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Emerging and Zoonotic Infections in Women

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Synopsis

Emerging infections, many of them zoonotic, are caused by a wide variety of pathogens with global distribution. Their impact on women is similarly diverse. Pathogens that were previously rare are emerging in recent years to cause disease in new populations, and global travel facilitates their rapid spread across continents. Finally, human encroachment on previously remote areas has brought people into contact with zoonotic diseases and vectors never before characterized. Although systematic study of rare outbreaks can be challenging, our knowledge of emerging pathogens and their differential effects on women, including those who are pregnant, has started to accumulate. We discuss the effects on women of lymphocytic choriomeningitis virus, West Nile virus, SARS coronavirus, avian influenza A (H5N1), virus, and the viral hemorrhagic fevers. We also explore the spirochetal illnesses and Chagas disease as they pertain to the pregnant patient. Finally, we review the potential impact of candidate bioterror agents on the female population, and address related issues of prophylaxis and therapy.

Introduction

In the inaugural issue of *Emerging Infectious Diseases*, Stephen Morse defined emerging infections as “infections that have newly appeared in the population, or have existed but are rapidly increasing in incidence or geographic range”[1]. Most of the infections to emerge in recent years (1996–2004, see figure 1) can be categorized as zoonoses, with West Nile virus, SARS (severe acute respiratory syndrome) coronavirus, and avian influenza A (H5N1) virus, accounting for some recent high-profile zoonotic outbreaks (Figure 1) [2]. Non-zoonotic infections deserving mention in any discussion of emerging infectious diseases include previously controlled human pathogens that are re-emerging, and antibiotic-resistant bacteria account for a proportion of these challenging infections. The increasing use of organ transplantation has also resulted in increased susceptibility to and transmission of re-emerging

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pathogens, most recently exemplified by the zoonotic infection lymphocytic choriomeningitis virus (LCMV) [3].

In examining the impact of emerging infections on the female population, one must consider factors unique to women. Pregnant women are uniquely susceptible to infectious diseases [4]. However, women in general manifest disease differently than men based on anatomic and hormonal factors. Consider the difference in severity of gonorrheal infection, usually asymptomatic, but occasionally manifesting as fertility-threatening pelvic inflammatory disease in women as opposed to the milder urethritis or prostatitis seen in men. In contrast, the female hormonal milieu seems to protect against disease development after infection with some pathogens, including *Coxiella burnettii*, the causative agent of Q fever [5]. Behavioral, cultural, and social factors must also be considered [6]. For example, in cultures where women tend the animal herds, they are more likely to be exposed to zoonoses such as Q fever and Rift Valley Fever [7]. In addition, health care workers must be prepared to encounter women with unique combinations of risk factors for emerging infectious diseases, such as the growing population of women who are becoming pregnant after kidney transplantation [8].

Old Pathogens, New Patterns

In 1999, an outbreak of West Nile virus (WNV) was identified in New York City, the first time this well-characterized mosquito-borne flavivirus had been found in the Western hemisphere. Originally isolated from a human case in Uganda in 1937, WNV was later shown to be maintained in bird reservoirs through mosquito vectors [9]. Since 1999, the virus has spread throughout the United States, causing more than 27,000 human cases of WNV illness [10]. WNV may be less likely to cause disease in women than in men, as suggested by a study reporting a higher incidence of WNV neuroinvasive disease in men and two others that demonstrated higher rates of mortality in infected men [11,12]. How much of the apparent difference is due to biology is unclear, as behavioral factors resulting in disproportionate exposure of men to the infected mosquito vector may have important roles.

In 2002, a case of intrauterine transmission of WNV was reported in Syracuse, New York. In this case a pregnant woman suffered WNV encephalitis at 27 weeks' gestational age, and subsequently delivered at 38 weeks. The neonate had neurological sequelae including severe bilateral loss of white matter, a cystic lesion with focal cerebral destruction in one temporal lobe, lissencephaly, and chorioretinal scarring [13]. Cord blood from delivery as well as blood from heel-stick specimens tested positive for WNV-specific immunoglobulin M (IgM), which is consistent with intrauterine infection. The placenta also tested positive for WNV RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) in one of two tests [14,15]. This initial case of congenital WNV infection prompted the Centers for Disease Control and Prevention (CDC) and state health departments to establish a WNV surveillance system for pregnant women. In 2003–2004, 83 pregnant women with WNV illness were identified through surveillance, and clinical information was available on 77. Although three cases of possible congenital infection were found, intrauterine transmission was not confirmed. All three mothers had acute WNV illness within 3 weeks of delivery, allowing for the possibility of intrapartum or immediate postpartum transmission of infection. Cord blood specimens were not available in two of these cases, and testing for WNV-specific IgM and WNV RNA was negative in the third. One of the infected infants died at 7 weeks of age [16].

