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Assisted Reproductive Technology Surveillance — United States, 2004

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Abstract

Problem/Condition: In 1996, CDC initiated data collection regarding assisted reproductive technology (ART) procedures performed in the United States, as mandated by the Fertility Clinic Success Rate and Certification Act of 1992 (FCSRCA) (Public Law 102-493 [October 24, 1992]). ART includes fertility treatments in which both eggs and sperm are handled in the laboratory (i.e., in vitro fertilization and related procedures). Patients who undergo ART procedures are more likely to deliver multiple-birth infants than women who conceive naturally. Multiple births are associated with increased risk for mothers and infants (e.g., pregnancy complications, premature delivery, low-birthweight infants, and long-term disability among infants).

Reporting Period Covered: 2004.

Description of System: In 2004, CDC contracted with a statistical survey research organization, Westat, Inc., to obtain data from ART medical centers in the United States. Westat, Inc., maintains CDC's web-based data collection system called the National ART Surveillance System.

Results: In 2004, a total of 127,977 ART procedures were reported to CDC. These procedures resulted in 36,760 live-birth deliveries and 49,458 infants. Nationwide, 74% of ART procedures used freshly fertilized embryos from the patient's eggs, 15% used thawed embryos from the patient's eggs, 8% used freshly fertilized embryos from donor eggs, and 4% used thawed embryos from donor eggs. Overall, 42% of ART transfer procedures resulted in a pregnancy, and 34% resulted in a live-birth delivery (delivery of one or more live-born infants). The highest live-birth rates were observed among ART procedures that used freshly fertilized embryos from donor eggs (51%). The highest numbers of ART procedures were performed among residents of California (17,303), New York (11,123), Illinois (9,306), Massachusetts (8,906), and New Jersey (8,513). These five states also reported the highest number of infants conceived through ART. Of 49,458 infants born through ART, 50% were born in multiple-birth deliveries. The multiple-birth risk was highest for women who underwent ART transfer procedures that used freshly fertilized embryos from either donor eggs (40%) or their own eggs (33%). Approximately 1% of U.S. infants born in 2004 were conceived through ART. Those infants accounted for 18% of multiple births nationwide. Approximately 9% of ART singletons, 56% of ART twins, and 95% of ART triplets or higher-order multiples were low birthweight. The percentages of ART infants born preterm were 15% among singletons, 64% among twins, and 98% among triplets or higher-order multiples.

Interpretation: Whether an ART procedure resulted in a pregnancy and live-birth delivery varied according to different patient and treatment factors. ART poses a major risk for multiple births. This risk varied according to the patient's age, the type of ART procedure performed, the number of embryos transferred, the day of embryo transfer (day 3 or day 5), and embryo availability.

Public Health Actions: ART-related multiple births represent a sizable proportion of all multiple births nationwide and in selected states. To minimize the adverse maternal and child health effects that are associated with multiple pregnancies, ongoing efforts to limit the number of embryos transferred in each ART procedure should be continued and strengthened. Adverse maternal and infant outcomes (e.g., low birthweight and preterm delivery) associated with ART treatment choices should be explained fully when counseling patients who are considering ART.

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Introduction

Since 1978, assisted reproductive technology (ART) procedures have been used to overcome infertility. ART procedures include those infertility treatments in which both eggs and sperm are handled in the laboratory for the purpose of establishing a preg-

nancy (i.e., in vitro fertilization [IVF] and related procedures). Since the birth of the first U.S. infant conceived with ART in 1981, use of these treatments has increased dramatically. Each year, both the number of medical centers providing ART services and the total number of procedures performed have increased notably (*1*).

In 1992, Congress passed the Fertility Clinic Success Rate and Certification Act (FCSRCA),* which requires each medical center in the United States that performs ART procedures to report data to CDC annually on every ART procedure initiated. CDC uses the data to report medical center–specific pregnancy success rates. In 1997, CDC published the first surveillance report under this mandate (*2*). That report was based on ART procedures performed in 1995. Since then, CDC has continued to publish a surveillance report annually that details each medical center's success rates. CDC also has used this surveillance data file to perform more in-depth analyses of infant outcomes (e.g., multiple births) (*3–10*). Multiple-infant births are associated with greater health problems for both mothers and infants, including higher rates of caesarean deliveries, prematurity, low birthweight, and infant death and disability (*11,12*). In the United States, ART has been associated with a substantial risk for multiple gestation pregnancy and multiple birth (*3–10*). In addition to the multiple-birth risks, studies suggest an increased risk for low birthweight among singleton infants conceived through ART (*13,14*). This report is based on ART surveillance data provided to CDC's National Center for Chronic Disease Prevention and Health Promotion, Division of Reproductive Health, regarding procedures performed in 2004. A report of these data, according to the medical center in which the procedure was performed, was published separately (*1*). In this report, emphasis is on presenting state-specific data and more detailed data regarding risks associated with ART (e.g., multiple birth, low birthweight, and preterm delivery).

Methods

CDC contracted with Westat, Inc., to collect data on ART procedures performed in 2004 from medical centers in the United States and its territories. Data collected include patient demographics, medical history and infertility diagnoses, clinical information pertaining to the ART procedure, and information regarding resultant pregnancies and births. The data file is organized with one record per ART procedure performed. Multiple procedures from a single patient are not linked. Despite the federal mandate, 11% of ART medical centers did not report their 2004 data (*1*).

ART data and outcomes from ART procedures are presented by patient's state of residence at time of treatment. If the patient's state of residency was missing, the state of residency was assigned as the state in which the ART procedure was performed. In addition, data regarding the number of ART procedures in relation to the total population for each state are indicated.† Data regarding number of procedures also are presented by treatment type and stage of treatment. ART procedures are classified into four groups according to whether a woman used her own eggs or received eggs from a donor and whether the embryos transferred were freshly fertilized or previously frozen and thawed. Because both live-birth rates and multiple-birth risk vary substantially among these four treatment groups, data are presented separately for each type.

In addition to treatment types, within a given treatment procedure, different stages of treatment exist. A typical ART procedure begins when a woman starts taking drugs to stimulate egg production or has her ovaries monitored with the intent of having embryos transferred. If eggs are produced, the procedure progresses to the egg-retrieval stage. After the eggs are retrieved, they are combined with sperm in the laboratory, and if fertilization is successful, the resulting embryos are selected for transfer. If the embryo implants in the uterus, the procedure progresses to a clinical pregnancy (i.e., the presence of a gestational sac detectable by ultrasound). The resulting pregnancy might progress to a live-birth delivery, which is defined as the delivery of one or more live-born infants. Only ART procedures involving freshly fertilized eggs include an egg-retrieval stage; ART procedures using thawed eggs do not include egg retrieval because eggs were fertilized during a previous procedure and the resulting embryos were frozen until the current procedure. An ART procedure can be discontinued at any step for medical reasons or by the patient's choice.

Variations in a typical ART procedure are noteworthy. Although a typical ART procedure includes IVF of gametes, culture for ≥2 days, and embryo transfer into the uterus (i.e., transcervical embryo transfer), in certain cases, unfertilized gametes (eggs and sperm) or zygotes (early embryos [i.e., a cell that results from fertilization of the egg by a sperm]) are transferred into the fallopian tubes within 1–2 days of retrieval. These are known as gamete and zygote intrafallopian transfer (GIFT and ZIFT). Another adaptation is intracytoplasmic sperm injection (ICSI), in which fertilization is still in vitro but is accomplished by selection of a single sperm that is

* Fertility Clinic Success Rate and Certification Act of 1992 (FCSRCA), Public Law 102-493 (October 24, 1992).

† Data regarding population size are based on July 1, 2004, estimates from the U.S. Census Bureau (*15*).

injected directly into the egg. This technique was developed originally for couples with male factor infertility but now is commonly used for an array of diagnostic groups.

Data are presented in this report for each of the four treatment types: freshly fertilized embryos from the patient's eggs, freshly fertilized embryos from donor eggs, thawed embryos from the patient's eggs, and thawed embryos from donor eggs. In addition, detailed data are presented for the most common treatment type, those using freshly fertilized embryos from the patient's eggs. These procedures account for >70% of the total number of ART procedures performed each year. For those procedures that progressed to the embryo-transfer stage, the percentage distribution of selected patient and treatment factors were calculated. In addition, success rates, defined as live-birth deliveries per ART-transfer procedure, were calculated according to the same patient and treatment characteristics.

Patient factors included the age of the woman undergoing ART, whether she had previously given birth, the number of previous ART attempts, and the infertility diagnosis of both the female and male partners. The patient's age at the time of the ART procedure was grouped into five age groups: age <35 years, 35–37 years, 38–40 years, 41–42 years, and >42 years. Infertility diagnoses ranged from one factor in one partner to multiple factors in one or both partners and were categorized as follows:

- tubal factor — the woman's fallopian tubes are blocked or damaged, causing difficulty for the egg to be fertilized or for an embryo to travel to the uterus;
- ovulatory dysfunction — the ovaries are not producing eggs normally; such dysfunctions include polycystic ovarian syndrome and multiple ovarian cysts;
- diminished ovarian reserve — the ability of the ovary to produce eggs is reduced; reasons include congenital, medical, or surgical causes or advanced age;
- endometriosis — involves the presence of tissue similar to the uterine lining in abnormal locations; this condition can affect both fertilization of the egg and embryo implantation;
- uterine factor — a structural or functional disorder of the uterus that results in reduced fertility;
- male factor — a low sperm count or problems with sperm function that cause difficulty for a sperm to fertilize an egg under normal conditions;
- other causes of infertility — immunological problems or chromosomal abnormalities, cancer chemotherapy, or serious illnesses;
- unexplained cause — no cause of infertility was detected in either partner;
- multiple factors, female — diagnosis of one or more female cause; or
- multiple factors, male and female — diagnosis of one or more female cause and male factor infertility.

Treatment factos included the following:

- the number of days the embryo was cultured;
- the number of embryos that were transferred;
- whether the procedure was IVF-transfer only, IVF with ICSI, GIFT, ZIFT, or a combination of IVF with or without ICSI and either GIFT or ZIFT;
- whether extra embryos were available and cryopreserved; and
- whether a gestational carrier (i.e., surrogate) received the transferred embryos with the expectation of gestating the pregnancy.

The number of embryos transferred in an ART procedure was categorized as 1, 2, 3, 4, or ≥5. The number of days of embryo culture was calculated using dates of egg retrieval and embryo transfer and was categorized as 1, 2, 3, 4, 5, or 6. However, because of limited sample sizes, live-birth rates are presented only for the two most common days, day 3 and day 5. For the same reason, live-birth rates are presented for IVF with and without ICSI and not for GIFT and ZIFT. ICSI was subdivided as to whether it was used among couples receiving a diagnosis involving male factor (the original indication for ICSI treatment).

Chi-square tests were run to evaluate differences in live-birth rates by select patient and treatment factors within each age group. Multivariable logistic regression also was performed to evaluate the independent effects of patient factors (diagnosis, number of previous ART procedures, and number of previous births) on the chance to have a live birth as a result of an ART treatment. Because patient age is known to be a strong predictor for live birth, separate models were constructed for each age group; these models provide an indication of the variability in live births based on patient factors within each age strata. For these analyses, the referent groups included patients with a tubal factor diagnosis, no previous ART procedures, and no previous births. Multivariable models did not include treatment factors because of multicollinearity between certain treatment factors and multiple potential effect modifications. Rather, detailed stratified analyses were performed to elucidate additional detail related to associations among different treatment factors and the likelihood of live birth.

In addition to presenting live-birth rates as a measure of success, a second measure of success based on singleton live births also is presented according to patient age. Singleton live births are a key measure of ART success because they have a much lower risk than multiple-infant births for adverse health

outcomes, including prematurity, low birthweight, disability, and death.

Multiple birth as a separate outcome measure also was assessed in two ways. First, each multiple-birth delivery was defined as a single event. A multiple-birth delivery was defined as the delivery of two or more infants, at least one of which was live-born. The multiple-birth risk thus was calculated as the proportion of multiple-birth deliveries among total live-birth deliveries. Multiple birth also was assessed according to the proportion of infants from multiple deliveries among total infants (i.e., each infant was considered separately in this calculation). The proportion of live-born infants who were multiples (twins and triplets or higher-order multiples) then was calculated.[§] Each of these measures represents a different focus. The multiple-birth risk, which is based on the number of deliveries or infant sets, provides an estimate of the individual risk posed by ART to the woman for multiple birth. The proportion of infants born in a multiple-birth delivery provides a measure of the effect of ART procedures on children in the population. Both measures are presented by type of ART procedure and by maternal age for births conceived with the patient's eggs. Multiple-birth risk is presented further by patient's age, number of embryos transferred, and whether additional embryos were available and cryopreserved for future use. Embryo availability (an indicator of embryo quality) has been demonstrated to be an independent predictor of the number of embryos transferred (*3,6*). In addition, multiple-birth risk is presented for embryos cultured on day 3 and day 5 by patient's age, number of embryos transferred, and whether additional embryos were available and cryopreserved for future use. The proportion of infants born in a multiple-birth delivery is presented separately by patient's state of residency at the time of ART treatment.

To assess the impact of ART procedures on total births in the United States in 2004, additional analyses, including all ART infants born in 2004, are presented. Because the goal of the analysis was to assess the effect of ART on the 2004 U.S. birth cohort and the ART surveillance system is organized according to the date of the ART procedure rather than the infant's date of birth, a separate ART data file was created for these analyses. This data file was drawn from two different ART reporting years and was composed of 1) infants conceived from ART procedures performed in 2003 and born in 2004 (approximately two of every three live-birth deliveries reported to the ART surveillance system for 2003); and 2) infants conceived from ART procedures performed in 2004 and born in 2004 (approximately one of every three live-birth deliveries reported to the ART surveillance system for 2004). Data regarding the total number of live births and multiple births in the United States in 2004 were obtained from birth certificate data (U.S. natality files) from CDC's National Center for Heath Statistics (*16*). These data represent all births registered in the United States in 2004. Data are presented in relation to the total number of infants born in the United States in 2004 by plurality of birth.

Adverse infant health outcomes, including low birthweight, very low birthweight, and preterm delivery also were evaluated. Because ART providers do not provide continued prenatal care after a pregnancy is established, birthweight and date of birth were collected via active follow-up with ART patients (85%) or their obstetric providers (15%). Although ART clinic staff collect limited information on infant outcomes, maternal health outcomes are not investigated systematically. Low birthweight and very low birthweight were defined as <2,500 grams and <1,500 grams, respectively. Gestational age was calculated as date of birth minus date of egg retrieval (and fertilization). If the date of retrieval was missing, and for procedures that used frozen embryos, gestational age was calculated as date of birth minus date of embryo transfer. For comparability with the general population, date of theoretical last menstrual period (LMP) was adjusted by adding 14 days to the gestational age estimate. Preterm delivery was defined as gestational age <37 weeks. Preterm low birthweight was defined as gestational age <37 weeks and birthweight <2,500 grams. Term low birthweight was defined as gestational age ≥37 weeks and birthweight <2,500 grams. The rates for low birthweight, very low birthweight, preterm low birthweight, and term low birthweight among ART infants born in 2004 are presented by plurality of birth. In addition, data for each of the five outcomes are presented for ART singletons born in 2004 by type of procedure. For the most common procedure type, those using freshly fertilized embryos from the patient's eggs, the rates for each outcome also are presented according to maternal age and number of previous live births. Chi-square tests were run separately to evaluate differences in the five outcomes by type of ART procedure, maternal age, and number of previous births. All analyses were performed using the SAS® software system (*17*).

Results

Of 461 medical centers in the United States and surrounding territories that performed ART procedures in 2004, a total of 411 (89%) provided data to CDC (Figure 1). The

[§] Includes only the number of infants live-born in a multiple-birth delivery. For example, if three infants were born in a live-birth delivery and one of the three infants was stillborn, the total number of live-born infants would be two. However, these two infants still would be counted as triplets.

majority of medical centers that performed ART procedures were in the eastern United States, in or near major cities. Within states, the number of medical centers performing ART procedures varied. States with the largest number of ART medical centers that reported data in 2004 were California (55), New York (35), Texas (30), Illinois (28), and Florida (27). Four states (Alaska, Maine, Montana, and Wyoming) and two U.S. territories (Guam and U.S. Virgin Islands) had no ART medical centers.

Number and Type of ART Procedures

A total of 127,977 ART procedures performed in 2004 were reported to CDC (Table 1). This number excludes <1% (n = 239) of ART procedures performed in 2004 that involved the evaluation of a new treatment procedure. The largest number of ART procedures occurred among patients who used their own freshly fertilized embryos (94,242 [74%]). Of the 127,977 procedures started, 107,050 (84%) progressed to embryo transfer. Overall, 42% of ART procedures that progressed to the transfer stage resulted in a pregnancy; 34% resulted in a live-birth delivery; and 23% resulted in a singleton live birth. Pregnancy rates, live-birth rates, and singleton live-birth rates varied according to type of ART. The highest success rates were observed among ART procedures that used donor eggs and freshly fertilized embryos (59% pregnancy rate, 51% live-birth rate, and 30% singleton live-birth rate). The lowest rates were observed among procedures using the patient's eggs and thawed embryos (35% pregnancy rate, 28% live-birth rate, and 21% singleton live-birth rate).

The 36,760 live-birth deliveries from ART procedures performed in 2004 resulted in 49,458 infants (Table 1); the number of infants born was higher than the number of live-birth deliveries because of multiple-infant births. A total of 24,921 singleton infants were born as a result of ART. The largest proportion of infants born (71% [35,191]) were from ART procedures in which patients used freshly fertilized embryos from their own eggs.

