–9
25. WHO. *Revised BCG vaccination guidelines for children with HIV infection.* http://www.who.int/immunization/sage/BCGvaccination_revsd_13Apr_07.pdf
26. Menendez C, D'Alessandro U, ter Kuile FO. Reducing the burden of malaria in pregnancy by preventive strategies. *Lancet Infect Dis* 2007;7:126–35
27. Coll O, Menendez C, Botet F, *et al*. Treatment and prevention of malaria in pregnancy and newborn. *J Perinat Med* 2008;36:15–29
28. Lindsay S, Ansell J, Selman C, Cox V, Hamilton K, Walraven G. Effect of pregnancy on exposure to malaria mosquitoes. *Lancet* 2000;355:1972
29. Desai M, ter Kuile FO, Nosten F, *et al*. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007;7:93–104
30. WHO. *A strategic framework for malaria prevention and control during pregnancy in the African region*. Brazzavile: WHO Regional Office for Africa, 2004
31. Arguin PM, Steele SF. Malaria. *Traveler's Health: Yellow Book*. Atlanta, GA: Centers for Disease Control, 2010
32. Black RE, Cousens S, Johnson HL, *et al*. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010;375:1969–87
33. Lu MC, Kotelchuck M, Culhane JF, Hobel CJ, Klerman LV, Thorp JM Jr. Preconception care between pregnancies: the content of internatal care. *Matern Child Health J* 2006;10:S107–22
34. Wardlaw T, Johansson EW, Hodge M. *Pneumonia: The Forgotten Killer of Children*. New York: The United Nations Children's Fund/World Health Organization, 2006
35. Shahid NS, Steinhoff MC, Hoque SS, Begum T, Thompson C, Siber GR. Serum, breast milk, and infant antibody after maternal immunisation with pneumococcal vaccine. *Lancet* 1995;346:1252–7
36. Santosham M, Englund JA, McInnes P, *et al*. Safety and antibody persistence following Haemophilus influenzae type b conjugate or pneumococcal polysaccharide vaccines given before pregnancy in women of childbearing age and their infants. *Pediatr Infect Dis J* 2001;20:931–40
37. Kretsinger K, Broder KR, Cortese MM, *et al*. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR Recomm Rep* 2006;55:1–37
38. WHO. Pertussis vaccines--WHO position paper. *Wkly Epidemiol Rec* 2005;80:31–9
39. Gerbie MV, Tan TQ. Pertussis disease in new mothers: effect on young infants and strategies for prevention. *Obstet Gynecol* 2009;113:399–401
40. Murphy TV, Slade BA, Broder KR, *et al*. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008;57:1–51
41. Coonrod DV, Jack BW, Boggess KA, *et al*. The clinical content of preconception care: immunizations as part of preconception care. *Am J Obstet Gynecol* 2008;199:S290–5
42. Shindo M. *Global view of pandemic and seasonal influenza disease burden*. http://www.ifpi2010.com/speakers/NahokoShindo.pdf
43. CDC. *Updated CDC Estimates of 2009 H1N1 Influenza Cases, Hospitalizations and Deaths in the United States, April 2009 – April 10, 2010*. http://

www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm
44. WHO. *WHO recommendations for the post-pandemic period*. http://www.who.int/csr/disease/swineflu/notes/briefing_20100810/en/index.html
45. Fiore AE, Uyeki TM, Broder K, *et al*. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010;59:1–62
46. CDC. Diphtheria. In: Atkinson W, Wolf S, Hamborsky J, McIntyre L, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Washington, DC: Public Heath Foundation, 2009
47. WHO. *Recommended Routine Immunization* - Summary of WHO Position Papers. http://www.who.int/immunization/policy/Immunization_routine_table1.pdf