During the surveillance efforts, 42 specimens of breastmilk from infected women were tested for WNV RNA, and two of these tested positive. One of the infants fed WNV positive breastmilk had negative serology at age 7 months of age, and the other was not available for testing [16]. Earlier, in 2002, a probable case of transmission through breastfeeding was reported in Michigan [17]. Shortly after delivery, a woman received 2 units of blood from a

WNV-infected donor and subsequently developed documented WNV meningoencephalitis. WNV was also isolated from her breastmilk, and her breastfed neonate developed WNV-specific IgM antibody but did not become ill. From the limited information available, it appears that WNV is rarely transmitted transplacentally, but that congenital WNV infection may result in severe neurological sequelae and even death. Mothers with febrile illnesses suspicious for WNV infection should be counseled regarding the possible risk of transmission during pregnancy and via breastmilk [18].

Another previously studied but clinically rare pathogen has re-emerged recently as a cause of disease in the U.S. LCMV, an arenavirus carried by the house mouse and other small rodents, appeared in several recipients of transplanted organs in 2003 and again in 2005. All had received their organs from one of two donors, and the resulting infections were fatal in seven of the eight recipients. The second donor had a history of exposure to a pet hamster with LCMV infection, but the initial donor could not be linked to any rodent exposure and his tissues tested negative for LCMV infection. The sole surviving recipient was treated with ribavirin, which has been shown *in vitro* to control replication of LCMV, and he improved clinically with therapy. Only one of the recipients was a woman, and she died on post-liver transplantation day 17 with multi-organ LCMV involvement demonstrated immunologically at autopsy [3]. In 2005, the clusters of LCMV infection in transplant recipients prompted the CDC to issue interim guidelines on exposure to LCMV, recommending that immunosuppressed persons and pregnant women or women who may become pregnant avoid exposure to all rodents, including pet hamsters [19]. LCMV is known to infect pregnant women, causing fetal wastage, hydrocephalus, and chorioretinitis in affected offspring [20,21]. Ribavirin, the only therapeutic option for LCMV disease, is not generally recommended in pregnancy due to findings of teratogenicity in animal models [22].

The Viral Hemorrhagic Fevers

The viral hemorrhagic fevers (VHFs) originate from multiple virus families, including the flaviruses (Dengue hemorrhagic fever, yellow fever), arenaviruses (Lassa fever, Argentine, Bolivian, and Venezuelan hemorrhagic fevers), bunyaviruses (Rift Valley fever, Hantaviruses, Crimean Congo hemorrhagic fever) and filoviruses (Ebola and Marburg hemorrhagic fevers). Although evolutionarily divergent, these viruses have in common natural animal reservoirs and rapidly mutating RNA genomes, with humans as incidental victims in the viral life cycle. The possible exception is the flaviviruses, which are thought to survive via arthropod-human-arthropod infectious cycles, the isolation of yellow fever and Dengue fever viruses from non-human primates notwithstanding [9]. The sporadic nature of VHF outbreaks--as well as their often remote locations--makes systematic epidemiologic study difficult. However, the limited existing data suggest a pattern of increased severity of disease in women and increased mortality in pregnant compared to non-pregnant patients across a range of viruses. Fetal pathology and pregnancy wastage have been documented as sequelae of some VHF infections as well.

Yellow fever virus, an important tropical mosquito-borne pathogen, remains an important cause of disease. Despite the effectiveness of the available vaccine, the World Health Organization (WHO) estimates that 200,000 cases and 30,000 deaths from yellow fever occur annually worldwide, and these numbers have been increasing since the 1980s [23]. Endemic to South America, the Caribbean, and Africa, yellow fever case fatality rates have been estimated at 10–20%. Max Theiler received the 1951 Nobel Prize in medicine for development of the vaccine, which in concert with mosquito control measures dramatically decreased the incidence of yellow fever worldwide. Some controversy exists regarding the safety of yellow fever vaccination during pregnancy, since early studies suggested increased risk of miscarriage among women receiving the live attenuated vaccine during the first trimester of pregnancy.