The two states that had the most ART medical centers (California and New York) also reported the highest numbers of ART procedures performed (Table 2). The greatest numbers of ART procedures performed in 2004 were among residents of California (17,303), New York (11,123), Illinois (9,306), Massachusetts (8,906), and New Jersey (8,513). The five states with the largest number of ART procedures performed also ranked highest for numbers of live-birth deliveries and infants born. ART procedures were performed for residents of certain states and territories without an ART medical center (Alaska, Maine, Montana, Guam, Wyoming, and U.S. Virgin Islands); however, each accounted for a limited percentage of total ART usage in the United States. Non-U.S. residents accounted for <1% of ART procedures, live-birth deliveries, and infants born. The ratio of number of ART procedures per 1 million population ranged from 17 in Puerto Rico to 1,384 in Massachusetts, with an overall average of 436 ART procedures started per 1 million persons.

Characteristics of Patients and ART Treatments Among Women Who Used Freshly Fertilized Embryos from Their Own Eggs

Forty-six percent of ART transfer procedures that used freshly fertilized embryos from the patient's eggs were performed on women aged <35 years, 23% on women aged 35–37 years, 19% on women aged 38–40 years, 8% on women aged 41–42 years, and 4% on women aged >42 years. Patient and treatment characteristics of these women varied by age (Table 3). Tubal factor and male factor were reported more commonly for ART procedures in women aged <35 years than for women in older age categories. In contrast, diminished ovarian reserve, reported for only 2% of women aged <35 years, was reported for 19% of women aged 41–42 years and 31% of women aged >42 years. Among all women, 8%–14% of ART transfer procedures were reported as involving unexplained infertility, 9%–18% as multiple female factors, and 18%–19% as both male and female factors.

Approximately 64% of women aged <35 years were undergoing their first ART procedure. The percentage of women who had undergone at least one previous ART procedure increased with age: only 42% of women aged >42 years were undergoing their first ART procedure. The percentage of women who had had a previous birth followed similar patterns: 21% of women aged <35 years reported at least one previous birth, a proportion that increased steadily with age, and 37% of women in the oldest age group had had a previous birth.[¶]

The majority of ART procedures used IVF with or without ICSI. Less than 1% of ART procedures used GIFT or ZIFT. ICSI use among couples with and without a diagnosis of male factor infertility varied by patient age. Despite variation among all age groups, the total proportion of ICSI use (i.e., combined ICSI for male factor and ICSI for other diagnoses) was greater than the proportion of in vitro fertilization with transcervical embryo transfer (IVF-ET) without ICSI.

Among all age groups, the majority of procedures included embryo culture for 3 days; the next most common procedure

[¶] Data were not available to distinguish whether previous births were conceived naturally or conceived with ART or other infertility treatments.

involved embryo culture to day 5. Culture to day 5 coincides with development of the embryo to the blastocyst stage; this technique was used more frequently among younger women, possibly because ART procedures performed in younger women yielded more embryos that can survive in culture through day 5.

The majority of ART procedures involved transfer of more than one embryo. Among women aged <35 years, 94% of procedures involved transfer of two or more embryos, and 41% involved transfer of three or more embryos. For women aged >42 years, 82% involved transfer of two or more embryos, and 62% involved transfer of three or more embryos. The availability of extra embryos (an indicator of overall embryo quality) decreased with age. Extra embryos were available and cryopreserved for 43% of women aged <35 years, whereas only 4% of women aged >42 years had extra embryos available and cryopreserved. Data were not available regarding extra embryos that were not cryopreserved for future use. Overall, 1% of ART transfer procedures used a gestational carrier or surrogate. Limited variation existed by patient age.

Live-Birth Rates Among Women Who Used Freshly Fertilized Embryos from Their Own Eggs

Live-birth rates for women who underwent ART procedures that used freshly fertilized embryos from their own eggs also varied by patient age and selected patient and treatment factors (Table 4). Although the average live-birth rate for ART-transfer procedures performed among women who used their own freshly fertilized eggs was 34%, live-birth rates ranged from 43% among women aged <35 years to 6% among women aged >42 years. Couples in which the woman was aged ≤40 years whose infertility diagnosis was classified as ovulatory dysfunction or male factor infertility had higher than average live-birth rates. Women aged ≤40 years with an infertility diagnosis of diminished ovarian reserve tended to have lower-than-average–live-birth rates. In addition, women aged >40 years with an infertility diagnosis of endometriosis or uterine factor experienced higher-than-average–live-birth rates; however, the variation in success rates across diagnostic categories was not statistically significant. Across all age groups, women who had undergone a previous ART procedure had lower live-birth rates than women who had undergone their first ART procedure. However, the number of previous ART procedures cannot be subdivided by whether they were successful because data were not available. The variation in success rates by number of previous ART procedures was not statistically significant for women aged >40 years. Women who had one or more previous births had higher live-birth rates than those with no previous births. However, the difference in live-birth rates for the number of previous births was not statistically significant for women aged >40 years. Multivariable adjustment for patient factors within each age strata demonstrated similar patterns to those described above (data not presented).

Among women aged ≤42 years, live-birth rates were higher among women who had ART procedures that used IVF-ET without ICSI, in comparison with procedures that used ICSI, regardless of whether male factor was reported (Table 4). In all age groups, live-birth rates were lowest among couples who used ICSI in the absence of male factor infertility; however, the variation in live-birth rates was not statistically significant for women aged >42 years. In all age groups, live-birth rates were increased among women who had extended embryo culture to day 5, transferred two or more embryos, and had extra embryos available and cryopreserved for future use. Variations in live-birth rates were statistically significant for these treatment factors within all age groups, except for women aged >42 years who had extra embryos available and cryopreserved for future use. Although live-birth rates also appeared to increase across all age groups when a gestational carrier was used, these results did not reach statistical significance in any age group. All of the results for treatment factors need to be considered cautiously because treatment was not randomized but rather based on medical center assessment and patient choice.

Although variability in live-birth rates among patients who used different treatment options cannot be adjusted completely, stratified analyses were used to examine associations between treatment factors and live-birth rates among more homogenous groups of patients. To address concerns that, in the absence of male factor infertility, ICSI might be used preferentially for women considered difficult to treat, multiple groups of patients with an indication of being difficult to treat were evaluated separately (data not presented). These groups included women with previously failed ART procedures (i.e., women who underwent previous ARTs but had no previous pregnancies or births), women diagnosed with diminished ovarian reserve, and women with a low number of eggs retrieved (i.e., less than five). Within each of these groups, age-specific live-birth rates for IVF-ET with and without ICSI were examined. In all analyses, except for women aged >42 years with less than five eggs retrieved, women who used IVF with ICSI had lower success rates than women who used IVF without ICSI; the pattern of these results (data not presented) is consistent with the findings presented in this report (Table 4). Data regarding women deemed to have a higher likelihood of success (i.e., women with >10 eggs retrieved, women with diagnoses other than diminished ovarian reserve, and women with extra embryos cryopreserved for future use)

were evaluated separately (data not presented) to adjust for the possibility that day 5 embryo transfers might have been used preferentially for women with a presumed better prognosis. Again, within each of these subgroups, age-specific–live-birth rates were lower for embryo transfers on days 1–4 compared with day 5 transfers. Finally, analyses were conducted in which the data were stratified by patient age, number of embryos transferred, day of embryo transfer (day 3 or day 5), and number of embryos available simultaneously. These results are included with the discussion regarding multiple-birth risk.

Total live-birth rates are compared with singleton live-birth rates for women who underwent ART procedures in which freshly fertilized embryos from their own eggs were used (Figure 2). Both live-birth rates and singleton live-birth rates decreased with patient age. Across all age groups, singleton live-birth rates were lower than live-birth rates. However, the magnitude of the difference between these two measures declined with patient age.

Multiple-Birth Risks Associated with ART

Of 11,839 multiple-birth deliveries, 8,478 (72%) were from pregnancies conceived with freshly fertilized embryos from the patient's eggs, 1,129 (10%) were from thawed embryos from the patient's eggs, 1,878 (16%) were from freshly fertilized embryos from a donor's eggs, and 354 (3%) were from thawed embryos from a donor's eggs (Table 5). In comparison with ART procedures that used the patient's eggs and freshly fertilized embryos, the risks for multiple-birth delivery were increased when eggs from a donor were used and decreased when thawed embryos were used. Among ART procedures in which freshly fertilized embryos from the patient's own eggs were used, a strong inverse relation existed between multiple-birth risk and patient age. The average multiple-birth risk for ART procedures in which freshly fertilized embryos from the patient's eggs were used was 33%. The multiple-birth risk varied from 36% among women aged <35 years to 8% among women aged >42 years.

Of 49,458 infants born through ART, 50% (24,537) were born in multiple-birth deliveries (Table 5). The proportion of infants born in a multiple-birth delivery also varied by type of ART procedure and patient age. Among ART transfer procedures in which the patient used freshly fertilized embryos from their own eggs, the proportion of infants born in a multiple-birth delivery ranged from 54% in women aged <35 years to 16% in women aged >42 years. Among ART transfer procedures in which thawed embryos from the patient's eggs were used, the proportion of infants born in a multiple-birth delivery ranged from 42% in women aged <35 years to 30% in women aged >42 years. When thawed embryos from donor eggs were used, the proportion of infants born in a multiple-birth delivery was 42%. The proportion of infants born in a multiple-birth delivery was highest (58%) in women who used freshly fertilized embryos from donor eggs.

A more detailed examination of multiple-birth risk for women who underwent ART procedures in which freshly fertilized embryos from their own eggs were used revealed that number of embryos transferred was a risk factor for multiple-birth delivery, but the magnitude of the risk varied by patient age (Table 6). Among all age groups, transfer of two or more embryos was associated with increased live-birth delivery rates. However, the multiple-birth risk also was increased substantially. Among women aged ≤40 years, the percentage of triplet or higher order deliveries increased steadily with increasing number of embryos transferred from two to five or more. For women aged 41–42 years, the percentage of twin deliveries increased steadily with two to five or more embryos transferred. For women aged >42 years, the multiple-birth deliveries did not demonstrate a trend by number of embryos (two or more) having been transferred, possibly because women in this age group have embryos with reduced implantation potential and therefore are less likely to have multiple births.

An assessment of multiple-birth risk among patients who used freshly fertilized embryos from their own eggs and set aside extra embryos for future use also is presented (Table 6). These patients can be thought of as those with elective embryo transfer because they chose to transfer fewer embryos than the total number that were available. For women with elective embryo transfer who were aged <35 years, live-birth rates were 45% when only one embryo was transferred and 53% when two embryos were transferred. For women aged 35–37 years, live-birth rates were 35% with elective embryo transfer of a single embryo and 50% when two embryos were transferred. Whereas an increase in live-birth rates was noted among patients with single compared with double elective embryo transfers, transferring two embryos posed a substantial multiple-birth risk for both age groups (38% and 32%, respectively).**

Among patients who used freshly fertilized embryos from their own eggs, the live-birth rates and multiple-birth risks typically were higher for embryo transfers on day 5 than on day 3 (Table 7). Overall, across all age groups, embryo transfers on day 5 were associated with fewer embryos transferred than those on day 3. For example, among day 3 embryo transfers in women aged <35 years, 52% involved the transfer of two or fewer embryos whereas 82% of day 5 embryo transfers

** Results are based on total multiple-birth risk and therefore do not provide an indication of pregnancies that began as twins, triplets, or a higher order but reduced (either spontaneously or through medical intervention) to singletons or twins (Tables 6 and 7).

in women aged <35 years involved the transfer of two or fewer embryos. Similarly, in women aged <35 years, 62% of day 3 elective embryo transfers and 90% of day 5 elective embryos transfers involved the transfer of two or more embryos. As noted previously for all day of embryo transfers (Table 6), live-birth rates and multiple-birth risks were even higher for patients who had elective embryo transfers. For women with elective embryo transfer on day 5 who were aged <35 years, live birth rates were 52% when one embryo was transferred and 57% when two embryos were transferred. By contrast, the multiple-birth risks in these two groups were 4% and 45%, respectively. Thus, the 5% increase in the live-birth rate was accompanied by a 41% increase in the risk for a multiple delivery. If success is measured in terms of singleton live-birth, the highest success rates for this group were with one embryo transferred. This also was true for women aged 35–37 or 38–40 years with elective single embryo transfer on day 5 (Table 7).

The states with the highest number of ART-associated live-birth deliveries also had the highest number of infants born in multiple-birth deliveries (Table 8). These include California (3,313), New York (1,731), New Jersey (1,608), Illinois (1,549), Texas (1,518), and Massachusetts (1,463). Nationwide, the percentage of infants born in multiple-birth deliveries after ART treatment was 50%; the percentage of twins was 44% and that of triplets or higher-order multiples was 6%. The percentage of infants born in multiple-birth deliveries was ≥50% in the majority of states. The states with the highest proportion of infants born in multiple-birth deliveries were New Mexico (64%), Colorado (58%), Kentucky (58%), Mississippi (55%), Alabama (54%), Oklahoma (53%), Texas (53%), and Utah (53%); however, these findings should be interpreted with caution because of an overall low number of live births resulting from ART in certain states.

Of 4,112,052 infants born in the United States in 2004, a total of 49,376 (1%) were conceived with ART (Table 9). Infants conceived with ART accounted for 0.6% of singleton births and 18% of multiple births nationwide; 17% of all twins and 40% of infants born in triplets or higher order multiples were conceived with ART.

Perinatal Risks Associated with ART

The percentage of infants with low birthweight varied from 9% among singletons to 95% among triplets or higher order multiples. The percentages of very low birthweight, preterm, and preterm low birthweight followed similar patterns (Table 10).

The percentages of ART singletons that were low birthweight, very low birthweight, preterm, preterm low birthweight, and term low birthweight varied by procedure type and selected maternal factors (Table 11). In comparison with singletons born after procedures that used freshly fertilized embryos derived from the patient's eggs, singletons born after procedures that used freshly fertilized embryos derived from donor eggs were at increased risk for three perinatal outcomes: low birthweight, preterm delivery, and preterm low birthweight. Singletons born after procedures that used thawed embryos were at decreased risks for low birthweight; however, they were at increased risk for preterm delivery overall. The variation in risk across procedure types was not statistically significant for very low birthweight and preterm low birthweight.

More detailed analysis of maternal factors among singletons born after procedures that used freshly fertilized embryos derived from the patient's eggs indicated limited variation in risk for very low birth weight, preterm delivery, preterm low birth weight, and term low birthweight according to maternal age. Lower risks for low birthweight, preterm delivery, and preterm low birthweight were observed among mother-infant pairs with one previous birth; the variation in risks was statistically significant ($p<0.01$) for all five adverse perinatal outcomes.

Discussion

According to the most recent estimates of infertility in the United States, 10% of women of reproductive age (15–44 years) reported a previous infertility-associated health-care visit, and 2% reported a visit during the previous year (*18*). Among married couples in which the woman was of reproductive age, 7% reported they had not conceived after 12 months of unprotected intercourse. With advances in ARTs, couples are increasingly turning to these treatments to overcome their infertility.

Since the birth of the first infant through ART in the United States in 1981, use of ART has grown substantially. Since 1996, CDC has been monitoring ART procedures performed in the United States. During that time, the use of ART has consistently increased. The increased use of ART, coupled with higher ART success rates, has resulted in dramatic increases in the number of children conceived through ART each year. From 1996 (i.e., the first full year for which CDC collected data) through 2004, the number of ART procedures performed has almost doubled, from 64,681 to 127,977 (*1*). In addition, during 1996–2004, live-birth rates for all types of ART procedures increased substantially. For the most common type of ART procedure, use of freshly fertilized embryos from the patient's eggs, overall live-birth rates increased from 28% in 1996 to 34% in 2004. The number of infants conceived

through ART procedures performed in 2004 (49,458) was more than two times higher than that in 1996 (20,840).

This report documents that in 2004, ART use varied according to the patient's state of residency. Residents of California, New York, Massachusetts, Illinois, and New Jersey reported the highest number of ART procedures. These states also reported the highest number of infants conceived through ART. In 2004, ART use by state of residency was not completely in line with expectations based on the total population within states (*15*). Whereas Massachusetts had the fourth highest number of ART procedures performed, it ranked fourteenth in total population size.†† Similarly, residents of District of Columbia, New Jersey, Connecticut, and Rhode Island underwent more ART procedures than would have been expected based on their population sizes. As a result, state-specific ratios of ART procedures by population varied according to state of residency. The highest ratios of the number of ART procedures among state residents per 1 million population were observed in Massachusetts (1,384), District of Columbia (1,227), New Jersey (981), Connecticut (823), and Rhode Island (790). This divergence is not unexpected because, in 2004, Massachusetts, New Jersey, and Rhode Island had statewide mandates for insurance coverage for ART procedures. Variation within states also might be related to availability of ART services within each state. However, the relation between demand for services and availability cannot be disentangled (e.g., increased availability in certain states might reflect the increased demand for ART among state residents).

Among women who used fresh fertilized embryos from their own eggs, patient factors (e.g., infertility diagnoses, history of previous ART procedures, and previous births) varied considerably by age. The proportion of procedures in which the couple received a diagnosis of ovulatory dysfunction, endometriosis, or male factor infertility decreased with the woman's age, while the proportion of procedures in which the couple received a diagnosis of diminished ovarian reserve increased with the woman's age. History of previous ART and previous births were more common among older women. In addition, treatment factors varied considerably by the age of the woman. The proportion of procedures in which embryo transfer occurred on day 5 (i.e., the blastocyst stage) declined with the age of the woman, whereas the proportion of procedures in which three or more embryos were transferred increased steadily with age.

Because ART success rates are affected by multiple patient and treatment factors, using a single measure of success is not sufficient to evaluate ART efficacy. At a minimum, ART procedures should be subdivided on the basis of the source of the egg (patient or donor) and the status of the embryos (freshly fertilized or thawed) because success rates vary substantially across these types. Within the type of ART procedure, further variation exists in success rates by patient and treatment factors, most notably patient age. Other factors to consider when assessing success rates are infertility diagnosis, number of previous ART procedures, number of previous births, method of embryo fertilization and transfer, number of days of embryo culture, number of embryos transferred, availability of extra embryos, and use of a gestational carrier (i.e., surrogate). Variation exists in success rates according to each of these factors.

