

# Epidemiology and Management of Infectious Diseases in International Adoptees

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## INTRODUCTION

### Trends in International Adoption

International adoption has become an increasingly common means of creating and growing families in the United States. As evidence of this phenomenon, the number of international adoptees in the United States has increased dramatically over the past decade. In 1995 10,641 orphan visas were issued by the U.S. State department. This number increased to 17,718 in 2000 and to 21,616 in 2003. Since 2000, China has been the leading source of international adoptees in the United States, followed by Russia, Guatemala, South Korea, and Kazakhstan (78) (Table 1). Given the distinct epidemiology of infectious diseases in these primarily developing countries, international adoptees represent a group of patients with unique health care needs.

The majority of studies examining the health of international adoptees have relied on retrospective reviews of medical

records. However, in 1991 Hostetter et al. published a seminal prospective study documenting the high prevalence of infectious diseases and other serious medical problems in international adoptees, many of which were not identified by routine physical exams (36). Multiple studies have subsequently confirmed that international adoptees are at risk for viral, bacterial, and parasitic infections. This review focuses on the epidemiology of those infectious diseases most prevalent in international adoptees, as well as offer guidelines for the medical management of infections commonly encountered in this unique population of children.

## EPIDEMIOLOGY OF INFECTIOUS DISEASES IN INTERNATIONAL ADOPTEES

A summary of infectious diseases seen in international adoptees is given in Table 2.

### Viral Infections

**HIV.** The human immunodeficiency virus (HIV) is a single-stranded RNA virus that is transmitted via intimate exposure to blood or body fluids. Potential modes of infection of inter-

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TABLE 1. Numbers of international adoptees in the United States

| Country of origin | No. of orphan visas issued 2003 (% of total) |
|-------------------|--|
| China .....       | 6,859 (31.7)                                 |
| Russia .....      | 5,209 (24.1)                                 |
| Guatemala.....    | 2,328 (10.7)                                 |
| South Korea.....  | 1,790 (8.2)                                  |
| Kazakhstan.....   | 825 (3.8)                                    |
| Ukraine .....     | 702 (3.2)                                    |
| India.....        | 472 (2.1)                                    |
| Vietnam.....      | 382 (1.7)                                    |
| Colombia.....     | 272 (1.2)                                    |
| Haiti.....        | 250 (1.1)                                    |
| Total .....       | 21,616                                       |

national adoptees include both mother-to-child (perinatal) transmission and transmission through contact with contaminated needles or sexual abuse within institutional settings. The risk of perinatal HIV transmission is approximately 25%, although the incidence can be dramatically reduced through the use of peripartum antiretroviral therapy (2). Although many children infected perinatally with HIV are asymptomatic, others exhibit a variety of clinical signs and symptoms, including growth delay, hepatosplenomegaly, and recurrent bacterial infections. Advanced HIV infection is also associated with a number of well described opportunistic infections, including recurrent oral candidiasis (thrush) and *Pneumocystis carinii* pneumonia, conditions that are also associated with malnutrition, a common finding in international adoptees.

In Eastern Europe and Russia there were an estimated 280,000 new cases of HIV in 2003, mostly associated with injection drug use (23). Although the overall prevalence of HIV infection in China is low, estimates suggest that up to 1 million people may currently be infected (62). This number may rise to more than 10 million by 2010. Importantly, little is known about regional variation in seroprevalence, thus making the overall risk among Chinese adoptees difficult to estimate. HIV is also a major public health problem in other Asian countries, as recent estimates suggest that there are more than 100,000 active infections in Vietnam and Cambodia and more than 300,000 in India (65). In Vietnam, the seroprevalence of HIV among pregnant women may be as high as 0.28%, representing a small but measurable risk to international adoptees

TABLE 2. Infectious diseases in international adoptees

| Infection  |
|--|
| <b>Viral</b>   |
| Varicella-zoster virus, hepatitis B virus, hepatitis C virus, measles virus, HIV   |
| <b>Bacterial</b>   |
| <i>Mycobacterium tuberculosis</i> (active or latent), syphilis, gastroenteritis, urinary tract infection   |
| <b>Parasitic</b>   |
| Intestinal protozoa ( <i>Giardia lamblia</i> , <i>Blastocystis hominis</i> , <i>Dientamoeba fragilis</i> ), ectoparasites (scabies, head lice), intestinal nematodes ( <i>Strongyloides stercoralis</i> , <i>Trichuris trichiura</i> , <i>Ascaris lumbricoides</i> , hookworm), visceral larva migrans ( <i>Toxocara</i> spp.) |

(26). The HIV seroprevalence in South Korea is estimated to be less than 0.1% (84). Data on the prevalence of HIV in Guatemala is limited, but one U.S. government report estimated that in 2002 there were 203 children under the age of 14 years infected with HIV (77).

The above data suggest that there might be a significant risk of HIV infection in international adoptees, especially those from Eastern Europe. One study published in 1993 reported an HIV seroprevalence of 20% in a Romanian orphanage, although the route of infection in these children was most likely related to exposure through contaminated needles (32). More recent studies have failed to identify a confirmed case of HIV infection in an international adoptee (56, 59). Although Saimen et al. identified 2 out of 490 adoptees (0.4%) with antibodies to HIV, both tested negative for infection by HIV PCR, suggesting that the initial test detected maternal antibody (66). The likely explanation for the very low rates of HIV infection among recent international adoptees is that preadoption testing is now common, especially in China and Eastern Europe. Thus, although concern about HIV infection remains a source of great anxiety for adoptive families, there is little evidence to date that this disease represents a major health risk for international adoptees.