For this reason, the WHO recommends vaccinating pregnant women against yellow fever only during an epidemic [23]. Recent data from 480 women who were vaccinated early in pregnancy, however, demonstrate no increase in adverse pregnancy outcomes including miscarriage, malformations, and preterm delivery. This study also documented 98% seroconversion among the women studied, suggesting that the vaccine is both safe and effective in pregnancy [24].

Dengue virus infection manifests clinically as several different entities, including dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Four dengue virus serotypes have been characterized, and primary infection with any of them generally causes a self-limited mild febrile illness. A history of dengue infection, however, is a risk factor for developing the more severe DHF or DSS upon secondary infection with another serotype. This antibody enhancement effect is thought to be mediated by IgG and has significant implications for pregnant women contracting secondary dengue infection. A disease of the urban tropics, dengue is transmitted from person to person by *Aedes* mosquitos, with no obligate vertebrate intermediate. Serological surveys indicate no difference in the prevalence of dengue antibodies between women and men in endemic areas, with seropositivity approaching 100% in adult populations in hyperendemic parts of the world [25,26]. Dengue infection during pregnancy can result in complications for both mother and infant, especially if the mother has previously been infected with another serotype. Dengue infection with manifestations of maternal thrombocytopenia and elevated transaminases may present similarly to HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, being differentiated in the early stages only by the lack of hypertension and the presence of fever. Peripartum DHF can result in life-threatening coagulopathies postpartum or intraoperative hemorrhage. The presence of maternal IgG specific to another serotype in the neonatal blood can lead to DHF or DSS during vertically acquired primary dengue infection, with one reported case resulting in death of the infant from intracranial hemorrhage [27]. The mechanism of vertical dengue transmission is unclear, but at least 17 cases have been documented in the English literature [28]. Transplacental infection has been hypothesized after reports of increased rates of stillbirth in pregnant women with DF, but fetal and placental dengue virus infections were not documented [29]. One congenitally infected term infant did have dengue virus RNA detected in cord blood by RT-PCR, suggesting fetal viremia and transplacental infection [30]. Most reported cases of vertical transmission have occurred with maternal infection around the time of delivery, also raising the possibility of transmission to the infant during the intrapartum period and/or through breastfeeding.

Endemic to West Africa, Lassa fever is caused by a zoonotic arenavirus carried by common rodents of the *Mastomys* genus. Transmission is thought to occur via aerosol and direct contact with excreta from the animal. Data have been presented demonstrating the increased severity of Lassa fever in pregnancy and the postpartum period, but non-pregnant women infected with the virus fare as well as men in most studies. Case fatality rates in pregnancy and the puerperium are as high as 40%, with the worst prognosis for women in the final trimester [31]. Fetal outcome is even more bleak; first- and second- trimester Lassa infections result in spontaneous abortion in approximately 80% of cases. In the third trimester, stillbirth and neonatal deaths approach 75% [32]. Placental and fetal infection with high titer Lassa virus has been demonstrated in such cases, suggesting that the virus directly infects and causes disease in the fetus [31,33]. Virus is also shed in the milk of infected mothers, and vertical transmission through breastfeeding is suspected to occur [33]. It has been suggested that uterine evacuation improves maternal prognosis at every gestational age, with the highest mortality occurring in those women with a fetus remaining *in utero* [32].

Although fewer reports have been published about Ebola infection during pregnancy, available evidence suggests that it can also present devastating consequences for mother and fetus. Most of the available data were gathered by retrospective review of 15 Ebola cases in pregnant patients during the 1995 Ebola outbreak in the Democratic Republic of the Congo [34]. Of the

15 pregnant patients, only one survived, for a case fatality rate of 93%. This was not a statistically significant difference from the overall 77% fatality rate during the outbreak. However, fetal outcomes were worse than maternal outcomes, with only one live birth of a neonate who subsequently died of a febrile illness 3 days later. The mother in this case died from postpartum hemorrhage. Four other infected women died during the third trimester. One woman gave birth to a stillborn infant at 32 weeks estimated gestational age and died herself during the postpartum period. Fetal viral infection was not documented in these cases, but it seems clear that maternal Ebola virus infection results in devastating outcomes for the fetus. As for the effects on nonpregnant women versus men, no survival advantage has been demonstrated for either group. One analysis suggested an increased risk of death for infected males, but this finding was not statistically significant [35]. Ebola virus has been found in semen and vaginal secretions of infected patients even after clinical recovery, suggesting risk of transmission via sexual or occupational exposure to these fluids [36].