CDC's primary focus in collecting ART data has been on live-birth deliveries as an indicator of success because ART surveillance activities were developed in response to a federal mandate to report ART success rate data. This mandate requires that CDC collect data from all ART medical centers and report success rates, defined as all live births per ovarian stimulation procedures or ART procedures, for each ART medical center. Therefore, a key role for CDC has been to publish standardized data related to ART success rates, including information regarding factors that affect these rates. With these data, persons and couples can make informed decisions regarding whether to undergo this time-consuming and expensive treatment (*19*).§§ However, success-rate data also should be balanced with consideration of effects on maternal and infant health. CDC receives data on pregnancy outcomes of public health significance, which enables CDC to monitor multiple-birth rates, preterm delivery, and low birthweight associated with ART.

In the United States, multiple births have increased substantially since the 1980s (*16,20*). The increase in multiple births has been attributed to an increased use of ART and delayed childbearing (*5,21,22*). Although infants conceived with ART accounted for 1% of the total births in the United States in 2004, the proportion of twins and triplets or higher order multiples attributed to ART were 17% and 40%, respectively. In 1999, the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine issued voluntary guidelines (*23*) on the number of embryos transferred; these guidelines were revised in 2004 (*24*) and 2006 (*25*).

In certain states, ART procedures are not covered by insurance carriers, and patients might feel pressured to maximize the opportunity for live-birth delivery. In addition, if success is defined solely as total live-birth delivery, anecdotal evidence

†† Data regarding population size are based on July 1, 2004, estimates from the U.S. Census Bureau (*15*).

§§ Estimated cost for one procedure of IVF averages $12,400 (*19*).

suggests that certain ART providers might feel pressure to transfer multiple embryos to maximize their publicly reported success rates (*26*). In the United States, multiple embryo transfer was still a common practice in 2004; approximately 52% of ART procedures that used fresh, nondonor eggs or embryos and progressed to the embryo-transfer stage involved the transfer of three or more embryos; approximately 21% of procedures involved the transfer of four or more; and 7% of procedures involved the transfer of five or more embryos (*1*). Among women aged <35 years, the proportion of ART procedures that involved four or more embryos transferred was approximately 10%, as women in this age category typically experience higher success rates with fewer embryos transferred. Multiple scientific reports have advocated that singleton live-birth rates be presented as a distinct indicator of ART success *(27–33)*. This report includes this measure (Figure 2) and presents it with total live-birth rates. Success rates based on singleton live-birth deliveries will provide patients with a measure that more directly highlights infant outcomes with the optimal short- and long-term prognosis. Twins, albeit to a lesser extent than triplets or higher-order multiples, have substantially increased risks for infant morbidity and mortality. The risks for low birthweight and preterm birth both exceed 56% for twins, and the risk for very low birthweight is 10% (*16*). In addition, because twins are at substantially increased risk for perinatal and infant mortality (*11,20*), singleton live-birth rates are a valid measure of success.

Data regarding multiple-birth deliveries and proportion of multiple-birth infants as distinct outcomes also are provided. Data in this report indicate that 50% of infants born through ART in 2004 were multiple births, compared with 3% in the general U.S. population (*16*). The twin rate was 44%, approximately 15 times higher than that in the general U.S. population (3%); the rate for triplets and higher-order multiples was 6%, approximately 42 times higher than the general U.S. population (0.2%). Regarding the specific type of ART procedure, multiple-birth rates were among the highest for women who underwent ART procedures that used freshly fertilized embryos from their own eggs (53%) or from donor eggs (60%).

In 23 states and Puerto Rico, ≥50% of infants conceived through ART were born in multiple-birth deliveries. Multiple births resulting from ART are an increasing public health concern, nationwide and for the majority of states.

For women who underwent ART procedures using freshly fertilized embryos from their own eggs, the multiple-birth risk increased when multiple embryos were transferred. Embryo availability, an indicator of embryo quality, also was a strong predictor of multiple-birth risk independent from the number of embryos transferred. In analyses stratified by patient age, number of embryos transferred, day of embryo culture (day 3 or 5), and embryo availability, high live-birth rates and singleton live-birth rates were achieved, particularly among younger women as transfer of a single embryo was efficacious. Among the majority of groups, multiple-birth risk likely can be minimized without compromising success rates by limiting the number of embryos transferred.

In addition to the known multiple-birth risks associated with ART, singleton infants conceived from ART procedures are at increased risk for low birthweight and preterm delivery. In 2004, of all singleton infants conceived with ART, 9% were low birthweight, compared with 6% in the general U.S. population (*16*). The percentage of singleton infants conceived from ART that were very low birthweight was twice that of singletons conceived in the general U.S. population (2% and 1%, respectively), and the percentage of ART singletons born preterm also was higher than the general U.S. population (15% and 11%, respectively). Thus, adverse infant health outcomes among singletons (e.g., low birthweight and preterm delivery) also should be considered when assessing the efficacy and safety of ART.

A comparison of perinatal outcomes among ART twins and triplets or higher-order multiples with their counterparts in the general population is not useful for at least two reasons. First, both ART and non-ART infertility treatments are estimated to account for a substantial proportion of multiple births in the United States, and distinguishing naturally conceived from iatrogenic multiple births is not possible. ART accounts for only 1% of the total U.S. births; however, it accounts for 17% of twins and 40% of triplets or higher-order multiples. Second, the majority of multiple births conceived after ART treatment are likely dizygotic from multiple embryo transfer. Among natural conceptions, approximately one third to one half of twins might be monozygotic, depending on maternal age (*34*). Monozygotic twins are at increased risk for adverse outcomes in comparison with dizygotic twins (*35*).

Multiple births are associated with an increased health risk for both mothers and infants (*11,12,20,22*). Women with multiple-gestation pregnancies are at increased risk for maternal complications (e.g., hemorrhage and hypertension). Infants born in a multiple-birth delivery are at increased risk for prematurity, low birthweight, infant mortality, and long-term disability.

The contribution of ARTs to preterm births in the United States also is a key concern. This report documents that approximately 42% of ART infants born in 2004 were preterm (Table 10), compared with approximately 13% of preterm births in the general U.S. population (*16*). Preterm infants have increased risk of death and have more health and devel-

opmental problems than full-term infants (*36–39*). The health risks associated with preterm births have contributed to rising health-care costs. The economic burden associated with preterm births in the United States in 2005 has been estimated to be $26 billion ($51,600 per infant born preterm) (*39*). ART infants born preterm accounted for approximately 4% of all preterm births in the United States in 2004, for a total economic burden estimated at $1 billion. ASRM and SART guidelines on the number of embryos transferred in an ART cycle might help in further reducing the incidence of preterms, the majority of which are multiples.

The findings in this report are subject to several limitations. First, ART surveillance data were reported for each ART procedure performed rather than for each patient who used ART. Linking procedures among patients who underwent more than one ART procedure in a given year is not possible. Because patients who underwent more than one procedure in a given year were most likely to include those in which a pregnancy was not achieved, the success rates reported might underestimate the true per-patient success rate. In addition, ratios of ART procedures per population might be higher than the unknown ratio of the number of persons undergoing ART per population. Second, these data represent couples who sought ART services in 2004; therefore, success rates do not represent all couples with infertility who were potential ART users in 2004. Third, because treatment was not randomized but rather based on medical center assessment and patient choice, results for treatment factors must be considered with caution. Finally, approximately 11% of medical centers that performed ART in 2004 did not report their data to CDC as required.

ART data are reported to CDC by the ART medical center in which the procedure was performed rather than by the state in where the patient resided. In this report, ART data are presented by the female patient's state of residence. In 2004, residency data were missing for approximately 8% of all live-birth deliveries reported to CDC. In cases of missing residency data, residency was assigned as the state in which the ART procedure was performed. Thus, the number of procedures performed among state residents, number of infants, and number of multiple-birth infants might have been overestimated for certain states. Concurrently, the numbers might be underestimated in states that border states with missing residency data, particularly states in the Northeast region of the United States. Nonetheless, the effects of missing residency data were not substantial. Statistics were evaluated separately according to the location of the ART medical center rather than the patient's state of residence. The rankings of the ART medical center location by total number of infants and multiple-birth infants were similar to the rankings based on patient's state of residence (data not presented).

The patient's state of residence was reported at the time of ART treatment. The possibility of migration during the interval between ART treatment and birth exists. U.S. Census Bureau data indicate that approximately 3% of the U.S. population moves between states annually; this rate is even higher for persons aged 20–34 years (*40*).

Members of the U.S. armed forces have a high potential for migration. Therefore, ART procedures performed among patients who attended military medical centers were evaluated separately. In 2004, a total of 799 (0.6%) ART procedures were performed in four military medical centers (California, District of Columbia, Hawaii, and Texas). In certain facilities, a substantial number of distinct states were listed for patient's state of residence. States and territories for which ≥1% of ART procedures among residents were performed in a military medical center were Alaska, District of Columbia, Hawaii, Kansas, Louisiana, Maryland, North Carolina, North Dakota, Oklahoma, South Carolina, Texas, Virginia, and Wyoming. States for which >5% of ART procedures among state residents were performed in a military medical center were Alaska and District of Columbia.

Despite these limitations, findings from national surveillance of ART procedures performed in the United States provide useful information for patients contemplating ART, ART providers, and health-care policy makers. ART surveillance data can be used to monitor trends in ART use and outcomes from ART procedures. Data from ART surveillance can be used to assess patient and treatment factors that contribute to higher success rates. Ongoing surveillance data can be used to assess the risk for multiple births and adverse perinatal outcomes among singleton births. Surveillance data provide information to assess changes in clinical practice related to ART treatment.

Increased use of ART procedures and the practice of transferring multiple embryos during ART treatments have led to high multiple-birth rates in the United States (*5,10*). Balancing the chance of success of ART against the risk for multiple births is challenging. Implementation of approaches to limit the number of embryos transferred for patients undergoing ART should reduce the occurrence of multiple births resulting from ART. Such efforts ultimately might lead ART patients and providers to view treatment success in terms of singleton pregnancies and births. In addition, continued research is needed to understand the adverse effects of ART on maternal and child health. CDC will continue to provide updates of ART use in the United States as data become available.

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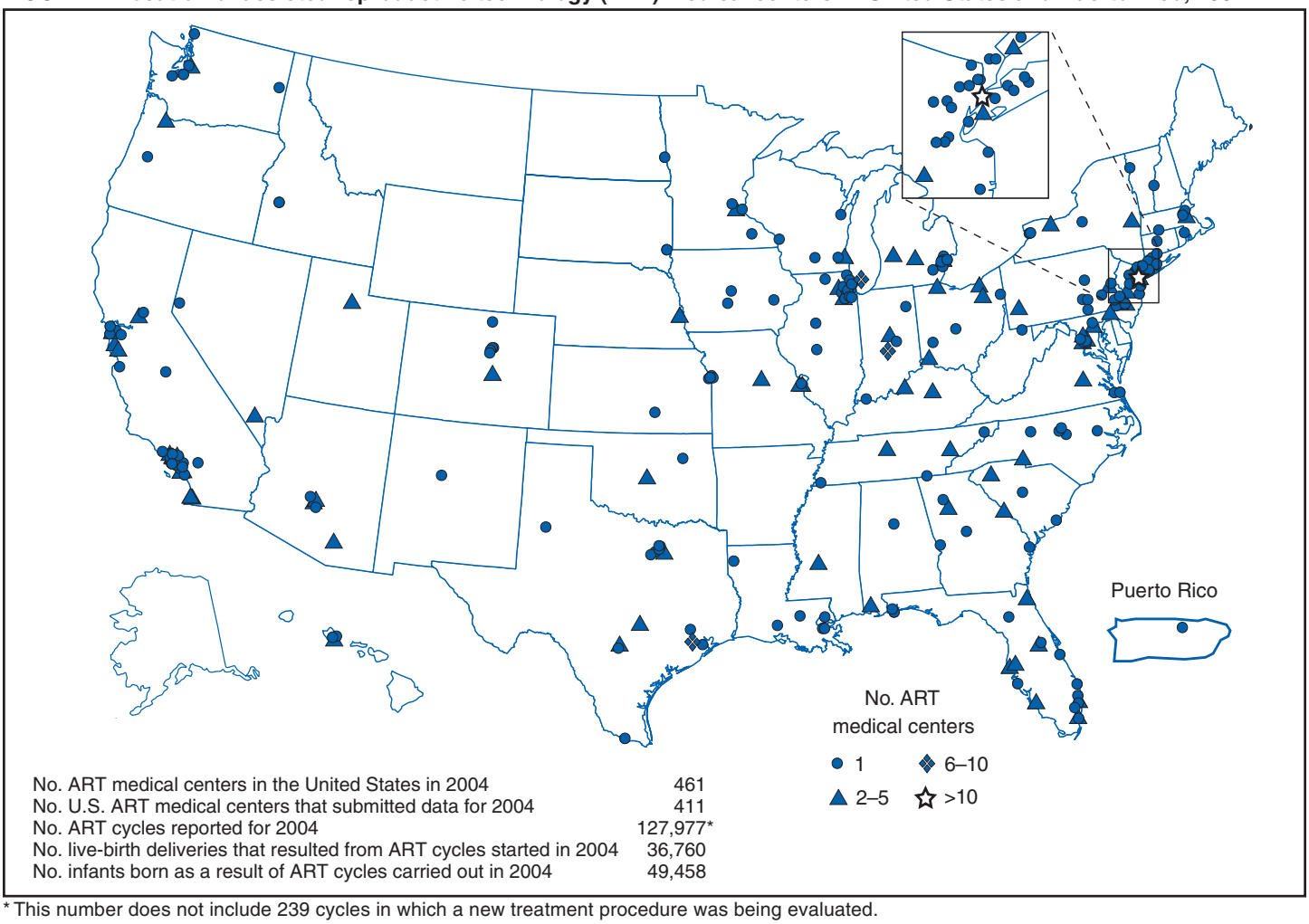
FIGURE 1. Location of assisted reproductive technology (ART) medical centers — United States and Puerto Rico, 2004



*This number does not include 239 cycles in which a new treatment procedure was being evaluated.

FIGURE 2. Live births per transfer and singleton live births per transfer for assisted reproductive technology procedures performed among women who used freshly fertilized embryos from their own eggs, by patient's age group — United States, 2004

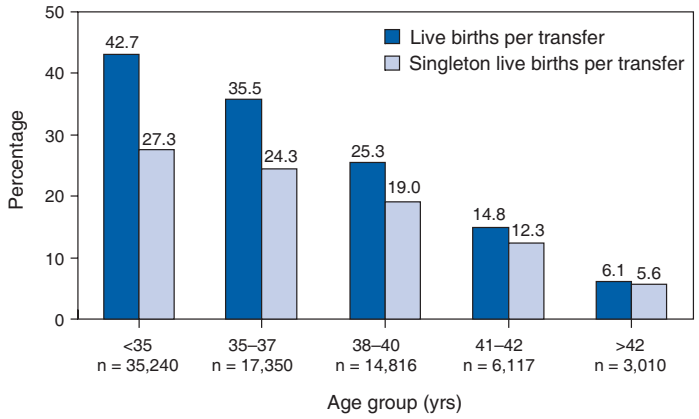


TABLE 1. Number and outcomes of assisted reproductive technology (ART) procedures, by procedure type — United States, 2004

ART procedure type	No. ART procedures started	No. ART procedures progressing to retrievals	No. ART procedures progressing to transfers	No. pregnancies	Pregnancies per transfer procedure (%)	No. live-birth deliveries	Live-birth deliveries per transfer procedure (%)	No. singleton live births	Singleton live births per transfer procedure (%)	Total no. live-born infants
Patient's eggs used										
Freshly fertilized embryos	94,242	82,475	76,533	31,758	41.5	26,059	34.0	17,581	23.0	**35,191**
Thawed embryos	18,560	NA*	16,795	5,898	35.1	4,658	27.7	3,529	21.0	**5,881**
Donor eggs used										
Freshly fertilized embryos	10,256	9,589	9,283	5,449	58.7	4,690	50.5	2,812	30.3	**6,653**
Thawed embryos	4,919	NA	4,439	1,669	37.6	1,353	30.5	999	22.5	**1,733**
Total	**127,977†**	**NA**	**107,050**	**44,774**	**41.8**	**36,760**	**34.3**	**24,921**	**23.3**	**49,458**

* Not applicable.
† This number does not include 239 ART procedures in which a new treatment procedure was being evaluated.