**Hepatitis B virus.** Hepatitis B is a double-stranded DNA virus of the *Hepadnaviridae* family. Most hepatitis B virus infections in underdeveloped countries are acquired during childbirth. The risk of transmission from a hepatitis B surface antigen (HBsAg)-positive mother to her newborn is approximately 10%, although this number rises to 85% in women who are HBeAg positive (70). While the incubation period for hepatitis B virus in adults ranges from 4 weeks to 4 months, those who acquire the infection perinatally may remain asymptomatic for decades (48, 51). Symptoms are often insidious in onset and may include jaundice, vomiting, and anorexia. Serum hepatic transaminase levels and bilirubin may be elevated, and anemia is also common. Up to 90% of children who acquire hepatitis B virus perinatally will progress to chronic infection, with an increased risk of cirrhosis and hepatocellular carcinoma. The lifetime risk of hepatocellular carcinoma is 50% for men infected at birth and 20% for women (71). Studies in Taiwan clearly indicate that hepatitis B vaccination dramatically decreases the incidence of hepatocellular carcinoma as well as other long-term sequelae of hepatitis B virus infection (12).

According to estimates from the Centers for Disease Control and Prevention, 2 to 7% of the population in China, South America, and the southern part of Eastern Europe are HBsAg positive, consistent with chronic infection. In other countries of Eastern Europe, including Moldova, Bulgaria, Georgia, Armenia, and Azerbaijan, the prevalence of HBsAg is perhaps greater than 8% (11). Therefore, internationally adopted children should be considered at potentially significant risk of infection with hepatitis B virus. A variety of retrospective studies have evaluated international adoptees for serological evidence of hepatitis B virus infection. The percentage of infants with evidence of active infection (seropositive for HBsAg) ranged from 2.0% to 5.9% (36, 46, 56, 59, 66), while serological evidence for previous infection ranged from 22% to as high as 53% (39, 40). Although these data suggest a significant risk of hepatitis B virus infection in international adoptees, it is also

likely that an increased availability of preadoption medical screening has identified many infected children in orphanages.

**Hepatitis C virus.** Hepatitis C virus is an RNA virus of the *Flaviviridae* family. Infection is acquired most commonly via exposure to blood and/or other body fluids, often through transfusions or the use of contaminated needles. The risk of perinatal transmission is estimated at 2 to 8% (21), although the rate in mothers coinfecting with HIV may be as high as 15% (27). Up to 85% of infected individuals will eventually develop chronic hepatitis, as evidenced by elevated serum levels of hepatic transaminases (42). These patients are at significant risk of progressing to cirrhosis and/or developing hepatocellular carcinoma.

The Global Burden of Hepatitis C Working Group of the World Health Organization estimates that the prevalence of hepatitis C in Russia, China, and Eastern Europe is 2 to 2.9% (28). In South America, the prevalence is estimated at 1 to 1.9%. When these prevalence rates are compared to those of hepatitis B, the prediction would be that the risk of hepatitis C is significantly lower. Limited data from published studies appear to confirm that hypothesis, with reported seroprevalence rates of well under 1% in international adoptees, despite the fact that few children are likely to be screened for hepatitis C virus infection in foreign orphanages (56, 66).

**Measles virus.** Measles virus, a single-stranded RNA virus spread by contact with respiratory droplets, is common in many of the countries from which children are adopted into the United States. Following an incubation period of 8 to 12 days, initial symptoms include fever, cough, conjunctivitis, coryza, and Koplik's spots, which are whitish plaques on the buccal mucosa. Patients are infectious for several days before the onset of the rash. The diagnosis is often made based on the constellation of clinical symptoms described above, although serologic studies can be helpful to confirm the diagnosis. Therapy for measles is primarily supportive (61).

Although the World Health Organization estimates that 84% of children worldwide are presently vaccinated, millions of cases of measles occur annually (83). In 2001 there was an outbreak of measles in the United States that was traced to a group of adoptees from China (10). Epidemiologic investigations ultimately identified 10 adoptees from a single orphanage, as well as four additional cases resulting from exposure to one of the infected adoptees. In April 2004, adoptions from Hunan Province in China were temporarily suspended due to a separate outbreak among a group of adoptees (10). Overall, 9 of 12 children in a group of adoptees traveling to the United States developed clinical signs and symptoms of measles. All cases were ultimately traced to a single orphanage, which was in the midst of an outbreak involving many additional cases. This outbreak emphasizes that international adoptees, in particular those from Chinese orphanages, are at increased risk due to the failure of current immunization practices.

**CMV.** Cytomegalovirus (CMV) is a double-stranded DNA virus transmitted by contact with infected bodily fluids, including saliva or urine. CMV infection can also be acquired in utero or during the neonatal period. Based on data from large, population-based seroepidemiologic studies, most individuals living in developing and industrialized nations acquire infection by young adulthood. Both primary infection and reactivation during pregnancy are associated with some risk of con-

genital infection of the newborn (25). Congenitally infected newborns are frequently asymptomatic but may manifest a combination intracranial calcifications, retinitis, hepatitis, deafness, and thrombocytopenia. Importantly, the absence of clinical findings at birth does not necessarily predict a benign course, as sequelae may develop later in childhood. Ganciclovir has been evaluated in the treatment of congenitally acquired CMV, and small studies suggest that treatment initiated early in the postnatal period may reduce the incidence of deafness (54).

The clinical significance of CMV infection in international adoptees is most likely low. While Hostetter et al. cultured CMV from the urine of 111/245 international adoptees (45%), only three children demonstrated clinical evidence of congenitally acquired infection (36). Of these, two children had hepatitis and one had deafness with intracranial calcifications. One published report described two Chinese infants with CMV pneumonia and immunodeficiency, and the authors hypothesized that malnutrition increased their susceptibility to infection (8). The current prevalence of infection in international adoptees is unknown, as most adoption specialists do not routinely screen for CMV. Since CMV isolated from adoptees in most cases represents postnatally acquired infection, viral shedding in the absence of physical findings suggestive of congenital CMV is of limited clinical significance.