For many of the VHFs, few data exist regarding disease in women in general or during pregnancy in particular. Case reports suggest that Hantavirus infection during pregnancy runs essentially the same course as in non-pregnant patients, and fetal infection has not been diagnosed [37]. One case of fetal hypoxic brain injury occurred after maternal Hantavirus pulmonary syndrome with acute respiratory distress syndrome (ARDS), but serologic testing of the infant was negative [38]. A case of intrauterine fetal death was reported with Hantavirus hemorrhagic renal syndrome, but the fetus was not tested for evidence of infection [39]. One case of congenital Rift Valley Fever (RVF) has been reported, and women with RVF infection are thought to have increased rates of spontaneous abortion [40,41]. Little is known about the effect Marburg hemorrhagic fever on pregnancy outcome. The lessons of Lassa, Ebola, and dengue can be applied to clinical manifestations of other VHFs in pregnancy, however, as all conditions predisposing to hypotension, coagulopathy, and hemorrhage bring compounded risk to the pregnant patient and her fetus.

Avian Influenza A (H5N1) virus

Highly pathogenic avian influenza A (H5N1) virus has received much attention in recent years because of its widespread infection of bird populations in many countries and its high mortality among humans, raising concern for an approaching influenza pandemic. Wild birds are the natural reservoir for influenza A viruses and when infected, are usually asymptomatic, but they can infect other birds (e.g., domestic poultry) that may develop disease. Subtypes of influenza A virus are identified by two surface proteins (hemagglutinin [H] and neuraminidase [N]), with 16 known hemagglutinin and 9 known neuraminidase subtypes. Many different combinations of hemagglutinin and neuraminidase proteins are possible, and all known combinations can be found in avian influenza viruses that infect birds. Although avian influenza A viruses primarily affect birds, mutations in genes that produce surface proteins or gene reassortment with human viruses can result in a novel human influenza A subtype virus that can infect humans. If a novel subtype virus to which the human population lacks immunity develops the ability for efficient and sustained transmission among humans, an influenza pandemic could occur [42,43].

Highly pathogenic avian influenza A (H5N1) virus first appeared in humans in Hong Kong in 1997, infecting 18 people, of whom 6 died. Studies of these initial cases demonstrated that exposure to live poultry during the week before the onset of illness was a major risk factor for infection [44]. Culling of poultry in Hong Kong and implementation of other measures contributed to control of the outbreak. However, beginning in 2003, human cases were again observed [42], and as of January 24, 2008, 353 confirmed human cases of avian influenza A (H5N1) from 14 countries with 221 deaths had been reported to the WHO [45]. Cases with probable human-to-human transmission of H5N1 have recently been reported [46], further raising the threat of an influenza pandemic. Although H5N1 virus currently represents the

highest threat for a future pandemic, other avian influenza A viruses that have infected humans also have pandemic potential.

The incubation period for H5N1 appears to be 7 days or less after exposure to infected poultry, and 2 to 5 days, in many cases [47]. Patients with H5N1 influenza virus often develop severe pulmonary disease with rapid clinical deterioration even in previously healthy individuals. They often present with a fever and other symptoms typical of influenza, but manifestations often can extend beyond the lungs to other organ systems (e.g., the gastrointestinal tract) [42], and recent pathological evidence has suggested dissemination to other organs, including the brain [48].

Limited information is available on the effects of avian influenza A (H5N1) virus infection specifically on women. A survey of cases reported by the WHO [49] showed a relatively even distribution between males and females, except in two age groups; males were more often affected in the 4–6 year age group, while females were affected more often in the 25–30 year age group. The authors hypothesized that the increased risk of exposure in males ages 4–6 years was due to their being more active outdoors, while in women aged 25–30 years, the increased risk was due to their roles related to feeding, purchasing, or handling sick poultry in the affected countries.

Information on the effects of avian influenza A (H5N1) virus infection on pregnant women is limited, but there are several reasons for concern. Pregnant women have been shown to be at increased risk for severe complications from seasonal influenza [50–52]. Several reports have also suggested that pregnant women were at high risk of severe illness and death during the pandemics of 1918 and 1957 [53–55]. The WHO recently noted that four of the six pregnant women infected with avian influenza A (H5N1) virus have died [47,56]. A detailed clinical report of one of these women documents rapid progression to multi-organ failure and death, despite intensive supportive care [57].