48. Wardlaw T, Salama P, Brocklehurst C, Chopra M, Mason E. Diarrhoea: why children are still dying and what can be done. *Lancet* 2010;375:870–2
49. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. *Lancet* 2000;355:451–5
50. Christian P. Prenatal origins of undernutrition. *Nestle Nutr Workshop Ser Pediatr Program* 2009;63:59–73; discussion 4–7, 259–68
51. Felkner M, Hendricks K, Suarez L, Waller DK. Diarrhea: a new risk factor for neural tube defects? *Birth Defects Res A Clin Mol Teratol* 2003;67:504–8
52. CDC. Measles. In: Atkinson W, Wolf S, Hamborsky J, McIntyre L, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Washington, DC: Public Health Foundation, 2009
53. WHO. Measles vaccines: WHO position paper. *Wkly Epidemiol Rec* 2009;84:349–60
54. Strebel PM, Papnia MJ, Halsey NA. Measles vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. Philadelphia: Saunders, 2004
55. CDC. Tetanus. In: Atkinson W, Wolf S, Hamborsky J, McIntyre L, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Washington, DC: Public Health Foundation, 2009
56. WHO. *Maternal and Neonatal Tetanus (MNT) elimination: The initiative and challenges*. http://www.who.int/immunization_monitoring/diseases/MNTE_initiative/en/index.html
57. WHO. *Maternal and Neonatal Tetanus (MNT) elimination: The strategies*. http://www.who.int/immunization_monitoring/diseases/MNTE_initiative/en/index2.html
58. Blencowe H, Lawn J, Vandelaer J, Roper M, Cousens S. Tetanus toxoid immunization to reduce mortality from neonatal tetanus. *Int J Epidemiol* 2010;39 Suppl 1:i102–9
59. Thaver D, Zaidi AK. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. *Pediatr Infect Dis J* 2009;28:S3–9
60. Bang AT, Bang RA, Baitule SB, Reddy MH, Deshmukh MD. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet* 1999;354:1955–61
61. Anderson-Berry AL, Bellig LL, Ohnigh BL. *Neonatal sepsis*. http://emedicine.medscape.com/article/978352-overview
62. Dredge DC, Krishnamoorthy KS. *Neonatal meningitis*. http://emedicine.medscape.com/article/1176960-overview
63. Gellin BG, Broome CV. Listeriosis. *JAMA* 1989;261:1313–20
64. WHO. Meningococcal vaccines: polysaccharide and polysaccharide conjugate vaccines. *Wkly Epidemiol Rec* 2002;77:331–9
65. Healy CM, Baker CJ. Maternal immunization. *Pediatr Infect Dis J* 2007;26:945–8
66. Espinoza J, Erez O, Romero R. Preconceptional antibiotic treatment to prevent preterm birth in women with a previous preterm delivery. *Am J Obstet Gynecol* 2006;194:630–7
67. Newton ER. Preterm labor, preterm premature rupture of membranes, and chorioamnionitis. *Clin Perinatol* 2005;32:571–600
68. Iams JD, Berghella V. Care for women with prior preterm birth. *Am J Obstet Gynecol* 2010;203:89–100
69. Andrews WW, Goldenberg RL, Hauth JC, Cliver SP, Conner M, Goepfert AR. Endometrial microbial colonization and plasma cell endometritis after spontaneous or indicated

preterm versus term delivery. *Am J Obstet Gynecol* 2005;193:739–45
70. Offenbacher S, Beck JD, Jared HL, *et al*. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstet Gynecol* 2009;114:551–9
71. Tita AT, Cliver SP, Goepfert AR, *et al*. Impact of interconception antibiotics on the endometrial microbial flora. *Am J Obstet Gynecol* 2007;196:226 e1–6
72. Andrews WW, Goldenberg RL, Hauth JC, Cliver SP, Copper R, Conner M. Interconceptional antibiotics to prevent spontaneous preterm birth: a randomized clinical trial. *Am J Obstet Gynecol* 2006;194:617–23