TABLE 2. Number of reported assisted reproductive technology (ART) procedures performed, number of pregnancies, number of live-birth deliveries, and number of infants born, by patient's state/territory of residence* at time of treatment — United States, 2004

Patient's state/territory of residence	Procedures started		Transfer procedures		Pregnancies		Live-birth deliveries		Infants born		Ratio of no. ART procedures started/ population (millions)†
	No.	No. with missing residency	No.	No. with missing residency	No.	No. with missing residency	No.	No. with missing residency	No.	No. with missing residency	
Alabama	595	0	504	0	247	0	208	0	286	0	131.7
Alaska§	48	0	44	0	21	0	14	0	19	0	73.1
Arizona	1,715	52	1,432	37	592	11	496	8	678	10	298.5
Arkansas	129	0	111	0	48	0	38	0	48	0	47.0
California	17,303	1,799	14,849	1,545	5,892	531	4,828	442	6,536	589	482.8
Colorado	1,815	28	1,578	27	887	15	751	13	1,074	20	394.7
Connecticut	2,877	125	2,334	104	979	37	808	33	1,054	37	823.4
Delaware	451	0	336	0	163	0	132	0	172	0	544.2
District of Columbia§	711	215	581	171	231	80	177	60	231	79	1226.5
Florida	5,229	66	4,285	58	1,803	27	1,447	18	1,946	22	301.1
Georgia	2,808	1,464	2,353	1,224	1,055	557	852	437	1,164	602	314.3
Guam	¶	¶	¶	¶	¶	¶	¶	¶	¶	¶	¶
Hawaii§	831	2	713	2	229	0	183	0	246	0	659.9
Idaho	324	0	296	0	151	0	128	0	171	0	232.3
Illinois	9,306	61	7,490	47	2,838	21	2,308	20	3,113	26	732.0
Indiana	2,016	3	1,683	3	680	3	563	3	770	4	323.9
Iowa	971	1	763	1	389	0	332	0	436	0	328.7
Kansas§	626	1	506	1	238	0	200	0	264	0	228.6
Kentucky	956	3	832	3	368	2	320	2	463	4	230.9
Louisiana§	750	0	609	0	270	0	227	0	310	0	166.8
Maine	218	0	166	0	73	0	59	0	79	0	165.9
Maryland§	4,205	53	3,523	44	1,415	24	1,121	15	1,457	17	757.2
Massachusetts	8,906	3,351	7,521	2,856	2,953	950	2,404	783	3,153	1,012	1383.8
Michigan	3,498	6	2,868	5	1,164	2	970	2	1,325	2	346.6
Minnesota	2,123	5	1,824	4	870	1	735	0	979	0	416.7
Mississippi	416	0	350	0	137	0	116	0	162	0	143.8
Missouri	1,589	596	1,332	509	609	238	504	198	677	253	276.2
Montana	114	0	91	0	45	0	40	0	52	0	123.1
Nebraska	702	0	540	0	226	0	192	0	265	0	401.8
Nevada	1, 045	26	926	25	403	11	326	8	442	9	448.0
New Hampshire	669	2	556	2	223	0	181	0	236	0	515.4
New Jersey	8,513	584	6,890	467	3,025	158	2,452	127	3,279	172	981.2
New Mexico	250	0	230	0	129	0	106	0	159	0	131.5
New York	11,123	171	9,266	161	3,530	51	2,769	39	3,666	47	576.6
New York City	5,051	2,573	4,070	2,114	1,712	896	1,344	693	1,758	903	637.9
North Carolina§	2,350	6	1,966	6	874	5	765	3	1,048	4	275.5
North Dakota§	193	0	170	0	63	0	57	0	76	0	303.5
Ohio	3,429	70	2,893	63	1,283	34	1,084	30	1,505	40	299.2
Oklahoma§	601	0	531	0	271	0	236	0	324	0	170.6
Oregon	894	3	791	2	380	2	330	2	442	3	249.1
Pennsylvania	4,767	428	3,848	340	1,462	127	1,184	95	1,571	118	385.1
Puerto Rico	65	0	64	0	21	0	18	0	22	0	16.7
Rhode Island	852	0	726	0	263	0	217	0	276	0	789.7
South Carolina§	928	2	812	2	405	0	349	0	461	0	221.2
South Dakota	188	0	169	0	59	0	55	0	64	0	244.1
Tennessee	1,072	1	901	1	392	1	330	1	456	2	182.1
Texas§	6,192	32	5,315	24	2,456	10	2,055	8	2,841	10	275.0
Utah	604	2	534	2	256	2	231	2	317	2	249.4
Vermont	202	0	171	0	71	0	58	0	77	0	325.4
U.S. Virgin Islands	¶	¶	¶	¶	¶	¶	¶	¶	¶	¶	¶
Virginia§	3,757	41	3,240	39	1,366	12	1,147	10	1,536	15	502.8
Washington	1,192	3	1,026	3	463	1	382	1	519	1	192.1
West Virginia	231	0	205	0	94	0	75	0	98	0	127.6
Wisconsin	1,553	12	1,333	9	556	4	485	4	657	8	282.4
Wyoming§	51	0	43	0	17	0	15	0	21	0	100.9
Non-U.S. resident	960	0	847	0	423	0	352	0	471	0	—**
Total	**127,977**	**11,787**	**107,050**	**9,901**	**44,774**	**3,813**	**36,760**	**3,057**	**49,458**	**4,011**	**435.8**

* In cases of missing residency data, the patient's place of residency was assigned as that in which the ART procedure was performed.
† Source of population size: July 1, 2004 state population estimates. Population Division, U.S. Census Bureau.
§ Of all ART procedures, 0.6% were reported from military medical centers in California, District of Columbia, Hawaii, and Texas. States and territories for which ≥1% of ART procedures among state residents were performed in a military medical center in Alaska, District of Columbia, Hawaii, Kansas, Louisiana, Maryland, North Carolina, North Dakota, Oklahoma, South Carolina, Texas, Virginia, and Wyoming. In Alaska and District of Columbia, >5% of ART procedures among residents were performed in a military medical center.
¶ Data not provided to preserve confidentiality but included in totals.
** Non-U.S. residents excluded because the appropriate denominators were unknown.

TABLE 3. Percentage distribution of selected patient and treatment factors for assisted reproductive technology (ART) transfer procedures among patients who used freshly fertilized embryos from their own eggs, by patient's age group — United States, 2004

	Patient age group (yrs)				
Patient/Treatment factors	**<35 (n = 35,240) (%)**	**35–37 (n = 17,350) (%)**	**38–40 (n = 14,816) (%)**	**41–42 (n = 6,117) (%)**	**>42 (n = 3,010) (%)**
Patient factors					
Diagnosis					
Tubal factor	12.1	13.4	11.6	8.6	5.7
Ovulatory dysfunction	8.8	5.4	3.5	2.4	1.4
Diminished ovarian reserve	2.1	4.2	10.0	19.4	30.7
Endometriosis	7.9	6.4	4.7	2.2	1.2
Uterine factor	1.0	1.4	1.7	1.7	1.4
Male factor	24.3	19.5	15.0	10.2	6.7
Other causes	5.6	6.6	7.8	9.1	8.3
Unexplained cause	11.7	14.3	13.4	11.2	8.0
Multiple factors, female only	9.1	11.1	12.9	15.8	17.8
Multiple factors, female and male	17.6	17.8	19.4	19.4	18.8
No. previous ART procedures					
0	63.7	53.8	49.3	45.5	41.8
≥1	36.4	46.2	50.7	54.5	58.2
No. previous births					
0	78.9	68.2	65.6	65.6	63.3
≥1	21.1	31.8	34.4	34.4	36.7
Treatment factors					
Method of embryo fertilization and transfer*					
IVF-ET without ICSI	32.1	33.6	34.9	35.6	36.5
IVF-ET with ICSI	67.6	66.0	64.6	63.9	62.7
IVF-ET with ICSI among couples receiving a diagnosis of male factor infertility	38.4	33.8	30.9	26.0	22.9
IVF-ET with ICSI among couples not receiving a diagnosis of male factor infertility	29.2	32.2	33.7	37.9	39.8
GIFT	0.1	0.1	0.1	0.1	0.3
ZIFT	0.3	0.3	0.3	0.3	0.3
Combination	<0.1	0.1	0.1	0.1	0.3
No. days of embryo culture†					
1	0.3	0.3	0.3	0.4	0.3
2	3.0	3.4	3.9	4.6	4.8
3	67.6	72.1	75.8	78.2	79.5
4	3.1	3.8	4.6	5.5	5.8
5	23.9	18.8	13.9	10.2	8.8
6	1.8	1.4	1.2	0.8	0.5
No. embryos transferred					
1	5.8	7.7	10.4	13.2	18.1
2	53.6	35.7	21.9	19.7	19.7
3	30.8	37.1	34.1	22.9	19.3
4	7.5	15.1	23.3	22.5	18.0
≥5	2.2	4.4	10.2	21.7	24.7
Extra embryo(s) available and cryopreserved					
Yes	42.7	30.9	18.6	9.3	4.3
No	57.3	69.1	81.4	90.7	95.7
Use of gestational carrier					
Yes	0.7	0.9	0.9	1.0	0.9
No	99.3	99.1	99.1	99.0	99.1

* IVF-ET = in vitro fertilization with transcervical embryo transfer; ICSI = intracytoplasmic sperm injection; GIFT = gamete intrafallopian transfer; ZIFT = zygote intrafallopian transfer; and Combination = a combination of IVF with or without ICSI and either GIFT or ZIFT.
† In cases of GIFT, gametes were not cultured but were transferred on day 1.

TABLE 4. Live-birth rates for assisted reproductive technology (ART) transfer procedures performed among patients who used freshly fertilized embryos from their own eggs, by patient's age group and selected patient and treatment factors — United States, 2004

	Live births per transfer procedure				
Patient/Treatment factors	**<35 yrs (%)**	**35–37 yrs (%)**	**38–40 yrs (%)**	**41–42 yrs (%)**	**>42 yrs (%)**
Patient factors					
Diagnosis					
Tubal factor	42.0*	35.5*	27.8*	13.1	7.0
Ovulatory dysfunction	45.7	40.0	27.8	11.1	7.3
Diminished ovarian reserve	35.1	30.3	21.5	15.4	5.2
Endometriosis	43.9	33.7	28.0	20.6	8.3
Uterine factor	38.7	35.4	25.6	16.2	11.6
Male factor	44.2	37.8	28.1	15.8	6.0
Other causes	39.9	35.1	24.9	17.1	8.0
Unexplained cause	42.6	36.7	27.0	13.8	5.4
Multiple factors, female only	40.8	33.4	23.8	14.0	5.0
Multiple factors, female and male	42.3	34.1	22.3	14.3	7.2
No. previous ART procedures					
0	44.5*	37.7*	26.6*	15.1	6.4
≥1	39.7	33.0	24.0	14.6	5.9
No. previous births					
0	41.7*	34.1*	24.1*	14.2	5.5
≥1	46.7	38.7	27.5	16.0	7.2
Treatment factors					
Method of embryo fertilization and transfer†					
IVF-ET without ICSI	44.8*	38.7*	28.0*	16.5*	6.5
IVF-ET with ICSI among couples receiving a diagnosis of male factor infertility	43.2	35.3	24.5	14.5	7.1
IVF-ET with ICSI among couples not receiving a diagnosis of male factor infertility	39.8	32.5	23.2	13.5	5.2
No. days of embryo culture§					
3	41.3*	34.2*	24.5*	14.1*	5.2*
5	48.8	42.5	31.0	21.6	13.6
No. embryos transferred					
1	22.9*	15.4*	8.8*	4.8*	2.4*
2	46.5	38.8	21.9	11.8	3.9
3	42.0	36.8	28.6	15.0	4.6
4	37.4	35.6	29.4	18.2	8.5
≥5	33.5	34.2	29.1	20.1	10.1
Extra embryos available and cryopreserved					
Yes	51.5*	45.6*	37.1*	27.0*	7.8
No	36.2	31.0	22.6	13.6	6.0
Use of gestational carrier					
Yes	46.6	40.4	31.5	20.3	14.8
No	42.7	35.5	25.2	14.8	6.0
Total live births¶	**42.7**	**35.5**	**25.3**	**14.8**	**6.1**

* $p<0.05$, chi-square to test for variations in live-birth rates across patient and treatment factor categories within each age group.
† IVF-ET = in vitro fertilization with transcervical embryo transfer, and ICSI = intracytoplasmic sperm injection. ART procedures including gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), and a combination of IVF with or without ICSI and either GIFT or ZIFT were not included because each of these accounted for a small proportion of procedures.
§ Limited to 3 and 5 days to embryo culture. ART procedures including 1, 2, 4, and 6 days to embryo culture were not included because each of these accounted for a limited proportion of procedures.
¶ Per transfer procedure.

TABLE 5. Multiple-birth risk, by type of assisted reproductive technology (ART) transfer procedure performed — United States, 2004

Procedure type	Patient age group (yrs)	No. live-birth deliveries	Multiple-birth deliveries		No. infants born	Infants born in multiple-birth deliveries	
			No.	(%)*		No.	(%)
Patient's eggs used							
Freshly fertilized embryos	All ages	26,059	8,478	(32.5)	35,191	17,610	(50.0)
	<35	15,059	5,435	(36.1)	20,919	11,295	(54.0)
	35–37	6,165	1,944	(31.5)	8,269	4,048	(49.0)
	38–40	3,744	932	(24.9)	4,737	1,925	(40.6)
	41–42	907	152	(16.8)	1,065	310	(29.1)
	>42	184	15	(8.2)	201	32	(15.9)
Thawed embryos	All ages	4,658	1,129	(24.2)	5,881	2,352	(40.0)
	<35	2,692	695	(25.8)	3,452	1,455	(42.1)
	35–37	1,142	275	(24.1)	1,434	567	(39.5)
	38–40	605	121	(20.0)	735	251	(34.1)
	41–42	143	25	(17.5)	170	52	(30.6)
	>42	76	13	(17.1)	90	27	(30.0)
Donor's eggs used†							
Freshly fertilized embryos	All ages	4,690	1,878	(40.0)	6,653	3,841	(57.7)
Thawed embryos	All ages	1,353	354	(26.2)	1,733	734	(42.4)
Total	**All ages**	**36,760**	**11,839**	**(32.2)**	**49,458**	**24,537**	**(49.6)**

* Multiple-birth risk.
† Age-specific statistics are not presented for procedures that used donor eggs because only limited variation by age exists among these procedures.

TABLE 6. Live-birth rates and percentages of singletons, twins, and triplets or higher-order multiples for assisted reproductive technology (ART) transfer procedures that used freshly fertilized embryos from the patient's own eggs, by patient's age group, number of embryos transferred, and embryo availability — United States, 2004

	All ART transfer procedures					ART transfer procedures for women known to have more embryos available than transferred				
Patient age group (yrs)/No. embryos transferred	No.	Live births per transfer* (%)	Singletons (%)	Twins (%)	Triplets or higher-order deliveries (%)	No.	Live births per transfer (%)	Singletons (%)	Twins (%)	Triplets or higher-order deliveries (%)
<35										
1	2,051	22.9	97.9	2.1	0	397	45.3	96.1	3.9	0
2	18,887	46.5	64.6	34.5	0.9	10,244	52.7	61.6	37.4	1.0
3	10,860	42.0	59.8	34.0	6.2	3,712	49.8	54.4	38.1	7.6
4	2,645	37.4	61.6	31.2	7.2	574	47.7	51.5	39.4	9.1
≥5	772	33.6	58.3	34.4	7.3	133	42.9	50.9	42.1	7.0
35–37										
1	1,327	15.4	98.5	1.5	0	116	34.5	97.5	2.5	0
2	6,191	38.8	72.1	27.2	0.7	2,576	49.6	68.5	30.7	0.8
3	6,432	36.8	66.7	29.9	3.4	2,010	43.1	60.5	35.5	4.0
4	2,622	35.6	58.6	35.7	5.8	530	41.1	51.4	40.8	7.8
≥5	763	34.2	62.5	31.4	6.1	130	33.1	48.8	41.9	9.3
38–40										
1	1,536	8.8	97.0	3.0	0	34	23.5	100.0	0	0
2	3,245	21.9	79.8	20.0	0.3	669	38.1	73.7	25.9	0.4
3	5,053	28.6	76.4	22.2	1.5	1,191	37.7	70.8	26.5	2.7
4	3,458	29.4	70.0	28.1	2.0	639	35.5	66.1	30.0	4.0
≥5	1,504	29.1	68.4	27.7	3.9	225	36.9	60.2	32.5	7.2
41–42										
1	807	4.8	100.0	0	0	5	*	*	*	*
2	1,202	11.8	88.0	12.0	0	76	31.6	75.0	25.0	0
3	1,398	15.0	81.9	16.7	1.4	169	23.7	80.0	15.0	5.0
4	1,377	18.2	84.0	14.8	1.2	191	24.1	82.6	15.2	2.2
≥5	1,326	20.1	78.6	20.7	0.8	126	34.1	74.4	25.6	0
>42										
1	544	2.4	92.3	7.7	0	0	*	*	*	*
2	594	3.9	87.0	8.7	4.4	19	21.1	75.0	0	25.0
3	581	4.7	100.0	0	0	29	13.8	100.0	0	0
4	543	8.5	89.1	8.7	2.2	38	2.6	100.0	0	0
≥5	743	10.1	92.0	8.0	0	43	2.3	100.0	0	0

* Statistics not provided for cases in which the denominator is <10.

TABLE 7. Live-birth rates and multiple-birth risk for assisted reproductive technology (ART) transfer procedures using freshly fertilized embryos from the patient's own eggs, by patient age group, number of embryos transferred, day of embryo transfer, and embryo availability — United States, 2004

	Day 3						Day 5					
	All ART transfer procedures			ART transfer procedures for women known to have more embryos available than transferred			All ART transfer procedures			ART transfer procedures for women known to have more embryos available than transferred		
Patient age group (yrs)	No.	Live births per transfer (%)	Multiple-birth deliveries (%)	No.	Live births per transfer (%)	Multiple-birth deliveries (%)	No.	Live births per transfer (%)	Multiple-birth deliveries (%)	No.	Live births per transfer (%)	Multiple-birth deliveries (%)
<35												
1	1,193	18.3	1.8	102	31.4	6.3	561	37.6	2.8	273	52.4	3.5
2	11,085	44.1	31.0	5,716	50.6	33.8	6,345	52.1	42.5	3,859	56.9	44.5
3	8,742	42.6	40.3	3,009	50.1	46.2	1,250	40.4	41.2	423	48.7	46.1
4	2,174	37.6	38.9	484	48.4	47.9	197	35.0	36.2	47	40.4	57.9
≥5	599	32.7	40.3	97	40.2	51.3	53	28.3	40.0	11	27.3	0
35–37												
1	820	11.5	1.1	31	22.6	0	282	25.9	1.4	76	39.5	3.3
2	3,524	34.2	21.0	1,215	44.7	25.0	2,143	47.7	35.4	1,195	55.2	36.4
3	5,207	36.7	33.5	1,652	43.0	39.5	682	36.7	34.0	210	41.0	38.4
4	2,309	36.5	41.2	473	42.5	48.3	125	29.6	40.5	23	26.1	33.3
≥5	644	34.5	38.7	112	33.9	55.3	25	16.0	25.0	3	*	*
38–40												
1	1,021	6.6	1.5	11	0	0	269	15.2	2.4	18	38.9	0.0
2	2,001	17.1	15.2	261	33.7	20.5	865	32.5	28.1	349	41.3	31.9
3	3,886	27.6	21.6	891	35.5	26.6	697	36.9	30.7	207	46.9	40.2
4	3,013	29.6	29.3	580	35.7	32.9	172	27.3	38.3	27	37.0	60.0
≥5	1,301	29.1	31.6	198	35.9	38.0	46	21.7	30.0	5	*	*
41–42												
1	525	3.2	0	0	*	*	121	7.4	0	5	*	*
2	858	9.7	6.0	25	20.0	0	176	19.9	20.0	45	40.0	27.8
3	1,060	13.4	16.2	113	22.1	20.0	193	25.9	26.0	48	27.1	23.1
4	1,169	17.0	16.6	168	22.6	15.8	90	28.9	23.1	15	46.7	28.6
≥5	1,169	19.7	19.7	117	35.0	24.4	43	34.9	26.7	1	*	*
>42												
1	391	1.0	0	0	*	*	61	14.8	11.1	0	*	*
2	435	3.2	7.1	8	*	*	65	6.2	25.0	8	*	*
3	453	3.3	0	20	0	0	57	12.3	0	5	*	*
4	452	6.9	6.5	33	0	0	46	21.7	30.0	3	*	*
≥5	661	9.1	8.3	42	2.4	0	33	18.2	16.7	0	*	*

*Statistics are not provided for cases in which the denominator is <10.