The potential for effects of avian influenza A (H5N1) virus infection on the fetus also needs to be considered. An increased risk for some birth defects following seasonal influenza infection or its associated fever has been observed in some studies (reviewed in [58] and [59]). High rates of spontaneous pregnancy loss and preterm birth were reported during the influenza pandemic of 1918 [54,55], and possible increases in defects of the nervous system, spontaneous pregnancy loss, fetal death, and preterm delivery were reported following the pandemic of 1957 [60,61]. The effects of H5N1 virus on the fetus are unknown; however, among the two pregnant women with avian influenza A (H5N1) virus who survived, both women had spontaneous abortions [47]. In addition, transmission of H5N1 virus from mother to fetus has recently been documented in one case [48]. During infection with other influenza viruses, viremia and placental transmission appear to occur infrequently [62,63], so the finding of vertical transmission of avian influenza A (H5N1) virus infection might suggest a higher risk for adverse fetal effects with H5N1 virus compared to other influenza viruses [63].

SARS Coronavirus

The 2003 epidemic of severe acute respiratory syndrome (SARS) started in China and rapidly spread throughout the world, affecting more than 8000 people and claiming at least 750 lives. A novel coronavirus (CoV), SARS CoV, was isolated from patients and has been identified as the causative agent in the epidemic. This virus is thought to have been originally transmitted to humans from the palm civet, a feline that can be found in food markets in China [64]. The epidemic in Hong Kong involved 1755 patients diagnosed with SARS, resulting in 302 deaths. In this cohort, the rates of acute respiratory distress syndrome (ARDS) and overall case mortality among women were significantly lower than those in men after adjustment for

multiple variables, including age [65]. The basis for the more benign course in female SARS patients is not known.

Twelve pregnant women were known to be infected with SARS in Hong Kong, and most information regarding the course of SARS in pregnancy comes from this cohort. When compared with matched non-pregnant SARS patients, the pregnant women who were studied demonstrated more severe pulmonary disease and higher case fatality rates and were more likely to develop renal failure and disseminated intravascular coagulopathy [66]. Perinatal outcomes in these women were dismal, with four of seven early trimester patients spontaneously aborting and four of five whose pregnancy continued beyond 24 weeks gestation delivering preterm. Two infants who were born to mothers with acute illness showed intrauterine growth restriction, but no evidence of vertical transmission. Systematic evaluation failed to detect any evidence of neonatal or placental infection, even in babies born during acute maternal SARS infection with demonstrable viral shedding [67]. Two women with pregnancy-associated SARS in the U.S. and one in Canada recovered from their acute illness and went on to deliver healthy, uninfected neonates [68–70]. Eleven of the 12 pregnant patients in Hong Kong received intravenous ribavirin therapy, versus none of the three North American patients, leaving the possibility that the difference in perinatal outcomes could be related to the drug rather than the virus. Interestingly, however, the differences in outcome noted for pregnant women (in a comparison with non-pregnant women) in the Hong Kong case-control study were independent of ribavirin, as it was used equally in the two groups [66]. Ribavirin is a known teratogen in animals, and toxicity has not been systematically evaluated in human pregnancy because of its category X status as designated by the Food and Drug Administration [22].

Spirochetes

Less commonly categorized as emerging infections, nonviral pathogens nonetheless have been described as the source of newly discovered or newly expanding diseases. The spirochetes comprise a group of bacterial pathogens with a particular tendency for perinatal transmission, with the best known of this group being *Treponema pallidum*, the causative agent of syphilis. The impact of syphilis on women has historically been substantial because of its sexual transmission and association with stillbirth and other adverse pregnancy outcomes. However, since the advent of penicillin in the 20th century this disease has been largely brought under control. Other spirochetal illnesses, however, still fall into the category of emerging infectious diseases. During the 1970s, *Borrelia burgdorferi* was identified as the cause of a chronic, relapsing febrile illness named Lyme disease after the Connecticut town where it was discovered. The Lyme spirochete was found to be disseminated through bites from species of deer tick found throughout North America. During the subsequent epidemiologic characterization of Lyme disease, it was shown to cause transplacental infection of the fetus and was associated with stillbirth [71,72]. Multiple reports of congenital Lyme disease prompted large serosurveys of pregnant women; these studies also suggested a link with pregnancy wastage and congenital defects. Subsequent systematic inquiries, however, have failed to show any significant relationship between Lyme serostatus and adverse pregnancy outcomes (reviewed in [73]). Thus, although *B. burgdorferi* has been shown to cause fetal infection, the combination of low disease prevalence and poor sensitivity of diagnostic tests has left doubt as to the clinical significance of these findings. Current recommendations suggest symptom-based antibiotic treatment of pregnant women with suspected Lyme disease before serologic results are available.