**SARS virus and avian influenza virus.** International adoptees, as well as prospective adoptive family members, are at potential risk for acquiring two newly emerging respiratory viral infections (44). From November 2002 to March 2003, approximately 300 cases of pneumonia of unknown etiology were reported in Guangdong Province, China (15). In the ensuing months, the illness, which became known as severe acute respiratory syndrome (SARS), rapidly spread to nearly 30 countries, with over 8,000 infections and a case fatality rate of approximately 10%. The etiologic agent of SARS is a novel coronavirus with genetic similarity to a strain identified in palm civets, which are commonly sold in live-animal markets in China (45, 64). Person-to-person transmission of SARS has occurred on commercial airplanes and within hospital settings, although the factors that contribute to the risk of secondary transmission have not been completely defined (60, 81).

Because of the established risk of person-to-person transmission of the SARS virus, the potential exists for international adoptees to acquire (and hence transmit) the infection within the orphanage setting. Prospective parents or family members are also at risk for acquiring the infection in China, as are fellow travelers on commercial airplanes who are exposed to an infected adoptee or adult. The clinical signs and symptoms of SARS in children are often milder than those in infected adults, perhaps lowering the index of suspicion for younger individuals with respiratory illness (34, 49). Out of concern for the spread of SARS, adoptions in China were temporarily suspended in 2003. Fortunately, through aggressive public health measures, the incidence of SARS has been dramatically reduced over the past year, and adoptions are now proceeding regularly.

In 2003, China and other Asian countries reported a number of cases of influenza caused by the H5N1 avian strain of influenza A virus (43, 44). These infections occurred primarily in individuals who had contact with infected poultry, although

evidence also suggested some degree of person-to-person transmission (43). In children, infection with avian influenza is associated with high mortality (31). Because of concern about the potential for the virus to undergo a genetic reassortment, thus altering its pathogenicity, there remains some risk for this strain to evolve into one that is easily transmitted among humans (9, 43). Of note, the currently available influenza vaccines do not confer protection against the avian H5N1 strain, although the antiviral drug oseltamivir may be useful for therapy in some settings (30). Should this strain of influenza A spread throughout China, there would be risk of international adoptees acquiring the infection and transmitting it to prospective family members and travelers (44).

### Bacterial Infections

***Mycobacterium tuberculosis.*** *Mycobacterium tuberculosis* is an acid-fast bacillus (AFB) transmitted via inhalation of airborne particles. More than one-third of the world's population is infected with *M. tuberculosis*. Most children with *M. tuberculosis* have latent (asymptomatic) infection and are diagnosed on the basis of a positive intradermal (Mantoux) skin test using a purified protein derivative (PPD) of the *M. tuberculosis* bacterium (69). Symptoms of primary pulmonary tuberculosis in infants and children include cough, fever, and occasionally growth delay. A variety of radiographic findings may be present on chest X ray, including perihilar lymphadenopathy, lobar consolidation, atelectasis, or diffuse pneumonitis. Children are also at significant risk for extrapulmonary manifestations of tuberculosis, including lymphadenitis (scrofula), nephritis, meningitis, osteomyelitis, and disseminated (miliary) disease (74).

The estimated incidences of all new cases (per 100,000 people) of *M. tuberculosis* infection in the most common countries of origin of international adoptees are as follows: China, 112.7; Russia, 126.4; Guatemala, 77.2; South Korea, 90.6; and Kazakhstan, 145.6 (82). These data suggest that exposure to *M. tuberculosis* is common in international adoptees and represents a potentially significant health risk to both the adoptees and their immediate families. This risk is illustrated in a published report documenting transmission of *M. tuberculosis* from an adopted child to family members in the United States (17).

Numerous studies have examined rates of latent *M. tuberculosis* infection in international adoptees. The percentage of children with a positive PPD skin test has ranged from as low as 1.0% to as high as 19% (1, 36, 40, 46, 56, 66). Of note, the majority of children with evidence of *M. tuberculosis* infection were adopted from Russia and China. Studies from the early 1990s reported a relatively high incidence of active tuberculosis in international adoptees with positive skin tests. For example, a study by Nicholson et al. that found 3/9 children with a positive Mantoux test had evidence of active disease (59), while a second study identified 4 of 10 children with positive skin tests and evidence of pulmonary tuberculosis (36). More recent reports, however, suggest that most international adoptees with positive PPD skin tests are unlikely to have active tuberculosis (1, 36, 40, 46, 56, 66). Nonetheless, global trends in transmission of *M. tuberculosis* suggest that international adoptees will remain at increased risk for infection.

**Syphilis.** Syphilis is caused by infection with the bacterial spirochete *Treponema pallidum*. In children, including international adoptees, the likely routes of *T. pallidum* transmission include perinatal acquisition and sexual abuse. Newborns frequently do not manifest the hallmark signs of congenital infection, which include anemia, thrombocytopenia, hepatosplenomegaly, and rash. If untreated, however, children with congenital syphilis may develop significant growth and cognitive delays, deafness, keratitis, and dental findings (Hutchinson teeth) (18).

A recent increase in the incidence of syphilis in the former Soviet Union has been well documented (63). In China, the prevalence of syphilis, including congenital syphilis, may be increasing, although published data are incomplete and may not accurately represent what is likely to be substantial regional variation. Of note, one report suggests that the incidence of syphilis in China increased from 0.18/100,000 in 1993 to 4.31/100,000 in 1998, suggesting a potential increase in the risk of congenital infection in adoptees (13). By contrast, the prevalence of syphilis in South Korea is only 0.2% (14), while data from Guatemala are unavailable.