73. Boggess KA. Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS). *Am J Obstet Gynecol* 2010;202:101–2
74. Lopez A, Dietz VJ, Wilson M, Navin TR, Jones JL. Preventing congenital toxoplasmosis. *MMWR Recomm Rep* 2000;49:59–68
75. ACOG. ACOG Practice Bulletin No. 20. Perinatal viral and parasitic infections. Washington: DC: American College of Obstetricians and Gynecologists, 2000
76. NICE. No. 62 *Antenatal Care: Routine care for the healthy pregnant woman*. London: National Institute for Health and Clinical Excellence, 2008
77. Robert-Gangneux F, Yera H, D'Herve D, Guiguen C. Congenital toxoplasmosis after a preconceptional or periconceptional maternal infection. *Pediatr Infect Dis J* 2009;28:660–1
78. Fuccillo DA, Madden DL, Tzan N, Sever JL. Difficulties associated with serological diagnosis of Toxoplasma gondii infections. *Diagn Clin Immunol* 1987;5:8–13
79. Breugelmans M, Naessens A, Foulon W. Prevention of toxoplasmosis during pregnancy--an epidemiologic survey over 22 consecutive years. *J Perinat Med* 2004;32:211–4
80. Pawlowski ZS, Gromadecka-Sutkiewicz M, Skommer J, *et al*. Impact of health education on knowledge and prevention behavior for congenital toxoplasmosis: the experience in Poznan, Poland. Health Educ Res 2001;16:493–502
81. Whitworth M, Dowswell T. Routine pre-pregnancy health promotion for improving pregnancy outcomes. *Cochrane Database Syst Rev* 2009;(4):CD007536
82. Inskip HM, Crozier SR, Godfrey KM, Borland SE, Cooper C, Robinson SM. Women's compliance with nutrition and lifestyle recommendations before pregnancy: general population cohort study. *BMJ* 2009;338:b481
83. WHO. *The Global elimination of congenital syphilis: rationale and strategy for action*. Geneva: World Health Organization, 2007
84. WHO. *Controlling sexually transmitted and reproductive tract infections: Elimination of congenital syphilis*. http://www.who.int/reproductive-health/topics/rtis/syphilis/en/index.html
85. USPSTF. *Screening for syphilis Infection*. http://www.uspreventiveservicestaskforce.org/uspstf/uspssyph.htm
86. CDC. *Parvovirus B19 infection and pregnancy*. www.cdc.gov/ncidod/dvrd/revb/respiratory/b19&preg.htm
87. Goldenberg RL, McClure EM, Saleem S, Reddy UM. Infection-related stillbirths. *Lancet* 2010;375:1482–90
88. Enders M, Weidner A, Zoellner I, Searle K, Enders G. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. *Prenat Diagn* 2004;24:513–8
89. ACOG. ACOG Practice Bulletin No.102 *Management of stillbirth*. Washington: DC: American College of Obstetricians and Gynecologists, 2009
90. CDC. Rubella. In: Atkinson W WS, Hamborsky J, McIntyre L, ed. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Washington, DC: Public Health Foundation, 2009
91. CDC. Rubella vaccination during pregnancy--United States, 1971-1988. MMWR Morb Mortal Wkly Rep 1989;38:289–93
92. Cannon MJ. Congenital cytomegalovirus (CMV) epidemiology and awareness. *J Clin Virol* 2009;46 Suppl 4:S6–10
93. Zalel Y, Gilboa Y, Berkenshtat M, *et al*. Secondary cytomegalovirus infection can cause severe fetal sequelae despite maternal preconceptional immunity. *Ultrasound Obstet Gynecol* 2008;31:417–20

94. Revello MG, Zavattoni M, Furione M, Lilleri D, Gorini G, Gerna G. Diagnosis and outcome of preconceptional and periconceptional primary human cytomegalovirus infections. *J Infect Dis* 2002;186:553–7