TABLE 8. Number and percentage of infants born in multiple-birth deliveries by patient's state/territory of residence* at time of assisted reproductive technology (ART) procedure — United States, 2004

Patient's state of residency	No. infants born		No. infants born in multiple-birth deliveries		Infant born in multiple-birth deliveries† (%)	Infants born in twin deliveries (%)	Infants born in triplet or higher-order deliveries (%)
	No.	No. with missing residency	No.	No. with missing residency			
Alabama	286	0	153	0	53.5	49.3	4.2
Alaska§	19	0	10	0	52.6	52.6	0.0
Arizona	678	10	347	4	51.2	44.5	6.6
Arkansas	48	0	20	0	41.7	41.7	0.0
California	6,536	589	3,313	287	50.7	45.7	5.0
Colorado	1,074	20	623	14	58.0	51.2	6.8
Connecticut	1,054	37	473	8	44.9	39.3	5.6
Delaware	172	0	79	0	45.9	44.2	1.7
District of Columbia§	231	79	106	37	45.9	43.3	2.6
Florida	1,946	22	963	8	49.5	44.1	5.3
Georgia	1,164	602	587	303	50.4	40.5	9.9
Guam	¶	¶	¶	¶	¶	¶	¶
Hawaii§	246	0	123	0	50.0	45.1	4.9
Idaho	171	0	83	0	48.5	43.3	5.3
Illinois	3,113	26	1,549	12	49.8	43.6	6.1
Indiana	770	4	390	2	50.6	41.2	9.5
Iowa	436	0	201	0	46.1	41.3	4.8
Kansas§	264	0	126	0	47.7	43.2	4.5
Kentucky	463	4	269	4	58.1	45.8	12.3
Louisiana§	310	0	159	0	51.3	42.9	8.4
Maine	79	0	39	0	49.4	45.6	3.8
Maryland§	1,457	17	658	4	45.2	41.5	3.6
Massachusetts	3,153	1,012	1,463	448	46.4	42.8	3.6
Michigan	1,325	2	672	0	50.7	41.2	9.5
Minnesota	979	0	476	0	48.6	44.9	3.7
Mississippi	162	0	89	0	54.9	45.7	9.3
Missouri	677	253	337	110	49.8	44.9	4.9
Montana	52	0	23	0	44.2	38.5	5.8
Nebraska	265	0	138	0	52.1	41.5	10.6
Nevada	442	9	225	2	50.9	45.7	5.2
New Hampshire	236	0	110	0	46.6	46.6	0.0
New Jersey	3,279	172	1,608	88	49.0	44.6	4.5
New Mexico	159	0	102	0	64.2	56.6	7.5
New York	3,666	47	1,731	16	47.2	42.0	5.2
New York City	1,758	903	810	410	46.1	43.0	3.1
North Carolina§	1,048	4	548	2	52.3	46.9	5.4
North Dakota§	76	0	38	0	50.0	50.0	0
Ohio	1,505	40	787	20	52.3	41.6	10.7
Oklahoma§	324	0	173	0	53.4	48.1	5.2
Oregon	442	3	220	2	49.8	47.1	2.7
Pennsylvania	1,571	118	747	45	47.5	42.3	5.3
Puerto Rico	22	0	8	0	36.4	36.4	0
Rhode Island	276	0	117	0	42.4	40.2	2.2
South Carolina§	461	0	218	0	47.3	43.4	3.9
South Dakota	64	0	18	0	28.1	28.1	0
Tennessee	456	2	236	2	51.8	41.7	10.1
Texas§	2,841	10	1,518	4	53.4	47.3	6.1
Utah	317	2	167	0	52.7	48.3	4.4
Vermont	77	0	38	0	49.4	49.4	0
U.S. Virgin Islands	¶	¶	¶	¶	¶	¶	¶
Virginia§	1,536	15	758	10	49.3	45.4	4.0
Washington	519	1	270	0	52.0	48.6	3.5
West Virginia	98	0	44	0	44.9	38.8	6.1
Wisconsin	657	8	332	7	50.5	44.9	5.6
Wyoming§	21	0	10	0	47.6	19.0	28.6
Non U.S. resident	471	0	231	0	49.0	44.6	4.5
Total	**49,458**	**4,011**	**24,537**	**1,849**	**49.6**	**44.1**	**5.5**

* In cases of missing residency data, the patient's place of residency was assigned as that in which the ART procedure was performed.
† Statistics might not sum to total because of rounding.
§ Of all ART procedures, 0.6% were reported from military medical centers in California, District of Columbia, Hawaii, and Texas. States and territories for which ≥1% of ART procedures among residents were performed in a military medical center were Alaska, District of Columbia, Hawaii, Kansas, Louisiana, Maryland, North Carolina, North Dakota, Oklahoma, South Carolina, Texas, Virginia, and Wyoming. In Alaska and District of Columbia, >5% of ART procedures among residents were performed in a military medical center.
¶ Data not provided to preserve confidentiality but included in total.

TABLE 9. Effect of assisted reproductive technology (ART) on the total number of live-born infants in the United States, by plurality — United States, 2004

Plurality	ART infants*†		U.S.-born infants§		Contribution of ART to total no. U.S.-born infants (%)
	No.	% of total	No.	% of total	
Infants born in singleton deliveries	24,222	(49.1)	3,972,558	(96.6)	0.6
Infants born in multiple-birth deliveries	25,154	(50.9)	139,494	(3.4)	18.0
Twins	22,226	(45.0)	132,219	(3.2)	16.8
Triplets or higher order	2,928	(5.9)	7,275	(0.2)	40.2
Total no. infants	**49,376**		**4,112,052**		**1.2**

* **Source:** Assisted Reproductive Technology Surveillance System.
† Includes infants conceived from ART procedures performed in 2003 and born in 2004 and infants conceived from ART procedures performed in 2004 and born in 2004.
§ **Source:** U.S. natality file, CDC, National Center for Health Statistics.

TABLE 10. Percentage of adverse perinatal outcomes* among assisted reproductive technology (ART) infants† born in 2004, by plurality — United States

Plurality	LBW (%)	VLBW (%)	Preterm (%)	Preterm LBW (%)	Term LBW (%)
ART singletons (n = 24,222)	9.3	1.8	14.7	7.1	2.2
ART twins (n = 22,226)	55.7	8.8	64.3	46.8	8.9
ART triplets or higher-order multiples (n = 2,928)	95.0	32.0	98.0	93.3	1.6

* LBW = low birthweight (<2,500 g); VLBW = very low birthweight (<1,500 g); preterm = gestational age <37 weeks; preterm LBW = gestational age <37 weeks and low birthweight; and term LBW = gestational age ≥37 weeks and low birthweight.
† Includes infants conceived from ART procedures performed in 2003 and born in 2004 and infants conceived from ART procedures performed in 2004 and born in 2004. Analysis excluded 580 infants for whom data on birthweight were missing and 316 infants for whom data on gestational age were missing.

TABLE 11. Adverse perinatal outcomes* among assisted reproductive technology (ART) singleton infants born in 2004, by procedure type and selected maternal factors — United States†

Procedure/maternal factor	LBW (%)	VLBW (%)	Preterm (%)	Preterm LBW (%)	Term LBW (%)
Freshly fertilized embryos, patient's eggs (n = 17,230)	**9.5§**	**1.8**	**13.4§**	**6.9**	**2.5§**
Maternal age group (yrs)					
<35	9.9	1.6	13.8	7.3	2.6
35–37	9.2	2.0	13.0	6.9	2.4
38–40	9.0	2.0	13.1	6.1	2.9
41–42	8.4	1.5	12.4	7.0	1.5
>42	5.9	2.0	12.0	3.3	2.6
No. previous births					
0	10.2¶	2.0¶	13.8¶	7.5¶	2.8¶
1	6.9	1.1	11.6	5.0	2.0
≥2	9.2	1.2	15.5	7.4	1.8
Freshly fertilized embryos, donors eggs (n = 2,772)	**10.4**	**1.9**	**16.2**	**8.3**	**2.1**
Thawed embryos (n = 4,220)**	**7.8**	**1.6**	**19.1**	**6.9**	**1.0**

* LBW = low birthweight (<2,500 g); VLBW = very low birthweight (<1,500 g); preterm = gestational age <37 weeks; preterm LBW = gestational age <37 weeks and low birthweight; and term LBW = gestational age ≥37 weeks and low birthweight.
† Includes infants conceived from ART procedures performed in 2003 and born in 2004 and infants conceived from ART procedures performed in 2004 and born in 2004. Analysis excluded 237 singletons for whom data on birthweight were missing and 137 singletons for whom data on gestational age were missing.
§ $p<0.01$; chi-squared to test for variations in adverse perinatal outcomes across procedure types.
¶ $p<0.01$; chi-squared to test for variations in adverse perinatal outcomes across maternal factor categories.
** Includes cycles in which thawed embryos were used from patient eggs and donor eggs.

Malaria Surveillance — United States, 2005

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Abstract

Problem/Condition: Malaria in humans is caused by any of four species of intraerythrocytic protozoa of the genus *Plasmodium* (i.e., *P. falciparum*, *P. vivax*, *P. ovale*, or *P. malariae*). These parasites are transmitted by the bite of an infective female *Anopheles* sp. mosquito. The majority of malaria infections in the United States occur among persons who have traveled to or from areas with ongoing malaria transmission. In the United States, cases can occur through exposure to infected blood products, congenital transmission, or local mosquitoborne transmission. Malaria surveillance is conducted to identify episodes of local transmission and to guide prevention recommendations for travelers.

Period Covered: This report summarizes cases in persons with onset of illness in 2005 and summarizes trends during previous years.

Description of System: Malaria cases confirmed by blood film or polymerase chain reaction (PCR) are mandated to be reported to local and state health departments by health-care providers or laboratory staff. Case investigations are conducted by local and state health departments, and reports are transmitted to CDC through the National Malaria Surveillance System (NMSS). Data from NMSS serve as the basis for this report.

Results: CDC received reports of 1,528 cases of malaria, including seven fatal cases, with an onset of symptoms in 2005 among persons in the United States or one of its territories. This number represents an increase of 15.4% from the 1,324 cases reported for 2004. *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 48.6%, 22.1%, 3.5%, and 2.5% of cases, respectively. Twelve patients (0.8% of total) were infected by two or more species. The infecting species was unreported or undetermined in 22.6% of cases. Compared with 2004, the largest increases in cases came from the Americas (23.1%; n = 213) and Asia and the Middle East (18.6%; n = 204). On the basis of estimated volume of travel, the highest estimated case rates of malaria among travelers occurred among those returning from West Africa. Of 870 U.S. civilians who acquired malaria abroad, only 160 (18.4%) reported that they had followed a chemoprophylactic drug regimen recommended by CDC for the area to which they had traveled. Two patients became infected in the United States, both attributed to congenital transmission; both were infected with *P. vivax*. Seven deaths were attributed to malaria, all caused by infection with *P. falciparum*.

Interpretation: The 15.4% increase in malaria cases in 2005, compared with 2004, resulted primarily from increases in the number of cases reported from Asia and the Middle East and from the Americas. This increase might in part reflect more complete reporting and in part increased travel to malarious areas. No change was noted in proportions of cases from other areas of the world, or in species responsible for the infection. In the majority of reported cases, U.S. civilians who acquired infection abroad had not adhered to a chemoprophylaxis regimen that was appropriate for the country in which they acquired malaria. U.S. civilians who traveled to West Africa had the highest estimated relative case rate.

Public Health Actions: Additional investigations were conducted for the seven fatal cases and two infections acquired in the United States. Persons traveling to a malarious area should take one of the recommended chemoprophylaxis regimens appropriate for the region of travel and use personal protection measures to prevent mosquito bites. Any person who has been to a malarious area and who subsequently has a fever or influenza-like symptoms should seek

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medical care immediately and report their travel history to the clinician; investigation should include at least one blood-film test for malaria. Malaria infections can be fatal if not diagnosed and treated promptly. Recommendations concerning malaria prevention can be obtained from CDC at http://www.cdc.gov/travel or by calling the Malaria Hotline (telephone 770-488-7788). Recommendations for malaria treatment can be obtained at http://www.cdc.gov/malaria/diagnosis_treatment/treatment.htm or by calling the Malaria Hotline.

Introduction

Malaria in humans is caused by infection with one or more of four species of *Plasmodium* (i.e., *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*) that can infect humans. Other *Plasmodium* species infect animals. The infection is transmitted by the bite of an infective female *Anopheles* sp. mosquito. Malaria remains a devastating global problem, with an estimated 350–500* million cases occurring annually (*1*). Forty-nine percent of the world's population lives in areas where malaria is transmitted (e.g., parts of Africa, Asia, the Middle East, Eastern Europe, Central and South America, Hispaniola, and Oceania), and approximately 1 million persons die from malaria each year, 80% of them in sub-Saharan Africa (*1*). Before the 1950s, malaria was endemic throughout the southeastern United States; an estimated 600,000 cases occurred in 1914 (*2*). During the late 1940s, a combination of improved housing and socioeconomic conditions, water management, vector-control efforts, and case management was successful at interrupting malaria transmission in the United States. Since then, malaria case surveillance has been maintained to detect locally acquired cases that could indicate the reintroduction of transmission and to monitor patterns of resistance to antimalarial drugs. Anopheline mosquitoes remain seasonally present in all states except Hawaii.

The majority of reported cases of malaria diagnosed each year in the United States and U.S. territories are imported from regions where malaria transmission is known to occur, although congenital infections and infections resulting from exposure to blood or blood products also are reported in the United States. In addition, a limited number of cases are reported that might have been acquired through local mosquitoborne transmission (*3*).

State and local health departments and CDC investigate malaria cases acquired in the United States, and CDC analyzes data from imported cases to detect trends in acquisition. This information is used to guide malaria prevention recommendations for international travelers. For example, an increase in *P. falciparum* malaria among U.S. travelers to Africa, an area with increasing chloroquine resistance, prompted CDC to change the recommended chemoprophylaxis regimen from chloroquine to mefloquine in 1990 (*4*).

The signs and symptoms of malaria illness are varied, but the majority of patients have fever. Other common symptoms include headache, back pain, chills, increased sweating, myalgia, nausea, vomiting, diarrhea, and cough. The diagnosis of malaria should be considered for persons with these symptoms who have traveled to an area with known malaria transmission. Malaria also should be considered in the differential diagnosis of persons who have fever of unknown origin, regardless of their travel history. Untreated *P. falciparum* infections can rapidly progress to coma, renal failure, pulmonary edema, and death. This report summarizes malaria cases reported to CDC regarding persons with onset of symptoms in 2005.

Methods

Data Sources

Malaria case data are reported to the National Malaria Surveillance System (NMSS) and the National Notifiable Diseases Surveillance System (NNDSS) (*5*). Although both systems rely on passive reporting, the numbers of reported cases might differ because of differences in collection and transmission of data. One difference is that NMSS receives more detailed clinical and epidemiologic data regarding each case (e.g., information concerning the area to which the infected person has traveled). This report presents only data from NMSS.

Cases of blood-film– or polymerase chain reaction (PCR)–confirmed malaria among civilians and military personnel are identified by health-care providers or laboratories. Each confirmed malaria case is reported to local or state health departments and to CDC on a uniform case-report form that contains clinical, laboratory, and epidemiologic information. CDC staff review all report forms when received and request additional information from the provider or the state, if necessary (e.g., when no recent travel to a malarious country is reported). Reports of other cases are telephoned to CDC directly by health-care providers, usually when they are seeking assistance with diagnosis or treatment. Information regarding cases reported directly to CDC is shared with the relevant state health department. All cases that have been

* The en dash in numeric ranges is used to represent inclusive hours, days, ages, dosages, or a sequence of numbered items.

reported as acquired in the United States are investigated, including all induced and congenital cases and possible introduced or cryptic cases (see Definitions). Information derived from uniform case report forms is entered into a database and analyzed annually.

A case rate was estimated for each country where cases of malaria were acquired on the basis of estimates of travel volume for U.S. travelers and the number of cases among U.S. travelers attributable to each country. Data used to estimate country-specific relative case rates were extrapolated from World Tourism Organization estimates of annual numbers of U.S. travelers to specified countries (*6*). The individual country-specific case rates were divided by the median individual country-specific case rate to determine estimated relative case rates.

Definitions

The following definitions are used in this report:

- **Laboratory criteria for confirmation of diagnosis:** Demonstration of malaria parasites on blood film or by PCR.
- **Confirmed case:** Symptomatic or asymptomatic infection that occurs in a person in the United States or one of its territories (American Samoa, Guam, Puerto Rico, and the U.S. Virgin Islands) who has laboratory-confirmed (by microscopy or PCR) malaria parasitemia, regardless of whether the person had previous episodes of malaria while in other countries. A subsequent episode of malaria is counted as an additional case if the indicated *Plasmodium* sp. differs from the initially identified species. A subsequent episode of malaria occurring in a person while in the United States could indicate a relapsing infection or treatment failure resulting from drug resistance if the indicated *Plasmodium* sp. is the same species identified previously.