Tick-borne relapsing fever (TBRF), endemic worldwide as a cause of severe intermittent febrile illness, is caused by multiple spirochete species of the *Borrelia* genus. There is now thought to be a rodent reservoir of *Borrelia* infection, making TBRF another zoonotic disease

[74]. The tick vector thrives in poor housing conditions, often causing outbreaks of TBRF in villages with tick-infested huts. That phenomenon makes epidemic TBRF more common in economically disadvantaged areas such as sub-Saharan Africa, but recent cases have also been reported in women throughout the western United States [75,76]. In endemic areas, the incidence of TBRF can be as great as 11 cases per 100 person-years-- the highest of any known bacterial pathogen in Africa—making it a major public health concern [74]. *Borrelia* infection has for years been known to cause severe disease in pregnant women, manifesting as stillbirth, preterm birth, neonatal death, and maternal death [77,78]. Adverse pregnancy outcomes occur in as many as 50% of patients, and the prevalence of TBRF among pregnant hospitalized patients at a hospital in southern Zaire was estimated at 6% [79]. Diagnosis can be made on clinical grounds in areas of high prevalence, but demonstration of spirochetemia on peripheral blood smear is the diagnostic criterion of choice. Treatment is with penicillin, doxycycline (contraindicated in the pregnant woman), or erythromycin. Especially during spirochetemia, treatment can be associated with Jarisch-Herxheimer reactions, and thus intensive monitoring is recommended [75]. It is not clear that antibiotic therapy improves short-term maternal or fetal outcomes [78].

Another zoonotic spirochetal illness, leptospirosis, has been strongly associated with spontaneous abortion. *Leptospirosa* species are generally transmitted through ingestion of water contaminated with infected animal urine or feces, and transmission may be associated with farm animals during outbreaks. Infection results in jaundice, malaise, fever, and myalgias, but is usually self-limiting. The organism is endemic to Latin America; however, it is found sporadically worldwide. As early as the 1960s, leptospires were observed in aborted fetal tissues from infected women, and the infection was thought to cause pregnancy wastage [80]. Multiple case reports have confirmed this association, but large studies have not been performed to further characterize the phenomenon. From case reports, it appears that first- and second-trimester maternal infection is more strongly associated with poor pregnancy outcome (50% loss rate or greater) than is third- trimester infection [81]. Congenital transmission to live born infants has been documented after third trimester maternal infection [81]. It is not known whether early treatment of maternal leptospirosis can prevent spontaneous abortion, but antimicrobial therapy is recommended to decrease the duration and severity of the illness.

Chagas Disease

Chagas disease, endemic to South America, Central America, and Mexico, has recently become a concern in the United States due to our large immigrant population [82]. The disease is caused by infection with *Trypanosoma cruzi*, a bloodborne protozoan parasite most commonly transmitted to humans from vertebrate intermediates via the reduvid bug vector. The vector is found throughout the endemic areas, and infected insects have also been identified across the southern United States [82]. Asymptomatic, seropositive women can transmit the parasite transplacentally, with a congenital transmission rate of 1–10% [83]. Clinical manifestations in the infected neonate range from asymptomatic infection in the majority to hepatosplenomegaly, hydrops, and neonatal death in some cases. In recent years, cases of adult Chagas disease have increasingly been diagnosed in the United States, even appearing in recipients of transplants from an infected donor [84]. Concern now exists regarding the safety of the U.S. blood supply, as newly approved screening tests yielded over 300 positive results in selected donors in 2007 [84–86]. One recent study found a 0.3% seroprevalence among the asymptomatic maternal population in Houston, TX, suggesting that many cases of congenital Chagas disease go undiagnosed each year in the U.S. [87]. Neonatal cure rates as high as 90% are achieved when appropriate antimicrobial therapy is initiated during the first year of life, so early diagnosis is imperative [88]. Maternal implications of chronic infection must also be considered, as *T. cruzi* chronically infects the myocardium and can lead to cardiomyopathy, a particularly dangerous condition in pregnancy. Cardiomyopathy or cardiac conduction defects of unknown

etiology in a pregnant woman from an endemic area should prompt testing for *T. cruzi* antibodies, followed by testing and—if necessary--treatment of the neonate with benznidazole or nifurtimox [88]. In the U.S., benznidazole and nifurtimox are not approved by the Food and Drug Administration, but can be obtained under investigational new drug protocols through the CDC drug service (phone 404-639-3670) [88,89].