Despite recent increases in the global incidence of syphilis, particularly in Eastern Europe, studies of international adoptees have reported a prevalence of less than or equal to 1.7% (36, 40, 46, 56, 59). As is the case with HIV infection, the relatively low prevalence suggests that many children are likely screened for syphilis before being referred for adoption. In support of this, many orphanage records, particularly for children adopted from Russia and Eastern Europe, contain references to syphilis treatment, in either the birth mother or child.

***Helicobacter pylori.*** *H. pylori* is a gram-negative bacillus that colonizes the gastric mucosa. Infection is often acquired during childhood and is frequently transmitted in institutional settings. Although the infection is more commonly diagnosed in adults with peptic ulcer disease, data suggest that children are also at risk for acquiring *H. pylori*. Although infection in children is usually asymptomatic, chronic infection has been associated with an increased risk of gastroesophageal reflux, growth delay, and gastric cancer. There are a variety of ways to diagnose *H. pylori* infection, including the [<sup>13</sup>C]urea breath test, a fecal antigen test, serologic testing, and endoscopy with gastric biopsy (29, 80). Treatment of *H. pylori* infection in otherwise asymptomatic children is not recommended, although combination antibiotic regimens are effective at eradicating the organism (29).

Miller et al. have published the only study examining the seroprevalence of *H. pylori* antibodies in international adoptees (57). They reported that 31% of children had evidence of *H. pylori* infection. Risk factors included residence in an orphanage and older age at adoption. Of note, children with *H. pylori* antibodies were twice as likely to have intestinal parasites on fecal examination, although infection was not associated with anemia, gastrointestinal symptoms, or growth delay (57). Thus, the clinical significance of *H. pylori* antibodies in international adoptees remains to be determined.

**Bacterial gastroenteritis.** Several studies have identified enteric bacterial pathogens by culturing stool samples from international adoptees. Published rates of bacterial gastroenteritis in international adoptees range from 2.5% to 7.0%. The two most common bacterial pathogens isolated on routine



fecal culture include *Salmonella* spp. and *Campylobacter jejuni* (36, 56, 59, 66). The above data suggest that internationally adopted children are at modest risk for colonization with pathogens known to cause bacterial gastroenteritis. However, in the absence of specific gastrointestinal symptoms, the value of routine stool culture for bacteria has not been established.

### Parasitic Infections

**Intestinal parasites.** Gastrointestinal parasites, particularly protozoa, are frequently transmitted via contaminated drinking water but also may be spread from person to person through fecal-oral contact. As numerous outbreaks in institutionalized settings have been reported, it is not surprising that intestinal protozoa are frequently identified on routine screening of international adoptees. Examination of a fresh fecal specimen by microscopy is an effective means of diagnosing intestinal parasites, although the sensitivity increases markedly if multiple samples are evaluated. In the case of the protozoan parasite *Giardia lamblia*, a commercially available fecal antigen test has high sensitivity for detecting mild to moderate infections.

Infection with intestinal parasites is common in international adoptees, with a prevalence of 14% to 33%. The most common intestinal parasite identified in adoptees is *Giardia lamblia*, which is found most often in children from Eastern Europe (40, 66). In addition to having giardiasis, international adoptees may also be infected with other parasites, including *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Blastocystis hominis*, and *Dientamoeba fragilis* (36, 39, 56, 59).

**Ectoparasites. (i) Scabies.** Scabies is a skin infection caused by the mite *Sarcoptes scabiei*. Outbreaks have been reported in a variety of institutional settings, including orphanages. Early infection may be asymptomatic, after which the host becomes highly sensitized to the infestation. In contrast to primary infection, reinfection is associated with significant symptoms, including diffuse pruritus and the development of a diffuse pustular rash. Intertriginous areas, as well as the wrist, ankles, and web spaces between the fingers and toes are most commonly involved. Scrapings of the pustular lesions may reveal adult scabies when examined under light microscopy. Lange and Warnock-Eckhart identified 4/360 (1.1%) Korean adoptees with scabies (46). Not surprisingly, all four infected children were living in an orphanage, rather than in foster homes as is typical for Korean adoptees. Nicholson et al. diagnosed scabies in 7/99 (7%) adoptees evaluated in a hospital-based clinic in Australia (59). Otherwise, data on the prevalence of scabies in international adoptees are limited.

**(ii) Lice (pediculosis).** Lice are bloodfeeding arthropods that infect the hair and scalp (*Pediculus capitis*), body (*Pediculus corporis*), or pubic area (*Phthirus pubis*). Risk factors for pediculosis include living in an institutionalized setting, such as an orphanage. Infection with *Pediculus capitis* may be asymptomatic, although pruritus of the scalp is a common feature. The diagnosis is made by identifying any of the major life cycle stages of the arthropod, including adults, nymphs, or eggs. The exact prevalence of head lice in international adoptees is unknown. However, Nicholson et al. reported that 4/99 (4%) of a group of international adoptees evaluated in their clinic were diagnosed with head lice (59). Hostetter et al. also identified

cases of head lice in their series of international adoptees, although the prevalence was not reported (36). Jenista and Chapman reported 13/124 (10.5%) children with head lice and/or scabies (39).

### INFECTIOUS DISEASES IN INTERNATIONAL ADOPTEES: THE YALE INTERNATIONAL ADOPTION CLINIC EXPERIENCE

The Yale International Adoption Clinic (YIAC), located in New Haven, Conn., is a hospital-based specialty clinic that provides preadoption counseling and medical/developmental evaluations of international adoptees. To date, the YIAC has evaluated more than 800 children adopted into families living primarily in Connecticut, New York, Vermont, Massachusetts, and Rhode Island. In order to compare the published literature with our recent experience, we reviewed the infectious disease diagnoses for the last 105 consecutive patients who underwent medical screening at the YIAC. All children underwent a routine physical examination and standard medical screening (see "Postadoption Medical Screening" below). Roughly one-third of these children were born in Russia, while another one-third were from China. The remaining one-third were adopted from 10 other countries. All 105 children (72 females and 33 males) were evaluated between 8 September 2003 and 14 March 2005, and the average age was 27 months (range, 4 months to 11 years).