This report also uses terminology derived from the recommendations of the World Health Organization (*7*). Definitions of the following terms are included for reference:

- **Autochthonous malaria:**
  - —**Indigenous.** Mosquitoborne transmission of malaria in a geographic area where malaria occurs regularly.
  - —**Introduced.** Mosquitoborne transmission of malaria from a person with an imported case in an area where malaria does not occur regularly.
- **Imported malaria:** Malaria acquired outside a specific area. In this report, imported cases are those acquired outside the United States and its territories (American Samoa, Guam, Puerto Rico, and the U.S. Virgin Islands).
- **Induced malaria:** Malaria acquired through artificial means (e.g., blood transfusion or by using shared common syringes).
- **Relapsing malaria:** Renewed manifestations (i.e., parasitemia with or without clinical symptoms) of malarial infection that are separated from previous manifestations of the same infection by an interval greater than the usual periodicity of the paroxysms.
- **Cryptic malaria:** A case of malaria for which epidemiologic investigations fail to identify a plausible mode of acquisition (this term applies primarily to cases found in countries where malaria is not endemic).

Laboratory Diagnosis of Malaria

The early and prompt diagnosis of malaria requires that physicians obtain a travel history from every febrile patient. Malaria should be included in the differential diagnosis of every febrile patient who has traveled to a malarious area. If malaria is suspected, a Giemsa-stained film of the patient's peripheral blood should be examined for parasites. Thick and thin blood films must be prepared correctly because diagnostic accuracy depends on blood-film quality and examination by experienced laboratory personnel[†] (Appendix). Select reference laboratories and health departments have the capacity to perform PCR diagnosis of malaria, although this usually is reserved for cases for which blood-film diagnosis of malaria or species determination is inadequate.

Results

General Surveillance

For 2005, CDC received 1,528 reports of cases of malaria occurring among persons in the United States and its territories, representing a 15.4% increase from the 1,324 cases reported with a date of onset in 2004 (*8;* Table 1). In 2005, a total of 870 cases occurred among U.S. civilians and 297 cases among foreign civilians (Table 1). Since 2003, the number of cases among U.S. civilians has been increasing (Figure 1).

Plasmodium Species

Of the 1,528 cases reported in 2005, the infecting species of *Plasmodium* was identified in 1,183 (77.4%) cases.

[†] To obtain confirmation diagnosis of blood films from questionable cases and to obtain appropriate treatment recommendations, contact either your state or local health department or CDC's National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Division of Parasitic Diseases, Malaria Branch at 770-488-7788.

P. falciparum and *P. vivax* were identified in blood films from 48.6% and 22.1% of infected persons, respectively (Table 2). The number of reported cases of *P. falciparum* increased 13.1%, from 656 in 2004 to 742 in 2005, and the number of *P. vivax* infections increased 7.0%, from 315 to 337. Among 1,081 cases for which both the region of acquisition and the infecting species were known, 83.4% of infections acquired in Africa were attributed to *P. falciparum* and 6.6% to *P. vivax*. The converse was true for infections acquired in the Americas and in Asia and the Middle East; 59.1% and 68.1%, respectively, were attributed to *P. vivax* and 33.9% and 13.2% to *P. falciparum*.

Region of Acquisition and Diagnosis

All but two reported cases were imported. Of 1,349 imported cases for which the region of acquisition was known, 902 (66.9%) were acquired in Africa, 204 (15.1%) in Asia and the Middle East, and 213 (15.8%) in the Americas (Table 3). A total of 30 (2.0%) imported cases were acquired in Oceania. West Africa accounted for 619 (68.6%) cases acquired in Africa, and India accounted for 137 (67.2%) cases acquired in Asia and the Middle East. In the Americas, 162 (76.0%) cases were acquired in Central America and the Caribbean, followed by 37 (17.3%) cases in South America and 14 (6.6%) cases in Mexico. Information regarding region of acquisition was missing for 177 (11.6%) imported cases. Compared with 2004, the number of reported malaria cases acquired in the Americas increased 23.1% (n = 213), the number acquired in Asia and the Middle East increased 18.6% (n = 204), and the number acquired in Africa increased 11.5% (n = 902). In the United States, the six health departments reporting the highest number of malaria cases were New York City (n = 192), California (n = 162), Texas (n = 144), Maryland (n = 97), New Jersey (n = 83), and Illinois (n = 79) (Figure 2). Of these, New York City was the only health department to report a decrease in the number of cases compared with 2004; all of the others in the top 6 reported increases.

Relative Case Rates in U.S. Civilians

In 2005, the countries with the lowest and highest estimated case rates of malaria among U.S. travelers were China and Nigeria, respectively (Figure 3). Other countries with low estimated relative case rates included Mexico, Thailand, Costa Rica, and South Africa. For many of these countries, malaria risk areas are focally located in small parts of the country. Countries with estimated relative case rates that fell in the middle range included India, Honduras, and Haiti, which had malaria transmission occurring more homogenously throughout the country. Estimated relative case rates were highest in countries in West and Central Africa, including Nigeria and Ghana, but also in two countries in Oceania: Vanuatu and Papua New Guinea. These high estimated case rates probably reflect not only widespread transmission areas but also higher transmission intensity.

Interval Between Arrival and Illness

Both the interval between date of arrival in the United States and onset of illness and the infecting *Plasmodium* species were known for 668 (43.7%) of the imported malaria cases (Table 4). Symptoms began before arrival in the United States for 81 (12.1%) persons and after arrival for 587 (87.9%) persons. Clinical malaria occurred <30 days after arrival in 380 (81.0%) of the 469 *P. falciparum* cases and in 61 (40.7%) of the 150 *P. vivax* cases (Table 4). Five (0.7%) of 668 persons became ill >1 year after returning to the United States.

Imported Malaria Cases

Imported Malaria Among U.S. Military Personnel

In 2005, a total of 36 cases of imported malaria were reported among U.S. military personnel, 30 of whom acquired malaria in Asia and the Middle East. These cases were reported by state health departments and might not include all cases reported through malaria surveillance activities conducted by the U.S. Department of Defense. Of the 32 patients for whom information regarding chemoprophylaxis use was available, 21 (65.6%) reported taking the correct prophylaxis, nine (28.1%) were not using any chemoprophylaxis, and two (6.3%) had adhered to an incorrect regimen.

Imported Malaria Among Civilians

Of 1,167 imported malaria cases reported among civilians, 870 (74.6%) occurred among U.S. residents and 297 (25.4%) among residents of other countries (Table 5). Of the 870 imported malaria cases among U.S. civilians, 611 (70.2%) were acquired in Africa, 100 (11.5%) were acquired in Asia and the Middle East, and 89 (10.2%) were acquired in the Central American and Caribbean regions; these percentages remained stable compared with 2004. Of the 279 imported cases among foreign civilians, 172 (57.9%) were acquired in Africa, a 4.9% decrease since 2004.

Chemoprophylaxis Use Among U.S. Civilians

Information on chemoprophylaxis use and travel area was known for 767 (88.2%) of the 870 U.S. civilians who had imported malaria. Of these 767 persons, 522 (68.1%) had not taken any chemoprophylaxis, and 42 (5.5%) had not taken

a CDC-recommended drug for the area visited (*9*). Only 160 (20.9%) U.S. civilians had taken a CDC-recommended medication (*9*). Data for the specific drug taken was missing for the remaining 43 (5.6%) travelers. A total of 93 (58.1%) patients on CDC-recommended prophylaxis reported taking mefloquine; 39 (24.4%) had taken doxycycline; 20 (12.5%) had taken atovaquone-proguanil; and seven (4.4%) who had traveled only in areas where chloroquine-resistant malaria has not been documented had taken chloroquine. Information on compliance to the drug regimen for these persons is presented in the following section. Eight patients (5.0%) had taken combinations of drugs that included one or more CDC-recommended drug for the travel region. Of the 42 patients who took a nonrecommended drug, 29 (69.0%) reported taking chloroquine either alone or in combination with another ineffective drug during travel to an area where chloroquine resistance has been documented.

Malaria Infection After Recommended Prophylaxis Use

A total of 190 patients (including 160 U.S. civilians, 21 persons in the U.S. military, four foreign civilians, and five persons for whom information regarding status was missing) contracted malaria after taking a recommended antimalarial drug for chemoprophylaxis. Of these, 72 (37.9%) reported complete compliance with the regimen, and 81 (42.6%) reported noncompliance; compliance was unknown for the remaining 37 (19.5%). Information regarding infecting species was available for 153 (80.5%) patients who had taken a recommended antimalarial drug and was undetermined for the remaining 37.

Cases of *P. vivax* or *P. ovale* After Recommended Prophylaxis Use. Of the 190 patients who had malaria diagnosed after recommended chemoprophylaxis use, 62 (32.6%) had cases that were caused by *P. vivax*, and seven (3.7%) had cases caused by *P. ovale*. Of the 69 total cases of *P. vivax* or *P. ovale*, 31 (44.9%) occurred >45 days after arrival in the United States. These cases were consistent with relapsing infections and do not indicate primary prophylaxis failures. Information was insufficient to assess whether 22 cases were relapsing infections. Sixteen cases, 14 caused by *P. vivax* and two caused by *P. malariae*, occurred ≤45 days after the patient returned to the United States. Six of the 16 patients were known to be noncompliant with their antimalarial chemoprophylaxis regimen. Four patients reported compliance with an antimalarial chemoprophylaxis regimen; two had traveled to Africa, one to Oceania, and one to South America. Two of these four patients who reported compliance reported taking mefloquine, and two reported using doxycycline; blood samples for serum drug levels were not available. Possible explanations for these cases include inappropriate dosing, unreported noncompliance, malabsorption of the drug, or emerging parasite resistance. For six patients, no information was available concerning compliance.

Cases of *P. falciparum* and *P. malariae* After Recommended Prophylaxis Use. The remaining 121 cases of malaria reported among persons who had taken a recommended antimalarial drug for chemoprophylaxis included 75 cases of *P. falciparum*, six of *P. malariae*, three of mixed infection, and 37 for which the infecting species was unidentified. Of the 75 *P. falciparum* cases among those who reported taking a recommended antimalarial drug, 70 were acquired in Africa, two in Asia, one in Central America, and two in South America. In 42 (56.0%) of these 75 cases, noncompliance with antimalarials was reported; in 20 (26.7%) cases, patients reported compliance with antimalarial chemoprophylaxis; 18 of these patients had traveled to Africa, one to South America, and one to Asia. Ten had reported taking mefloquine, eight doxycycline, and two took atovaquone-proguanil for malaria chemoprophylaxis. Blood samples were not available for the patients who reported compliance with a recommended regimen.

All of the six *P. malariae* cases among those who reported taking a recommended antimalarial drug were acquired in Africa. One (14.3%) of these patients reported noncompliance with antimalarials, and five (57.1%) reported compliance with a recommended chemoprophylaxis regimen. Three noncompliant patients used malarone, and two used mefloquine. All five patients had traveled to Africa; blood samples were not available.

Purpose of Travel

Purpose of travel to areas in which malaria is endemic was reported for 788 (90.6%) of the 870 U.S. civilians with imported malaria (Table 6). The largest proportion (56.1%) represented persons who had visited friends or relatives in malarious areas; the second and third highest proportions, 9.5% and 7.5%, represented persons who had traveled as missionaries or as tourists, respectively.

Malaria in Children

Of the 1,460 cases for whom age was known, 276 (18.9%) cases occurred in persons aged <18 years. Of these, 21 (7.6%) were aged <24 months, 50 (18.1%) were aged 24–59 months, 122 (44.2%) were aged 5–12 years, and 83 (30.0%) were aged 13–17 years. Of the 220 cases among those aged <18 years for whom species was known, 156 (70.9%) cases involved *P. falciparum* and 43 (19.5%) *P. vivax*. The proportion of children who received a diagnosis of *P. falciparum* infection was

1.57 times higher than that for adults (confidence interval [CI] = 1.13–2.18; p = 0.005). Of 231 children for whom country of exposure was known, Africa accounted for 176 (76.2%) cases, Asia and the Middle East accounted for 37 (16%) cases, and the Americas accounted for 14 (6.1%) cases. For 194 children whose reason for travel was known, 106 (54.6%) were visiting friends and relatives, and 55 (28.3%) were refugees or immigrants. Tourists and missionaries together accounted for 16 (8.2%) cases, and students accounted for 15 (7.7%) cases. Of the 276 persons aged <18 years who had malaria, 54 (19.6%) had taken prophylaxis. Of these, 28 (51.9%) had taken the correct regimen, and only eight reported complete compliance: seven children on mefloquine and one child on malarone.

Malaria During Pregnancy

A total of 21 cases of malaria were reported among pregnant women in 2005, representing 4.3% of cases among women. Of the 21 cases, 14 (66.7%) occurred among U.S. civilians. Ten women had traveled to Africa, two to Asia, and one each to the Caribbean and to Oceania; nine had traveled to visit friends and relatives. Approximately 28.6% of pregnant women and 21.2% of nonpregnant women reported taking malaria chemoprophylaxis. An infant born to one of the women with malaria during pregnancy received a diagnosis of *P. vivax* congenital malaria. Birth outcomes were not available for the other 20 women.

Malaria Acquired in the United States

Congenital Malaria

Two cases of congenital malaria were reported in 2005 and are described below:

- **Case 1.** On May 13, an infant male aged 3 weeks was admitted to an emergency department (ED) with fever and congestion. Routine septic work-up was unrevealing. His mother had emigrated from Honduras in July 2004 and had a history of malaria in 2003. She had been admitted for fever at 30 weeks' gestation, but blood and urine cultures were negative. She was treated with antibiotics, recovered uneventfully, and had a spontaneous vaginal delivery with no complications at $38^{6}/_{7}$ weeks. On the basis of this history, a peripheral blood film was performed on the newborn, revealing a low parasitemia with *P. vivax*. He was treated with chloroquine and primaquine and recovered. Record of subsequent maternal treatment was not available.
- **Case 2.** On July 15, an infant girl aged 16 days was admitted to a hospital with a history of fever, cough, and congestion. Physical and laboratory examinations did not identify an infectious etiology. While in the hospital, the child was noted to have rigors. Further maternal history was sought. The mother had emigrated from India 2 years before the infant's birth but had no known history of malaria. Her pregnancy and delivery had been uncomplicated. A peripheral blood film was performed on the infant and revealed low parasitemia with *P. vivax*. She was treated with chloroquine with good outcome. A peripheral blood film was also performed on the mother and demonstrated to be positive for *P. vivax*; the mother was subsequently treated.

Deaths Attributed to Malaria

Seven deaths attributable to malaria were reported in 2005 and are described in the following case reports:

- **Case 1.** On January 14, a woman aged 29 years was hospitalized with lethargy and dehydration, with a history of fever, chills, emesis, and weakness for 2 weeks. She was a resident of Mozambique who had left that country on December 28, 2004, to visit relatives in the United States. She had a history of several previous episodes of *P. falciparum* malaria that had been treated in Mozambique. She was mildly anemic, with a hemoglobin of 10.1 mg/dL and thrombocytopenic with a platelet count of 55,000/μL. She was transferred to a tertiary care center, where a diagnosis of malaria was considered and a peripheral blood film indicated *P. falciparum* (20% parasitemia). She was treated with IV quinidine and underwent exchange transfusion. She had a cardiac arrest and was resuscitated on January 17, but remained comatose. She died on January 26.
- **Case 2.** On April 19, a man aged 55 years was taken to an ED with a 4-day history of fever, emesis, and epigastric pain. He was a resident of the United States but had traveled to Uganda, his country of origin, for 3 months and had returned on April 12. He had not taken prophylaxis. On admission, he had sinus tachycardia and a temperature of 100.3°F (37.9°C). Routine laboratory analysis was significant only for thrombocytopenia (platelet count: 19,000/μL). A differential diagnoses list was generated, including malaria, dengue fever, and Chikungunya fever, but no further evaluation was performed. His symptoms improved with anti-emetics, normal saline, and pain control. He was discharged with a tentative diagnosis of dengue fever. Four days later, on April 23, he died abruptly. Samples sent to CDC were positive for *P. falciparum* by PCR but negative for other suspected pathogens.
- **Case 3.** On May 28, a man from the Philippines aged 32 years was taken to an ED with mental status changes and

a 3-day history of jaundice. He had recently traveled to the Philippine island of Palawan. He had onset of fever and chills in the Philippines on May 11; he visited a local clinic and was treated with antibiotics, with some relief. He subsequently traveled to the United States on May 20. On admission, his total bilirubin was 14 mg/dL. He was mildly anemic (hemoglobin 9.0 mg/dL), and thrombocytopenic (platelet count: 14,000/μL). Several hours after admission, information was obtained that three colleagues who had traveled with the patient to Palawan had been hospitalized in the Philippines with severe *P. falciparum* malaria. A peripheral blood film was performed and indicated *P. falciparum*. He was treated with oral quinine and doxycycline, as intravenous quinidine was not available, and transferred to a tertiary care center. On arrival, he was comatose and his temperature was 104.4° F (40.2° C). He was treated with intravenous quinidine and doxycycline and underwent exchange transfusion. He had acute respiratory distress syndrome (ARDS) during the exchange transfusion requiring endotracheal intubation and mechanical ventilation with increasing oxygen requirements. Although his parasitemia level diminished, his neurologic status remained unchanged. He subsequently developed anuric renal failure and died on June 2.