Bioterrorism

Most potential biological weapons agents are also emerging and/or zoonotic diseases found regularly under natural conditions. The CDC has compiled a list of select agents (available at www.cdc.gov) whose propagation and possession are regulated by federal law based on their lethality and potential for use as biological weapons [90]. Possession, use and transfer of select agents and toxins that pose a severe threat to public health and safety are regulated by federal law to protect both the public and laboratory workers. Many zoonotic diseases appear on the overlapping select agent list, meaning that they are regulated by both the CDC (under the U.S. Department of Health and Human Services (HHS)) and the Department of Agriculture (USDA) based on human and agricultural risk, respectively. The agents that cause viral hemorrhagic fevers and 1918 pandemic influenza virus are included, along with many bacterial pathogens that offer better environmental stability for weaponization. The ideal weapons agents offer a low infectious dose, high case fatality rate, environmental stability, and efficient human-to-human transmission, allowing a small inoculum to infect a large population.

Smallpox has been widely discussed as a biological weapons agent, having been actually weaponized by the former Soviet Union. After the worldwide eradication of smallpox in 1950, the need to vaccinate the population was deemed to be outweighed by the adverse effects of the vaccine. Thus, since the 1970s, people have no longer routinely been immunized against smallpox. After the 2001 anthrax attacks in the U.S., the military started once again vaccinating its personnel with the live attenuated vaccinia virus vaccine (a closely related virus), which provides 95% protection against smallpox infection for at least 5 years. Adverse effects include myocarditis, pericarditis, and occasional dilated cardiomyopathy [91]. Because this is a live attenuated vaccine, its routine prophylactic use is contraindicated in pregnancy. Rarely, the vaccination of pregnant women causes fetal vaccinia infection, which can cause pregnancy loss or neonatal death. However, during times of known exposure or outbreak, the vaccine should be administered to all exposed persons because the risk of smallpox in pregnancy far outweighs that of fetal vaccinia [92]. From limited historical data it is clear that smallpox infection in pregnancy results in case fatality rates as high as 50% and at least a 50% rate of pregnancy loss regardless of gestational age [93]. Pregnant women are also significantly more likely to develop a fatal form of smallpox, known as hemorrhagic smallpox, than are their nonpregnant counterparts [92]. Given the severity of disease, when planning for a possible smallpox attack, authorities clearly must prioritize early vaccination strategies for pregnant women.

Another biological warfare agent of concern, *Coxiella burnetii*, poses a disproportionate threat to women. *C. burnetii* is the causative agent of Q fever, a zoonotic disease generally acquired by handling or inhaling contaminated material from infected cattle or sheep [94]. Interestingly, the economic impact of endemic Q fever results from recurrent abortion in animal herds, with large numbers of bacteria demonstrable in the products of conception. Contact with infected sheep placenta has historically been the greatest risk factor for acute Q fever in humans [94]. Q fever is attractive as a bioterror agent because the bacterium forms environmentally stable spores with a low inhalational infectious dose [95]. The disease generally is not fatal, but it causes pneumonia with weeks of disability during the acute phase and can cause chronic infection associated with treatment-resistant bacterial endocarditis. Human-to-human transmission of Q fever is rare. After zoonotic acquisition, male to female sexual transmission

of *C. burnetii* has been documented, with bacterial DNA found in semen months after the acute infection [96]. Infection of the female genital tract can be chronic, but it has rarely been associated with fetal infection and pregnancy loss in humans [97]. *C. burnetii*-infected women are less likely than infected men to manifest the symptoms of acute Q fever, and pregnancy reduces the rates even more [98]. Pregnant women, however, are more likely to develop chronic Q fever with endocarditis than are infected nonpregnant women [98]. Chronic infection is thought to result from a diminished cell-mediated immune response to the intracellular bacteria, helping to explain the predisposition to chronic, rather than acute disease during pregnancy [4,95]. Although no prospective data are available, it has been recommended that pregnant women and immunosuppressed people receive prophylactic antibiotic therapy in the case of a bioterror attack [95]. Trimethoprim-sulfamethoxazole is recommended as first line prophylaxis and treatment of Q fever in pregnancy, but chronic infection may require long-term treatment with doxycycline and rifampin after delivery [95]. No vaccine for Q fever is available in the United States.