Table 3 lists various markers of infectious diseases identified in these children. The data suggest that the YIAC experience is similar to that gleaned from published reports from clinics specializing in the evaluation of international adoptees. In particular, the data demonstrate that the risk of serious infections, including HIV, hepatitis B virus, and hepatitis C virus, in recent adoptees is low. Other infections, however, remain common in adoptees, including varicella-zoster virus (VZV) infection (25%), giardiasis (20%), and scabies (10%). In addition, the YIAC data also reveal a high prevalence of hepatitis B virus surface antibody seropositivity (70%) in international adoptees, with little evidence of prior infection. This finding most likely reflects a high rate of hepatitis B virus immunization and confirms that most international adoptees are at low risk of infection. In support of this, only one child out of the 100 tested (1%) was found to have chronic hepatitis B virus infection.

The high seroprevalence rate (25%) for VZV is worth noting, as little is known about this infection in international adoptees. Further analysis revealed that those children who were seropositive tended to be older (mean age,  $57 \pm 35$  months) than those who were seronegative (mean age,  $22 \pm 20$  months), although the difference was not found to be statistically significant. These data confirm that, as expected, children acquire VZV over time in their country of origin and that routine screening for infection may be warranted. Other common infections in this cohort of recent adoptees included giardiasis and scabies, which were identified in 20% and 9.5% of adoptees, respectively. Taken together, these data confirm that adoptees, most of whom have lived in orphanages, are at risk for infections well known to be transmitted efficiently within institutional settings.

Three out of 98 (3.1%) children evaluated in the YIAC were

TABLE 3. Markers of selected infectious diseases (by country of origin) in children evaluated at the Yale International Adoption Clinic from September 2003 to March 2005<sup>a</sup>

| Country ( <i>n</i> ) | No. positive/no. tested (% positive) |                       |            |                         |              |
|----------------------|--------------------------------------|-----------------------|------------|-------------------------|--------------|
|                      | Giardia antigen                      | HBsAb                 | VZV IgG    | VDRL/FTA                | Scabies      |
| Russia (33)          | 7/26 (27)                            | 26/32 (81)            | 3/12 (25)  | 1/30 (3.3)              | 5/33 (15)    |
| China (32)           | 3/17 (17.6)                          | 20/30 (66)            | 1/18 (5.5) | 0/29                    | 4/32 (12.5)  |
| Guatemala (10)       | 0/8                                  | 7/9 (77)              | 0/6        | 1/10 (10)               | 0/10         |
| Kazakhstan (9)       | 0/5                                  | 7/9 (77)              | 4/8 (50)   | 0/9                     | 1/9 (11)     |
| Ukraine (5)          | 3/4 (75)                             | 2/5 (40)              | 0/3        | 0/5                     | 0/5          |
| Poland (3)           | 0/3                                  | 1/3 (33)              | 3/3 (100)  | 0/3                     | 0/3          |
| Ethiopia (3)         |                                      | 1/3 (33) <sup>b</sup> | 2/3 (66)   | 0/3                     | 0/3          |
| Korea (3)            | 0/2                                  | 3/3 (100)             | 0/1        | 0/3                     | 0/3          |
| Georgia (2)          | 0/1                                  | 0/2                   |            | 1/2 (50)                | 0/2          |
| Belarus (2)          | 1/2 (50)                             | 1/2 (50)              | 1/1 (100)  | 0/2                     | 0/2          |
| India (2)            | 0/2                                  | 2/2 (100)             |            | 0/2                     | 0/2          |
| Romania (1)          |                                      |                       |            |                         | 0/1          |
| Total (105)          | 14/70 (20)                           | 70/100 (70)           | 14/55 (25) | 3/98 (3.1) <sup>c</sup> | 10/105 (9.5) |

<sup>a</sup> All patients were seronegative for antibodies to HIV and hepatitis C virus. Additional infections diagnosed included visceral larva migrans in one child from Guatemala and head lice in one child from Ethiopia.

<sup>b</sup> One child was found to have circulating HBsAg and HBcAb in the absence of HBsAb, consistent with chronic hepatitis B virus infection.

<sup>c</sup> One child was FTA positive and VDRL negative in serum, with a preadoption record of treatment for congenital syphilis. The other two children were positive for both VDRL and FTA.

diagnosed with congenital syphilis (one from Russia, one from Guatemala, and one from Georgia). Although this rate of infection is somewhat higher than those reported in other studies, the small sample size make it difficult to draw conclusions as to the significance of this finding. Of note, two of the three children diagnosed with congenital syphilis had no mention of this infection in the preadoption record, raising concerns about the reliability of preadoption medical information (see below).

### PREADOPTION MEDICAL RECORD REVIEW

Anecdotal reports suggest that preadoption medical records are often misleading and inaccurate, although some experts maintain that records from certain countries (e.g., South Korea) may be more reliable than those from others (e.g., China and Russia) (38). Over the past decade, it has become increasingly common for prospective parents to ask specialists in international adoption, as well as primary care pediatricians, to review video tapes and/or medical records in order to help inform their decision whether or not to adopt a particular child. However, foreign medical records are often difficult to interpret because of incomplete information and inaccurate translation, as well as the presence of multiple, often confusing diagnoses. While several articles refer to these difficulties, few studies have rigorously examined the accuracy of foreign medical records by comparing them to laboratory data and physical exam findings after adoption.