95. Adler SP. Congenital cytomegalovirus screening. Pediatr Infect Dis J 2005;24:1105–6
96. Schlesinger Y. Routine screening for CMV in pregnancy: opening the Pandora box? *Isr Med Assoc J* 2007;9:395–7
97. CDC. *Cytomegalovirus (CMV) and congenital CMV infection: Prevention*. http://www.cdc.gov/cmv/prevention.html.
98. Vauloup-Fellous C, Picone O, Cordier AG, *et al*. Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital. *J Clin Virol* 2009;46 Suppl 4:S49–53
99. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus by changing behaviors: a randomized controlled trial. *Pediatr Infect Dis J* 1996;15:240–6
100. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus among pregnant women. *J Pediatr* 2004;145:485–91
101. Pass RF, Zhang C, Evans A, *et al*. Vaccine prevention of maternal cytomegalovirus infection. *N Engl J Med* 2009;360:1191–9
102. ACOG. ACOG Practice Bulletin No. 82 *Management of herpes in pregnancy*. Washington: DC: American College of Obstetricians and Gynecologists, 2007
103. Corey L, Wald A, Patel R, *et al*. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004;350:11–20
104. Martin ET, Krantz E, Gottlieb SL, *et al*. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. *Arch Intern Med* 2009;169:1233–40
105. Gardella C, Brown ZA. Managing varicella zoster infection in pregnancy. *Cleve Clin J Med* 2007;74:290–6
106. NHS. *Chickenpox (varicella) vaccination*. http://www.nhs.uk/conditions/varicella-vaccine/Pages/Introduction.aspx
107. Marin M, Guris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2007;56:1–40
108. WHO. *Sexually transmitted diseases: Chlamydia trachomatis*. http://www.who.int/vaccine_research/diseases/soa_std/en/index1.html
109. WHO. *Global prevalence and incidence of selected curable sexually transmitted infections: Overview and estimates*. Geneva: World Health Organization, 2001
110. Haggerty CL, Gottlieb SL, Taylor BD, Low N, Xu F, Ness RB. Risk of sequelae after Chlamydia trachomatis genital infection in women. *J Infect Dis* 2010;201 Suppl 2:S134–55
111. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep* 2006;55:1–94
112. WHO. Fact Sheet #110. *Sexually transmitted infections*. http://www.who.int/mediacentre/factsheets/fs110/en/index.html
113. USPSTF. Screening for chlamydial infection: recommendations and rationale. *Am J Prev Med* 2001;20:90–4
114. Scholes D, Stergachis A, Heidrich FE, Andrilla H, Holmes KK, Stamm WE. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. *N Engl J Med* 1996;334:1362–6
115. Ostergaard L, Andersen B, Moller JK, Olesen F. Home sampling versus conventional swab sampling for screening of Chlamydia trachomatis in women: a cluster-randomized 1-year follow-up study. *Clin Infect Dis* 2000;31:951–7
116. Gottlieb SL, Berman SM, Low N. Screening and treatment to prevent sequelae in women with Chlamydia trachomatis genital infection: how much do we know? *J Infect Dis* 2010;201 Suppl 2:S156–67
117. USPSTF. *Screening for chlamydial infection*. http://www.uspreventiveservicestaskforce.org/uspstf/uspschlm.htm
118. WHO. *Prevention and management of sexually transmitted and reproductive tract infections. Standards of maternal and neonatal care*. Geneva: World Health Organization, 2006
119. HPA. *Guidance for gonorrhoea testing in England and Wales*. London: Health Protection Agency, 2010

120. USPSTF. *Screening for gonorrhea*. http://www.uspreventiveservicestaskforce.org/uspstf/uspsgono.htm#ref12
121. Aledort JE, Ronald A, Rafael ME, *et al*. Reducing the burden of sexually transmitted infections in resource-limited settings: the role of improved diagnostics. *Nature* 2006;444 Suppl 1:59–72
122. CDC. *Hepatitis B FAQs for Health Professionals*. http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview
123. CDC. *Hepatitis C FAQs for Health Professionals*. http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview
124. WHO. Hepatitis B vaccines. *Wkly Epidemiol Rec* 2009;84:405–19
125. WHO. *Fact Sheet #204. Hepatitis B*. http://www.who.int/mediacentre/factsheets/fs204/en/index.html
126. Mast EE, Weinbaum CM, Fiore AE, *et al*. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* 2006;55:1–33; quiz CE1–4
127. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009;50:661–2
128. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005;5:558–67
129. ACOG. *ACOG Practice Bulletin No. 86: Viral hepatitis in pregnancy*. American College of Obstetricians and Gynecologists, 2007
130. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49:1335–74