Other high profile biological weapons agents include tularemia, plague, and anthrax. Treatment of pregnant women in the event of an attack with these agents has recently been reviewed [99], and the clinical manifestations in pregnancy generally do not differ from those in the general population. Several principles guide the treatment of pregnant women in the event of a biological weapons attack. Most important, maternal health must be considered the first priority. Second, live, attenuated vaccines are to be avoided except in the case of smallpox exposure. Finally, quinolones, tetracyclines, and ribavirin have been associated with fetal toxicity and alternative drugs should be used *when available*. However, in the case of maternal exposure to life-threatening infectious agents, prophylaxis or treatment with these drugs may be indicated [99].

Conclusions

As recently recognized by the American Medical Association and the American Veterinary Medical Association, the majority of emerging threats to humans are zoonotic infections [2]. Others pose no danger for reservoir animals, but when transmitted to humans they cause devastating disease. Because animals serve as the main natural reservoirs for emerging infections, the organisms can be maintained in nature for long periods in between human outbreaks. Thus, when outbreaks occur, they confront healthcare workers with clusters of severe disease they have likely never before encountered-- and may have difficulty diagnosing. In the case of a bioterrorist attack, the mass casualties could be abrupt and catastrophic. Physicians must recognize the atypical manifestations of emerging infectious threats in the female patient, and accord special emphasis to the unique immunologic state of pregnancy as it relates to both fetal and maternal risk. When outbreaks do occur, systematic and prospective collection of data including patient sex, pregnancy status, and complications must accompany epidemiologic characterization of disease [100].

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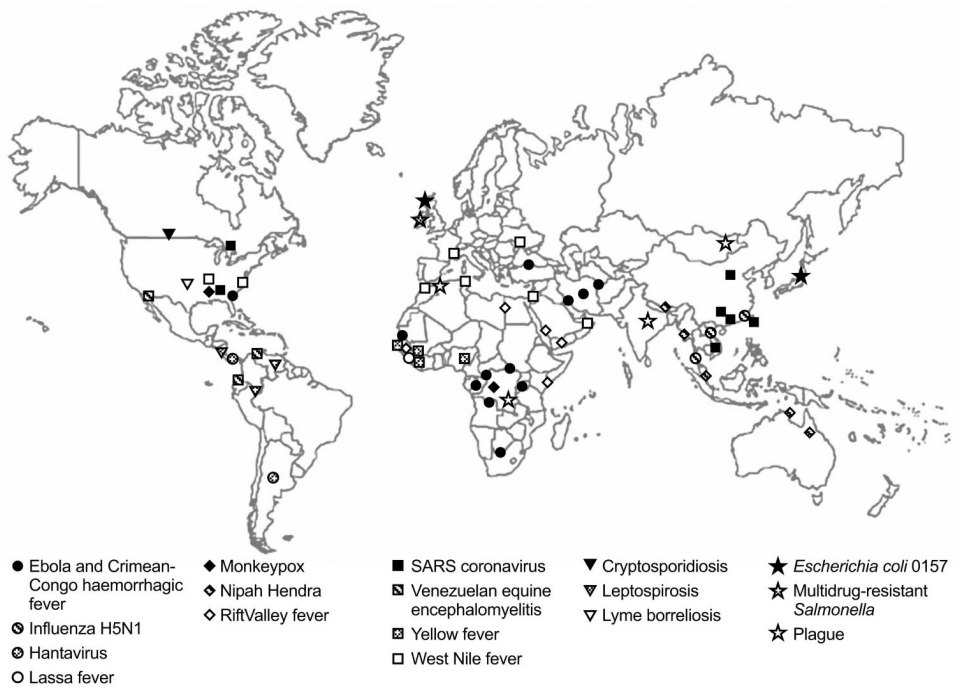

Figure 1. Selected Emerging and Reemerging Infectious Diseases, 1996–2004
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