Albers et al. reviewed preadoptive medical records for 43 children adopted from Eastern European orphanages (1). Pneumonia or bronchitis was listed as a prior medical diagnosis in 18/43 children (42%). Otitis media was listed in 7/43 records (16%), adenoidal hypertrophy in 2/43 (4.6%), diarrhea in 2/43 (4.6%), dysbacteriosis in 2/43 (4.6%), measles in 2/43 (4.6%), and pertussis in 2/43 (4.6%). Laboratory studies carried out postadoption also identified multiple infectious diseases not documented in the medical record. These included chronic

(2%) and prior (14%) hepatitis B infection, tuberculosis (5%), and intestinal pathogens (51%). Additionally, this study found significant discordance between the postadoptive physical exam and preadoptive medical record for noninfectious medical conditions as well. These data suggest that the preadoption medical record is neither sensitive nor specific for accurately assessing the risk of infectious diseases in international adoptees. Therefore, parents should be counseled on the inherent uncertainty of medical record review as a means of evaluating the health of prospective adoptees.

### POSTADOPTION MEDICAL SCREENING

In 1991, Hostetter et al. reported that 81% of the medical diagnoses for international adoptees were detected through the use of defined screening tests and not by routine history or physical examination (36). The authors concluded from that study that all children who are adopted from foreign countries should undergo thorough testing in order to identify occult conditions, most of which were infectious diseases. Original recommendations based on these findings included screening for infection with hepatitis B virus, HIV, tuberculosis, syphilis, CMV, and intestinal parasites. Additional medical tests included a complete blood count and urinalysis (36). These recommendations have been modified somewhat over the past decade (Table 4), although the principles upon which these original recommendations were based have not changed.

In the YIAC, adoptees are tested for antibodies to HIV types 1 and 2 by serum enzyme-linked immunosorbent assay (ELISA), with a confirmatory Western blot if the ELISA is positive. Although serologic testing for antibodies to HIV is useful for screening, a positive antibody test (ELISA or Western blot) in children less than 1 year of age may reflect acquisition of maternal antibody, and thus this test lacks specificity in young adoptees. Conversely, a negative HIV antibody test does not rule out recent infection, particularly if there is a possibility that a child was exposed through the use of a con-

TABLE 4. Medical screening tests for international adoptees

| Test   |
|--|
| Routinely recommended  |
| Hepatitis B virus surface antigen, surface antibody, and core antibody |
| Hepatitis C virus antibody   |
| HIV ELISA and RNA PCR if ELISA positive                                |
| Varicella-zoster virus antibody  |
| Fecal examination for parasite ova and <i>Giardia</i> antigen          |
| Urinalysis   |
| VDRL (RPR) and FTA   |
| PPD skin test for <i>M. tuberculosis</i>                               |
| Complete blood count with differential serum lead level                |
| Thyroid-stimulating hormone level                                      |
| Hearing  |
| Vision   |
| Developmental evaluation   |
| Occasionally recommended   |
| Stool culture for bacterial pathogens                                  |
| Urine culture  |
| Liver function tests   |
| Serum electrolytes   |
| Hemoglobin electrophoresis   |
| Serum G6P-D <sup>a</sup> level   |
| Generally not recommended  |
| <i>H. pylori</i> antibody  |
| CMV antibody and/or urine culture for CMV                              |

<sup>a</sup> G6P-D, glucose 6-phosphate dehydrogenase deficiency.

taminated needle just prior to adoption. Therefore, for recent adoptees, we also test for HIV by using an RNA PCR assay. If PCR testing is not available, we recommend repeating the ELISA at 4 to 6 months postadoption to definitively rule out infection with HIV.

We routinely test adoptees for hepatitis B virus infection by using standard serologic assays. Acute hepatitis B infection is characterized by the presence of HBsAg, HBeAg, and hepatitis B virus core antibody (HBcAb). Resolution of acute infection is associated with a rise in hepatitis B virus surface antibody (HBsAb) and the disappearance of HBsAg from the bloodstream. Chronic infection is characterized by the persistence of HBsAg, as well as HBcAb. The presence of HBcAb generally distinguishes those with past infection from those who have been previously immunized, as both groups will have measurable HBsAb (48, 51). In recent adoptees who do not have HBsAb on the initial screen, we recommend repeating the hepatitis B panel in 2 to 3 months in order to rule out infection immediately prior to adoption. For those children who are chronically infected with hepatitis B virus, interferon alfa-2b may be effective therapy (72).

Testing for serum antibodies to hepatitis C virus is the recommended method of screening international adoptees. However, because maternal antibodies to hepatitis C virus may persist for at least 1 year after birth, a positive antibody test does not necessarily indicate ongoing infection in an infant. Therefore, in children with a positive antibody test for hepatitis C virus, we confirm the infection by using an RNA PCR assay. Dunn et al. studied the appropriate timing of diagnostic tests for hepatitis C virus in neonates and determined that serologic testing for perinatally acquired infection was not conclusive

until a child reaches 18 months of age (20). However, a negative PCR test in an infant older than 4 weeks of age, even in the presence of antibodies to hepatitis C virus, suggests that the child is not infected. For children evaluated less than 2 months following adoption, repeating the hepatitis C virus antibody test will identify those who might have been exposed just prior to adoption. Children who are infected may benefit from therapy with alpha interferon, either alone or in combination with ribavirin (19, 21, 42, 52, 75).