- **Case 4.** On August 2, a woman aged 23 years was taken to an ED with a 4-day history of fever, confusion, and dyspnea. She had been in Namibia for 10 months, with short visits to South Africa and Mozambique, and had not taken prophylaxis. She had returned to the United States on July 22 and had onset of fever and chills on July 30. She had been brought to another ED on July 31, where a peripheral blood film was negative. Her symptoms continued, and she visited the second ED on August 2, where her peripheral blood film revealed *P. falciparum* (0.6% parasitemia). She was first treated with oral quinine and intravenous clindamycin because intravenous quinidine was not available and switched the following day to intravenous quinidine and clindamycin. She subsequently had respiratory failure secondary to ARDS, requiring endotracheal intubation and mechanical ventilation, in addition to coma and coagulopathy. She underwent exchange transfusion, but her pulmonary status deteriorated, and she died on August 7.
- **Case 5.** On September 6, a woman aged 19 years was taken to a local ED with mental status changes and a 5-day history of fever, headache, and influenza-like symptoms. She had traveled to Mozambique for 3 weeks on a mission trip and returned to the United States on August 24. She had not taken chemoprophylaxis. On examination, she was anemic (hemoglobin 9.5 mg/dL) and thrombocytopenic (platelet count: 22,000/μL), and her blood smear was positive for *P. falciparum*. She was admitted and treated with intravenous quinidine and doxycycline. She deteriorated, went into a coma, and had renal failure. She was intubated, placed on mechanical ventiliation, hemodialyzed, and transferred to a tertiary care center on September 7. She had 15% parasitemia on admission, and underwent an exchange transfusion. Computed tomography (CT) of the head indicated changes consistent with cerebral malaria, but no edema. On September 9, a repeat CT showed cerebral edema. Despite management to control increased intracranial pressure, she suffered cerebral herniation. An electroencephelogram performed on September 12 indicated no brain activity. Life support was withdrawn, and she died on September 13.
- **Case 6.** On October 29, a man residing in Haiti aged 56 years had emesis, diarrhea, headache, and fever. A blood smear in a local hospital on October 30 was negative, but his symptoms worsened, and mental status changes ensued. A smear performed in Port-au-Prince on November 2 was positive for *P. falciparum*. Treatment was started with oral chloroquine, but he subsequently had seizures, hematemesis, and hematuria and was hospitalized on November 3. The day after admission, he was comatose, hypotensive, and continued to seize. He was emergently endotracheally intubated, placed on mechanical ventialiation, and evacuated to the United States on November 4, where he suffered cardiac arrest and was resuscitated. Clinical evaluation indicated disseminated intravascular coagulation and renal failure. A blood film at that point indicated rare *P. falciparum* parasites. He was treated with intravenous quinidine and underwent hemodialysis. Parasitemia cleared on November 5, but he remained in multiorgan failure and on life support. He then had sepsis with *Clostridium perfringens* and died on November 7. PCR subsequently confirmed that the parasite was susceptible to chloroquine.
- **Case 7.** On December 12, a man aged 43 years returned from a 17-day trip to the Central African Republic; he had taken no chemoprophylaxis. He had onset of fever, chills, headache, nausea, cough, and hematuria the day of his return to the United States. He continued to work through December 16, although with worsening symptoms. He became unable to work and stayed home starting December 17, but he did not seek medical care. On the morning of December 19, he was found unresponsive. He was transported to an ED with resuscitation efforts in progress, but he remained unresponsive and pulseless and was pronounced dead 30 minutes after

arrival. Tissue and blood samples analyzed at autopsy revealed the diagnosis of *P. falciparum* malaria (39% parasitemia).

Discussion

A total of 1,528 cases of malaria were reported to CDC for 2005, representing an increase of 15.4% from the 1,324 cases reported for 2004, resulting from increases from all major malaria endemic regions. The absolute number of cases among travelers attributable to travel in certain countries can be affected by multiple factors, including the amount of transmission occurring in that country, the compliance with preventive measures (including mosquito avoidance and chemoprophylaxis) by travelers, the style of travel in the country (e.g., business or adventure travel), and the volume of travel to the country. The 15.4% increase in the number of cases in 2005 compared with 2004 also might reflect increased reporting by state health departments.

One reason for conducting malaria surveillance is to monitor for prophylaxis failures that might indicate emergence of drug resistance. However, approximately 80% of imported malaria cases among U.S. civilians occurred among persons who either were not taking prophylaxis or were taking nonrecommended prophylaxis for the region to which they were traveling. The majority of patients for whom information was sufficient to indicate that the infection was a primary one rather than a relapse either reported noncompliance with recommended regimen or provided insufficient information to determine whether these cases represented 1) problems with compliance while using correct antimalarial chemoprophylaxis, 2) malabsorption of the antimalarial drug, or 3) emerging drug resistance. Among patients who reported compliance with a recommended regimen, serum drug levels were not available. Therefore, differentiating among inaccurate reporting of compliance, malabsorption of the antimalarial drug, and emerging drug resistance was not possible. No conclusive evidence existed to indicate a single national or regional source of infection among this group of patients or the failure of a particular chemoprophylactic regimen. Healthcare providers are encouraged to contact CDC rapidly whenever they suspect chemoprophylaxis failure to enable CDC to measure serum drug levels of the antimalarial drugs in question.

Of the seven persons with fatal outcomes in the United States in 2005, none had taken prophylaxis, and substantial delays occurred in their seeking care or in diagnosis and treatment, or both. This underscores the importance of taking correct chemoprophylaxis, promptly seeking medical care if symptoms develop, and considering malaria in the differential diagnosis of fever in a returned traveler. An earlier review of deaths attributed to malaria in the United States indicated that failure to take and comply with a recommended antimalarial chemoprophylaxis regimen, promptly seek medical care for post-travel illness, and promptly diagnose and treat suspected malaria all contributed to fatal outcomes (*10*). In addition, in two cases, intravenous quinidine was not available in the hospital, resulting in a lengthy delay until appropriate therapy could be initiated. All hospitals caring for severely ill patients should maintain a supply of quinidine so it is available to rapidly initiate treatment of a patient with a case of severe malaria.

Pediatric malaria was analyzed separately for the first time this year. Children were more likely than adults to have acquired infection with *P. falciparum*. They were similar to adults in terms of region of acquisition, reason for travel, the percentage taking prophylaxis, and the percentage taking it correctly. Pediatricians should be aware of prophylaxis recommendations for children and encourage parents to ensure that their children receive chemoprophylaxis.

As in previous years, persons who traveled to visit friends and relatives made up the majority of persons with malaria cases. Foreign-born U.S. civilians should be aware that acquired immunity wanes quickly when exposure to malaria is interrupted and that they should take prophylaxis when returning to malarious areas.

Malaria during pregnancy among nonimmune women poses a high risk for severe disease and contributes to adverse reproductive outcomes (*11*). Pregnant travelers should be counseled to avoid travel to malarious areas. If deferral of travel is impossible, pregnant women should be informed that the risks for malaria outweigh those associated with prophylaxis and that safe chemoprophylaxis regimens are available. Specific guidance for pregnant travelers is available at http://www.cdc.gov/travel/mal_preg_pub.htm.

The two cases of congenital malaria highlight the importance of obtaining a complete travel and immigration history from pregnant women, including any febrile illnesses or confirmed episodes of malaria. For women with history of travel to or immigration from an area in which malaria is endemic or with a history of malaria before delivery, clinicians should remain alert to the diagnosis of malaria in the neonate or infant. Malaria blood films should be obtained from such neonates and infants should they become ill. For women with a confirmed diagnosis of malaria during the peripartum or postnatal periods, the need for presumptive treatment of the neonate or infant with an antimalarial appropriate for the mother's infecting species and region of acquisition should be considered. In certain cases, educating the mother about the risk for congenital malaria in her infant and instructing her to seek

medical care for her infant if the infant had symptoms of malaria might be sufficient. In other cases, presumptive treatment of the newborn might be warranted.

Signs and symptoms of malaria often are nonspecific, but fever usually is present. Other symptoms include headache, chills, increased sweating, back pain, myalgia, diarrhea, nausea, vomiting, and cough. Prompt diagnosis requires that malaria be included in the differential diagnosis of illness in a febrile person with a history of travel to a malarious area. Clinicians should ask all febrile patients for a travel history, including international visitors, immigrants, refugees, migrant laborers, and international travelers.

Prompt treatment of suspected malaria is essential because persons with *P. falciparum* infection are at risk for experiencing life-threatening complications soon after the onset of illness. Ideally, therapy for malaria should be initiated immediately after the diagnosis has been confirmed by a positive blood film. Treatment should be determined on the basis of the infecting *Plasmodium* species, the probable geographic origin of the parasite, the parasite density, and the patient's clinical status (*12*). If a diagnosis of malaria is suspected and cannot be confirmed, or if a diagnosis of malaria is confirmed but species determination is not possible, antimalarial treatment should be initiated that is effective against *P. falciparum*. Resistance of *P. falciparum* to chloroquine exists worldwide, with the exception of a limited number of geographic regions (e.g., Central America). Therefore, therapy for presumed *P. falciparum* malaria should entail the use of a drug effective against such resistant strains (*13*).

Health-care providers should be familiar with prevention, recognition, and treatment of malaria and are encouraged to consult appropriate sources for malaria prevention and treatment recommendations (Table 7). Physicians seeking assistance with the diagnosis or treatment of patients with suspected or confirmed malaria should call CDC (telephone 770-488-7788) during regular business hours; call CDC's Emergency Operations Center (telephone 770-488-7100) during evenings, weekends, and holidays (ask to page person on call for Malaria Branch); or access CDC's Internet site at http://www.cdc.gov/malaria/iagnosis_treatment/treatment.htm. These resources are intended for use by health-care providers only.

Detailed recommendations for preventing malaria are available to the general public 24 hours a day online at http://www.cdc.gov/travel/diseases.htm/malaria. In addition, CDC biannually publishes recommendations in *Health Information for International Travel* (commonly referred to as *The Yellow Book*) (*9*), which is available for purchase from Elsevier at http://www.elsevierhealth.com or by telephone at 1-800-545-2522. *The Yellow Book* is also available and updated more frequently on CDC's Internet site at http://www.cdc.gov/travel.

CDC provides assistance for diagnostic parasitology through DPDx, a project developed and maintained by CDC's Division of Parasitic Diseases. DPDx (available at http://www.dpd.cdc.gov/dpdx) provides free Internet-based laboratory diagnostic assistance (i.e., telediagnosis) to laboratorians and pathologists in suspected parasitic disease cases, such as malaria. Digital images captured from diagnostic specimens can be submitted for consultation through electronic mail. Telediagnosis assistance by CDC is available during regular business hours. Because laboratories can transmit images to CDC and obtain a rapid response (average time: minutes to several hours) to their inquiries, this system allows efficient diagnosis of challenging cases and rapid dissemination of information. As of January 2007, approximately 54 public health laboratories in 45 states and Puerto Rico either have or are in the process of acquiring the hardware needed to perform telediagnosis. Implementation of telediagnosis at public health laboratories receives full assistance from CDC, including training of personnel in digital imaging techniques. The DPDx Internet site also contains reference material with images, text, and videos on approximately 100 different species of parasites with information (including laboratory diagnosis, geographic distribution, clinical features, treatment, and life cycles) available for each parasite.

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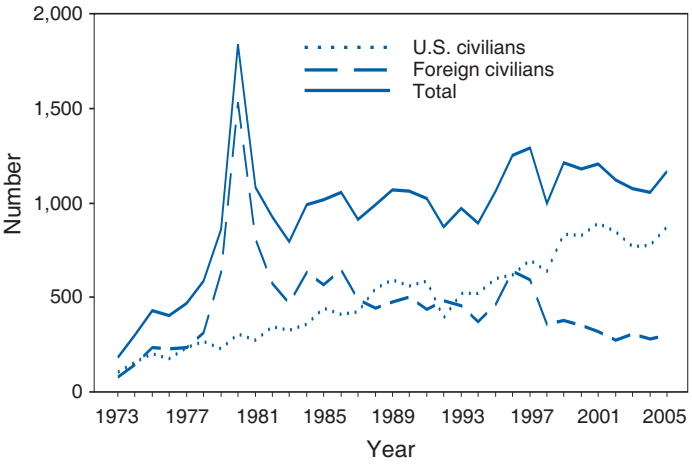
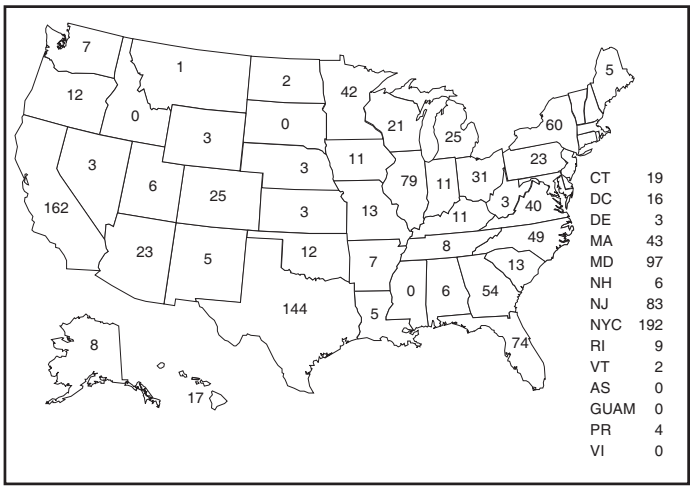
FIGURE 1. Number of malaria cases among U.S. and foreign civilians, by year — United States,* 1973–2005†



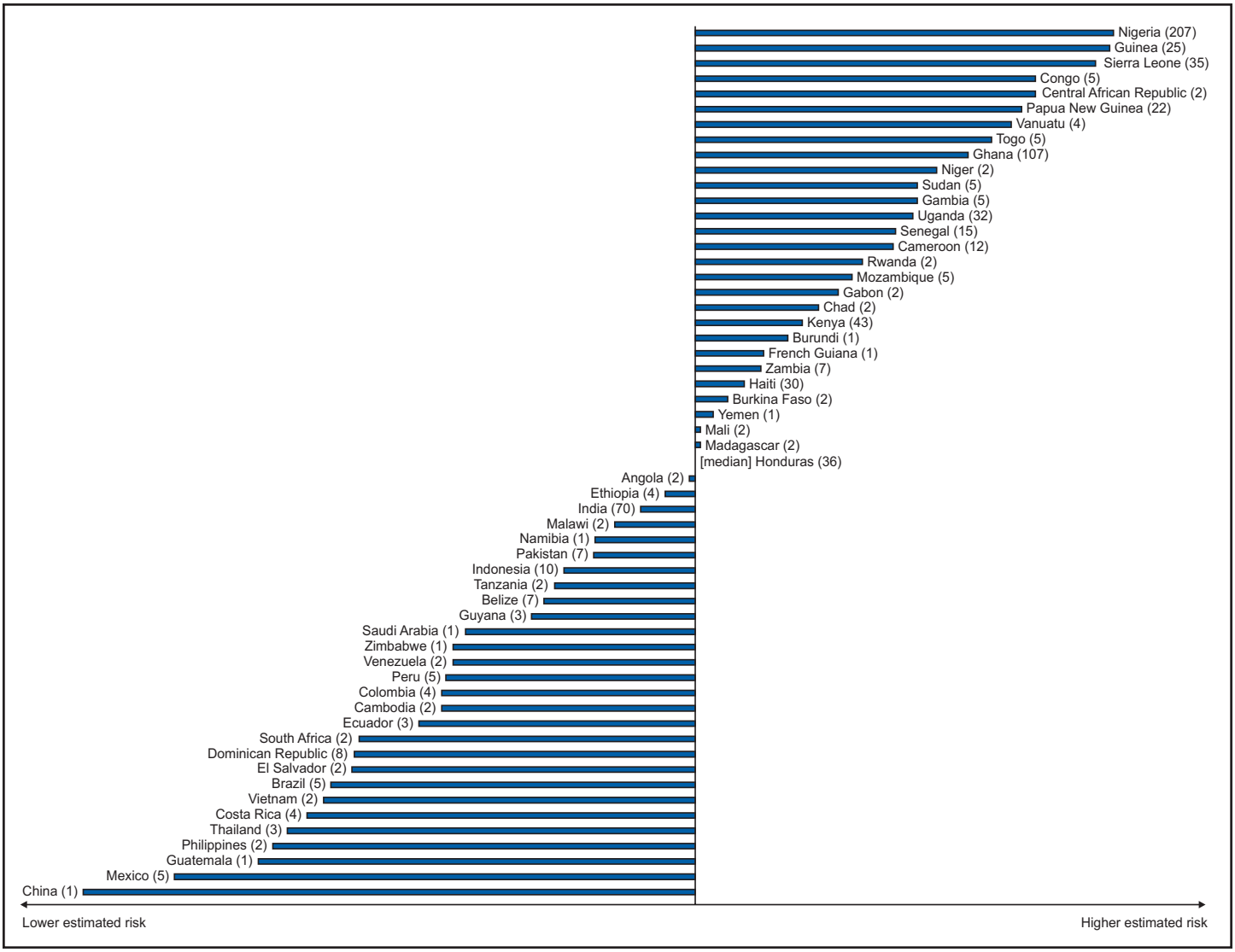
* Includes American Samoa, Guam, Puerto Rico , and the U.S. Virgin Islands.
† The substantial increase in the number of cases reported for 1980 primarily reflects cases diagnosed among immigrants from Southeast Asia.

FIGURE 2. Number of malaria cases, by state in which the disease was diagnosed* — United States, 2005



* For 27 cases, no state was reported.

FIGURE 3. Number of imported malaria cases and estimated relative case rates* among U.S. civilians, by country of acquisition — United States, 2005



* Travel volume for U.S. travelers to each country from which cases of malaria were acquired and the number of cases among U.S. travelers attributable to each country were estimated to derive a case rate for each country. Data used to estimate country-specific relative case rates were extrapolated from World Tourism Organization estimates of annual numbers of American travelers to specified countries (World Tourism Organization. Yearbook of Tourism Statistics. 2006 edition. Madrid, Spain: World Tourism Organization; 2006. Available at http://www.unwto.org/pub/doc/UNWTO_pub_cat_06_en.pdf). Relative case rates were determined by dividing the individual country-specific case rates by the median individual country-specific case rate. The number of cases of malaria among U.S. civilian travelers attributable to each country is displayed in parentheses next to the country name. Estimates of U.S. travelers to the following countries where malaria was acquired by U.S. civilians were not available: Cote d'Ivoire (18 cases), Liberia (10 cases), and Equatorial Guinea and Solomon Islands (one case each).