Given the fact that children with congenital syphilis are often asymptomatic, serologic testing should be performed for all international adoptees. The Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests are highly sensitive, although false-positive results may occur in individuals with rheumatologic or inflammatory conditions. All positive nontreponemal tests (VDRL or RPR) must be confirmed using the fluorescent treponemal antibody (FTA) absorption test, which is more specific (6). Infected children should undergo lumbar puncture for VDRL testing of the cerebrospinal fluid in order to rule out neurosyphilis, as well as a complete blood cell count, liver function tests, long-bone radiographs, and vision and hearing screening (18). For therapy of children with untreated congenital syphilis, we recommend 10 days of intravenous penicillin G (100,000 to 150,000 U/kg/day). The response to therapy should be monitored by following VDRL test levels every 3 to 6 months for up to 24 months, with the goal of documenting a fourfold drop in titer or reversion to negative. Those children with a positive VDRL test in the cerebrospinal fluid require a repeat lumbar puncture in 6 months to document a reduction in titer (6). Importantly, the FTA absorption test will remain positive, even after therapy. Because of the difficulty in validating orphanage records, we recommend therapy for all seropositive adoptees, even if there is written or verbal documentation of treatment prior to adoption.

In the absence of gastrointestinal symptoms, a single fecal sample should be evaluated for parasite ova and *Giardia* antigen. It is recommended that international adoptees receive treatment for *Giardia* infection because of the potential for transmission to close contacts (35). Metronidazole, tinidazole, and nitazoxanide are all effective (24, 85). Of note, Saimen et al. reported that 85/87 (97.7%) adoptees with giardiasis were cured after one course of therapy, while the remaining 2 responded to a second course (66). In our experience, some children may continue to experience gastrointestinal symptoms, particularly loose stools, for weeks to months following treatment. Treatment is also recommended for international adoptees infected with intestinal nematodes. Albendazole and mebendazole, two benzimidazole anthelmintics, are effective against *Ascaris*, *Enterobius*, hookworm, and *Trichuris* (58). Pyrantel pamoate is also approved for the treatment of intestinal nematodes, although it is not active against *Trichuris*. Nitazoxanide is also effective against a broad array of intestinal nematodes and may be a reasonable alternative (24). For those adoptees with evidence of gastroenteritis, we also obtain a stool culture for pathogenic bacteria and *Cryptosporidium*.

Although many international adoptees have records and/or a cutaneous scar (most commonly in the left deltoid) consistent with prior *Mycobacterium bovis* BCG vaccination, we routinely recommend a PPD skin (Mantoux) test as part of their post-

adoption medical screening. Interpreting the significance of a PPD skin test result requires an initial assessment of an individual's pretest probability of being infected. Therefore, because of the high rates of tuberculosis in countries from which children are adopted into the United States, most experts recommend greater than or equal to 10 mm of induration as the positive threshold for international adoptees. The risk of a "false-positive" PPD skin test associated with prior BCG immunization is considered low if the skin test is placed at least 1 year following the vaccine (50), although recent data suggest that prior BCG immunization is associated with significant PPD reactions years later (76). False-negative results may be due a number of factors, including malnutrition, concurrent inflammatory/rheumatologic disease, underlying immune deficiency, active *M. tuberculosis*, inactive antigen, or poor technique when placing the PPD test.

We recommend a chest radiograph for all children with a positive PPD skin test result. A child with a positive PPD skin test but no evidence of pulmonary disease should receive 9 months of therapy with isoniazid at a dose of 10 mg/kg/day. If the chest radiograph suggests active disease, then sputum or gastric aspirates should be obtained for AFB stain and culture (69, 86). All household contacts and close family members of any child with active pulmonary (or miliary) tuberculosis should also undergo PPD skin testing. A child with pulmonary or extrapulmonary disease should be treated with a regimen of at least three antituberculous medications for 2 months while the results of AFB cultures and sensitivity data are pending. The ultimate drug regimen and duration of therapy should be based on the sensitivity profile of the specific isolate (5). In order to detect those international adoptees whose initial PPD test might be negative due to malnutrition, a second PPD skin test at 4 to 6 months postadoption is recommended. Importantly, any child with a negative PPD skin test result who demonstrates clinical signs or symptoms of tuberculosis should undergo thorough evaluation, including gastric lavage, as active disease has been reported in this setting (47).

In light of the high prevalence of scabies in international adoptees, many children are treated empirically in the appropriate clinical setting. The treatment of choice is topical 5% permethrin cream (79). A second application in 1 week is recommended for complete cure. Family members and close contacts should be treated if they develop symptoms or signs of infection. Oral ivermectin, administered in one or two doses, is also highly effective in the treatment of scabies in adults (53), although its efficacy in children is unknown. Treatment options for head lice (pediculosis) include topical 1% permethrin, 1% lindane, or 0.5% malathion, which are applied to the scalp or skin and rinsed off after 10 min (16). Although reported cure rates approach 95% with these therapies, resistance to topical agents may represent an emerging challenge (33). Two doses of oral ivermectin, administered 10 days apart, may be an alternative (41).

In addition to the above screening for infectious diseases, we also obtain a complete blood count, routine urinalysis, serum lead level, and serum thyroid-stimulating hormone level to evaluate for noninfectious medical conditions. Additional screening tests recommended by adoption specialists include hemoglobin electrophoresis, serum liver transaminase levels, serum electrolytes, blood urea nitrogen and creatinine, and

bacterial cultures of the stool and urine (7, 59). As outlined above, depending on the results of the initial medical screening, some tests may need to be repeated (7, 73).