TABLE 1. Number of malaria cases* among U.S. and foreign civilians and U.S. military personnel — United States, 1973–2005

Year	U.S. military personnel	U.S. civilians	Foreign civilians	Status not recorded†	Total
1973	41	103	78	0	**222**
1974	21	158	144	0	**323**
1975	17	199	232	0	**448**
1976	5	178	227	5	**415**
1977	11	233	237	0	**481**
1978	31	270	315	0	**616**
1979	11	229	634	3	**877**
1980	26	303	1,534	1	**1,864**
1981	21	273	809	0	**1,103**
1982	8	348	574	0	**930**
1983	10	325	468	0	**803**
1984	24	360	632	0	**1,016**
1985	31	446	568	0	**1,045**
1986	35	410	646	0	**1,091**
1987	23	421	488	0	**932**
1988	33	550	440	0	**1,023**
1989	35	591	476	0	**1,102**
1990	36	558	504	0	**1,098**
1991	22	585	439	0	**1,046**
1992	29	394	481	6	**910**
1993	278	519	453	25	**1,275**
1994	38	524	370	82	**1,014**
1995	12	599	461	95	**1,167**
1996	32	618	636	106	**1,392**
1997	28	698	592	226	**1,544**
1998	22	636	361	208	**1,227**
1999	55	833	381	271	**1,540**
2000	46	827	354	175	**1,402**
2001	18	891	316	158	**1,383**
2002	33	849	272	183	**1,337**
2003	36	767	306	169	**1,278**
2004	32	775	282	235	**1,324**
2005	36	870	297	325	**1,528**

* A case was defined as symptomatic or asymptomatic illness that occurred in the United States or one of its territories in a person who had laboratory-confirmed (by microscopy or polymerase chain reaction) malaria parasitemia, regardless of whether the person had previous attacks of malaria while in other countries. A subsequent attack of malaria occurring in a person is counted as an additional case if the demonstrated *Plasmodium* species differs from the initially identified species. A subsequent attack of malaria occurring in a person while in the United States could indicate a relapsing infection or treatment failure resulting from drug resistance if the demonstrated *Plasmodium* species is the same species identified previously.

† The increase in persons with unknown civil status that began in the 1990s might be attributed to a change in the surveillance form.

TABLE 2. Number and percentage of malaria cases, by *Plasmodium* species — United States, 2003–2005

Plasmodium species	2003		2004		2005	
	No.	(%)	No.	(%)	No.	(%)
P. falciparum	682	(53.4)	656	(49.5)	742	(48.6)
P. vivax	293	(22.9)	315	(23.8)	337	(22.1)
P. malariae	46	(3.6)	47	(3.5)	54	(3.5)
P. ovale	33	(2.6)	27	(2.0)	38	(2.5)
Mixed	12	(0.9)	17	(1.3)	12	(0.8)
Undetermined	212	(16.6)	262	(19.8)	345	(22.6)
Total	**1,278**		**1,324**		**1,528**	

TABLE 3. Imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2005

Country of acquisition	*Plasmodium* species						
	P. falciparum	*P. vivax*	*P. malariae*	*P. ovale*	Unknown	Mixed	Total
Africa	**596**	**47**	**35**	**27**	**187**	**10**	**902**
Angola	1	1	0	0	0	0	**2**
Burkina Faso	2	0	0	0	0	0	**2**
Burundi	2	1	0	0	0	0	**3**
Cameroon	20	3	0	0	3	0	**26**
Central African Republic	2	0	0	0	1	0	**3**
Chad	2	0	0	0	1	0	**3**
Congo	5	1	2	1	1	0	**10**
Cote d'Ivoire	13	3	1	2	3	2	**24**
Equatorial Guinea	1	0	0	0	0	0	**1**
Eritrea	0	1	0	0	0	0	**1**
Ethiopia	3	8	0	0	4	0	**15**
Gabon	2	0	0	0	1	0	**3**
Gambia	6	0	0	1	1	0	**8**
Ghana	89	3	4	4	34	2	**136**
Guinea	23	0	0	0	4	1	**28**
Kenya	36	3	1	2	11	0	**53**
Liberia	12	1	1	3	12	2	**31**
Libya	1	0	0	0	0	0	**1**
Madagascar	0	2	2	0	0	0	**4**
Malawi	2	1	0	0	0	0	**3**
Mali	3	0	1	0	0	0	**4**
Mauritania	1	0	0	0	0	0	**1**
Mozambique	5	1	1	1	1	0	**9**
Namibia	1	0	0	0	0	0	**1**
Niger	2	0	0	0	0	0	**2**
Nigeria	213	9	10	3	65	2	**302**
Rwanda	1	0	1	0	0	0	**2**
Senegal	17	1	1	1	4	1	**25**
Sierra Leone	34	2	2	1	7	0	**46**
Somalia	3	0	0	0	0	0	**3**
South Africa	3	0	1	0	3	0	**7**
Sudan	3	2	0	0	1	0	**6**
Tanzania	3	0	1	0	1	0	**5**
Togo	8	0	0	0	1	0	**9**
Uganda	27	2	3	2	12	0	**46**
Zambia	8	0	0	0	1	0	**9**
Zimbabwe	2	0	0	0	0	0	**2**
West Africa, unspecified	15	1	1	1	4	0	**22**
Central Africa, unspecified	0	0	0	0	0	0	**0**
East Africa, unspecified	1	0	0	0	0	0	**1**
Southern Africa, unspecified	0	0	0	0	0	0	**0**
Africa, unspecified	24	1	2	5	11	0	**43**
Asia	**26**	**136**	**6**	**1**	**30**	**0**	**199**
Afghanistan	0	20	0	0	2	0	**22**
Burma (Myanmar)	0	0	0	0	1	0	**1**
Cambodia	0	2	0	0	0	0	**2**
China	0	1	0	0	1	0	**2**
India	21	92	4	1	19	0	**137**
Indonesia	1	7	0	0	3	0	**11**
Korea (South)	0	2	0	0	2	0	**4**
Pakistan	1	8	1	0	0	0	**10**
Philippines	1	0	1	0	0	0	**2**
Thailand	2	3	0	0	0	0	**5**
Vietnam	0	0	0	0	2	0	**2**
Asia, unspecified	0	1	0	0	0	0	**1**

TABLE 3. (*Continued*) Imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2005

Country of acquisition	*Plasmodium* species						
	P. falciparum	*P. vivax*	*P. malariae*	*P. ovale*	Unknown	Mixed	Total
Middle East	**1**	**3**	**0**	**0**	**1**	**0**	**5**
Iraq	0	3	0	0	0	0	**3**
Saudi Arabia	0	0	0	0	1	0	**1**
Yemen	1	0	0	0	0	0	**1**
Central America and the Caribbean	**50**	**65**	**6**	**2**	**37**	**2**	**162**
Belize	0	3	1	0	4	1	**9**
Costa Rica	0	1	0	0	3	0	**4**
Dominican Republic	6	1	0	0	1	0	**8**
El Salvador	0	9	1	0	2	0	**12**
Guatemala	1	7	1	0	3	0	**12**
Haiti	33	0	1	0	3	1	**38**
Honduras	9	42	2	2	18	0	**73**
Nicaragua	1	1	0	0	1	0	**3**
Central America, unspecified	0	1	0	0	2	0	**3**
North America	**1**	**11**	**1**	**0**	**1**	**0**	**14**
Mexico	1	11	1	0	1	0	**14**
South America	**7**	**25**	**1**	**0**	**4**	**0**	**37**
Brazil	1	8	0	0	1	0	**10**
Colombia	1	5	0	0	0	0	**6**
Ecuador	0	2	0	0	1	0	**3**
French Guiana	0	0	0	0	1	0	**1**
Guyana	5	3	0	0	0	0	**8**
Peru	0	4	1	0	1	0	**6**
Venezuela	0	2	0	0	0	0	**2**
South America, unspecified	0	1	0	0	0	0	**1**
Oceania	**3**	**19**	**0**	**0**	**8**	**0**	**30**
Papua New Guinea	3	14	0	0	7	0	**24**
Solomon Islands	0	2	0	0	0	0	**2**
Vanuatu	0	3	0	0	1	0	**4**
Eastern Europe	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Unknown	**58**	**29**	**5**	**8**	**77**	**0**	**177**
Total	**742**	**335**	**54**	**38**	**345**	**12**	**1,526**

TABLE 4. Number and percentage of imported malaria cases, by interval between date of arrival in the country and onset of illness and *Plasmodium* species* — United States, 2005

	P. falciparum		*P. vivax*		*P. malariae*		*P. ovale*		Mixed		Total	
Interval (days)	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**
<0†	62	(13.2)	13	(8.7)	3	(11.5)	0	(0)	3	(33.3)	**81**	**(12.1)**
0–29	380	(81.0)	61	(40.7)	16	(61.5)	6	(42.9)	6	(66.7)	**469**	**(70.2)**
30–89	23	(4.9)	28	(18.7)	6	(23.1)	5	(35.7)	0	(0)	**62**	**(9.3)**
90–179	2	(0.4)	23	(15.3)	1	(3.8)	1	(7.1)	0	(0)	**27**	**(4.0)**
180–364	2	(0.4)	21	(14.0)	0	(0)	1	(7.1)	0	(0)	**24**	**(3.6)**
>365	0	(0)	4	(2.7)	0	(0)	1	(7.1)	0	(0)	**5**	**(0.7)**
Total	**469**		**150**		**26**		**14**		**9**		**668**	

* Persons for whom *Plasmodium* species, date of arrival in the United States, or date of onset of illness is unknown are not included.
† Persons with these cases in this row are those with onset of illness before arriving in the United States.

TABLE 5. Number and percentage of imported malaria cases among U.S. and foreign civilians, by region of acquisition — United States, 2005*

	United States		Foreign		Total	
Area or region	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**
Africa	611	(70.2)	172	(57.9)	**783**	**(67.1)**
Asia and the Middle East	100	(11.5)	54	(18.2)	**154**	**(13.2)**
Central America and the Caribbean	89	(10.2)	53	(17.8)	**142**	**(12.2)**
South America	24	(2.8)	4	(2.7)	**28**	**(2.4)**
North America	5	(0.6)	8	(1.3)	**13**	**(1.1)**
Oceania	27	(3.1)	2	(0.7)	**29**	**(2.5)**
Europe/Newly Independent States	0		0		**0**	
Unknown†	14	(1.6)	4	(1.3)	**18**	**(1.5)**
Total	**870**		**297**		**1,167**	

* Persons for whom U.S. or foreign status is not known are excluded.
† Region of acquisition is unknown.

TABLE 6. Number and percentage of imported malaria cases among U.S. civilians, by purpose of travel at the time of acquisition — United States, 2005

Category	**No.**	**(%)**
Visiting friends/relatives	488	(56.1)
Missionary or dependent	83	(9.5)
Tourism	65	(7.5)
Business representative	55	(6.3)
Student/teacher	30	(3.4)
Peace Corps volunteer	7	(0.8)
Refugee/immigrant	4	0.5)
Air crew/sailor	3	(0.3)
Other/mixed purpose	53	(6.1)
Unknown	82	(9.4)
Total	**870**	

TABLE 7. Sources for malaria prophylaxis, diagnosis, and treatment recommendations

Type of information	Source	Availability	Telephone number, Internet address, or electronic mail address
Prophylaxis	CDC's Traveler's Health internet site (includes online access to *Health Information for International Travel*)	24 hours/day	http://www.cdc.gov/travel
Prophylaxis	*Health Information for International Travel* (*The Yellow Book)*	Order from Elsevier, Health Sciences Division Order Fulfillment 11830 Westline Industrial Drive St. Louis, MO 63146	800-545-2522 or http://www.elsevier.com
Diagnosis	CDC's Division of Parasitic Diseases (DPD) Diagnostic internet site (DPDx)	24 hours/days	http://www.dpd.cdc.gov/dpdx
Diagnosis	CDC's DPD diagnostic CD-ROM (DPDx)	Order by electronic mail from CDC Division of Parasitic Diseases	dpdx@cdc.gov
Treatment*	CDC's Malaria Branch	8:00 am–4:30 pm Eastern Time, Monday–Friday	770-488-7788*
Treatment*	CDC's Malaria Branch	4:30 pm–8:00 am Eastern Time, Monday–Friday, and all day weekends and holidays	770-488-7100* (This is the number for CDC's Emergency Operations Center. Ask staff member to page person on call for Malaria Branch.) http://www.cdc.gov/malaria/diagnosis_treatment/treatment.htm

* These telephone numbers are intended for use by health-care providers only.

Appendix

Microscopic Procedures for Diagnosing Malaria

To establish the diagnosis of malaria, a blood film must be prepared from fresh blood obtained by pricking a patient's finger with a sterile, nonreusable lancet (Figure A-1). Two types of blood films can be used: thin films (as used for hematology) and thick films. Thick and thin films can be made as separate or as combination slides (Figure A-2). Thick blood films are more sensitive in detecting malaria parasites because the blood is concentrated, allowing a greater volume of blood to be examined. However, thick films are more difficult to read.

The thin film should be air-dried, fixed with methanol, and allowed to dry before staining; the thick film also should be thoroughly dried but stained without fixation. For best staining results, blood films should be stained with a 2.5% Giemsa solution (pH of 7.2) for 45 minutes (alternate: 7.5% Giemsa for 15 minutes). A combined Wright-Giemsa stain can also detect malaria parasites but does not demonstrate Schüffner's dots as reliably as Giemsa.

Plasmodium parasites are always intracellular, and they demonstrate, if stained correctly, blue cytoplasm with a red chromatin dot. Common errors in reading malaria films can be caused by platelets overlying a red blood cell, concern regarding missing a positive slide, and misreading of artifacts as parasites. In *P. falciparum* infections, the parasite density should be estimated by counting the percentage of red blood cells infected (not the number of parasites) under an oil immersion lens on a thin film.

Persons suspected of having malaria, but whose blood films do not indicate the presence of parasites, should have blood films repeated approximately every 12–24 hours for 3 consecutive days. If films remain negative, then the diagnosis of malaria is unlikely. A useful complement to microscopy can be found in polymerase chain reaction (e.g., when microscopy fails to determine parasite species or for confirming negative blood smears). Additional information regarding collection and preparation of blood films is available at CDC's Division of Parasitic Diseases Internet site, DPDx — Laboratory Identification of Parasites of Public Health Concern (http://www.dpd.cdc.gov/DPDx).

FIGURE A-1. Blood collection for thin or thick blood films

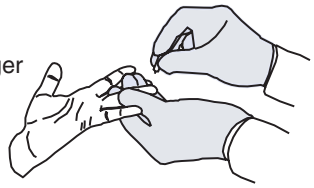
1
Wear gloves.

2
Clean slides with 70%–90% alcohol, dry them, and label them. Do not touch the surface of the slide where the blood film will be made.

3
Select the finger to puncture, usually the middle or ring finger. In infants, use the heel.

4
Clean the area to be punctured with 70% alcohol; let dry.

5
Puncture the ball of the finger or in infants, the heel.



6
Wipe away the first drop of blood with gauze.

7
Touch the next drop of blood with a clean slide. Repeat with multiple slides if multiple films are needed. If blood does not well up, gently squeeze the finger. Be careful not to touch the blood films when handling the slides!

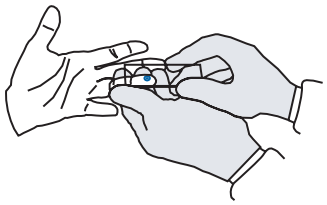
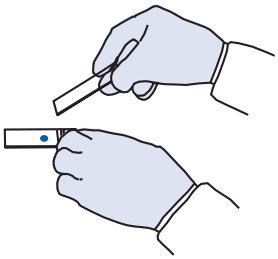


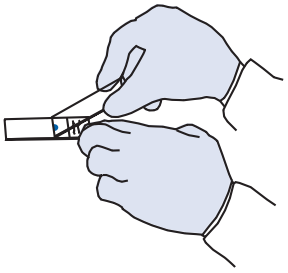
FIGURE A-2. Preparation of thin and thick blood films

1
Whenever possible, use separate slides for thick and thin films.

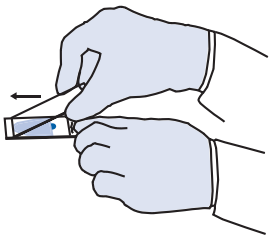
2
Thin film (a): Bring a clean spreader slide, held at a 45-degree angle, toward the drop of blood on the specimen slide.



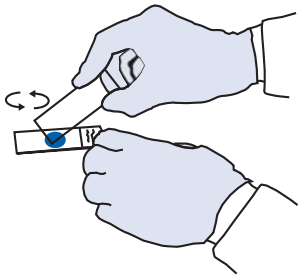
3
Thin film (b): Wait until the blood spreads along the entire width of the spreader slide.



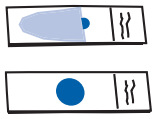
4
Thin film (c): While holding the spreader slide at the same angle, push it forward rapidly and smoothly.



5
Thick film: Using the corner of a clean spreader slide, spread the drop of blood in a circle the size of a dime (diameter 1–2 cm). Do not make the smear too thick or it will fall off the slide (you should be able to read newsprint through it).



6
Wait until the thin and thick films are completely dry. Fix the thin film with 100% (absolute) methanol. Do not fix the thick film.



7
If both the thin and thick films must be made on the same slide, fix only the thin film with 100% (absolute) methanol. Do not fix the thick film.

8
When the thin and thick films are completely dry, stain them. Thick smears might take ≥1–2 hours to dry. Protect unstained blood smears from excessive heat, moisture, and insects by storing in a covered box.

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