#### RECOMMENDATIONS FOR IMMUNIZATION OF INTERNATIONAL ADOPTEES

The recent cases of imported measles traced to a group of Chinese adoptees underscore the notion that these children are at risk of both acquiring and transmitting vaccine-preventable infections. Strategies aimed at assessing the likelihood of an international adoptee having been appropriately immunized are problematic for a variety of reasons. First, many of the preadoption medical records are incomplete, and they often do not contain information about vaccinations. Albers et al. reviewed the medical records of 32 international adoptees and found that many lacked documentation of complete age-appropriate vaccination (1). For example, 27/32 records contained documentation of vaccination against measles, 17/32 for poliomyelitis, 5/32 for mumps, 25/32 for BCG, and 5/32 for diphtheria-pertussis-tetanus. No child was documented to be vaccinated against rubella, hepatitis B, or *Haemophilus influenzae*. Shulte et al. examined 504 children evaluated at an adoption clinic in 1997 and 1998. Only 178/504 (35%) children had written documentation of immunization prior to arrival in the United States (68). Of those with immunizations recorded and determined to be valid, 112/167 (67%) were found to be current for at least one vaccine series. When immunization records of children older than 6 months were examined, only 14/150 (9%) were current for all recommended vaccines (68). Whether these data suggest incomplete documentation or limited immunization practices in resource-poor countries is unknown, but they clearly reinforce concerns about the failure of institutional care settings to meet even the most basic health needs of these children.

Data from studies of international adoptees with seemingly appropriate records suggest that children with documentation of vaccination may not have serologic evidence of protective immunity. Miller et al. reported data from a study of 70 children in whom serum antibodies against the standard vaccine-preventable infections were measured (55). Of these, 61% had levels of antibody that were consistent with immunity to tetanus, 88% to diphtheria, 50% to pertussis, 65% to polio, and 90% to measles. These children were adopted from a number of different countries, and the authors found no association between serologic evidence of vaccination and country of origin. Similarly, Schulpen et al. reported that only 60% of Chinese adoptees were positive for antibodies against diphtheria and tetanus (67). Of note, in both of these studies a substantial number of children had antibody levels that were considered to be in the marginal or borderline category. Saimen et al. found that a third of children reported to have received a complete hepatitis B virus immunization series were HBsAb negative upon testing in the United States (66).

There are a number of potential explanations for the apparent discordance between documentation of vaccination and serum antibody levels in some international adoptees. One obvious reason is that the records are intentionally falsified in order to give the impression that a child has received adequate care. A second potential explanation is that orphanages may



TABLE 5. Strategies for management of vaccine-preventable infections in international adoptees

| Strategy   |
|--|
| 1. Accept all appropriate preadoption records of immunization  |
| 2. Measure serum antibodies against vaccine-preventable pathogens for which reliable testing is available; if present, accept all corresponding preadoption records of immunization        |
| 3. Measure serum antibodies against vaccine-preventable pathogens for which reliable testing is available; if positive, consider the child to have received one immunization in the series |
| 4. Accept no preadoption records of immunization; immunize all adoptees with age-appropriate vaccinations  |

not have the resources to ensure proper storage of vaccines, particularly those that require refrigeration. It is also possible that children may receive outdated or diluted vaccine, perhaps due to the limited resources available to a particular orphanage. Lastly, certain effects of institutionalization, attributable perhaps to malnutrition, may impair host immunity, thus leading to a less robust response to immunization. In support of this, it is interesting that Hostetter and Johnson reported that adoptees who had resided in orphanages were less likely to have serologic evidence of adequate vaccination than those children from foster homes (37). Regardless of the underlying causes, it is clear that many international adoptees whose vaccination records are accepted as accurate may be at risk for acquiring vaccine-preventable infections.

Because of the above uncertainties, recommendations vary as to the appropriate management of international adoptees with regard to routine childhood immunizations. For children with questionable preadoption records, there seems to be little choice but to recommend that they receive all age-appropriate vaccinations according to current recommendations (3). For children with preadoption medical records that appear to document appropriate immunization, there are a variety of strategies to guide future decisions about vaccination (Table 5). One option is to accept the records as valid and complete the immunization schedule based on what is documented. A second strategy would be to test adoptees for antibodies to hepatitis B virus, diphtheria, tetanus, poliovirus (all three serotypes), measles virus, mumps virus, and rubella virus and then accept as valid those immunizations for which a child has appropriate levels of antibody. However, results of antibody testing must be interpreted with caution, in light of the possibility that a child might have received unrecorded immunizations immediately prior to adoption that could lead to a transiently elevated titer or antibody level. A third strategy is to consider a child to have received one immunization for each of the pathogens against which he or she has measurable antibody levels. This strategy would potentially eliminate one immunization in each of the multidose series, while still ensuring that adoptees are fully protected against vaccine-preventable illnesses. However, because it requires extensive testing with the potential for only a limited reduction in the number of vaccinations, this strategy is likely to be the least cost-effective. A fourth strategy is to ignore all preadoption records, and fully immunize each child based on age-appropriate recommenda-

tions (4). As there appears to be little evidence that immunization of international adoptees is associated with a substantial risk of adverse events, we have generally recommended that adopted children under 1 year of age receive the full series of most vaccinations. This recommendation is guided primarily by our concern about the potential risk of adoptees reaching adulthood without appropriate levels of immunity to vaccine-preventable infections.

The above recommendations apply to those vaccines that are routinely administered in orphanages and foster home settings, namely, hepatitis B virus, diphtheria-pertussis-tetanus, poliovirus, and measles virus. However, few adoptees have records documenting immunization against VZV, *Haemophilus influenzae* type b, and *Streptococcus pneumoniae*. Vaccination against *H. influenzae* and *S. pneumoniae* should be administered to international adoptees according to age-specific recommendations (4). We recommend testing for antibodies to VZV in children older than 1 year of age, since their presence in these children suggests prior infection and hence immunity. It has been suggested that this practice may be cost-effective for children who are older than 5 years (22), and data from the Yale Clinic confirm high rates of infection in adoptees (Table 3). For those children without measurable antibodies, we recommend vaccination with the live attenuated vaccine.

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