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Assisted Reproductive Technology Surveillance — United States, 2003

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Assisted Reproductive Technology Surveillance — United States, 2003

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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 (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 treatments 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: 2003.

Description of System: CDC contracted with the Society for Assisted Reproductive Technology (SART) to obtain data from ART medical centers located in the United States. Since 1997, CDC has compiled data related to ART procedures.

Results: In 2003, a total of 122,872 ART procedures were reported to CDC. These procedures resulted in 35,785 live-birth deliveries and 48,756 infants. Nationwide, 74% of ART procedures used freshly fertilized embryos from the patient's eggs; 14% 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 35% resulted in a live-birth delivery (delivery of one or more live-born infants). The highest live-birth rates were observed among ART procedures using freshly fertilized embryos from donor eggs (51%). The highest numbers of ART procedures were performed among residents of California (15,911), New York (15,534), Massachusetts (8,813), Illinois (8,676), and New Jersey (8,299). These five states also reported the highest number of infants conceived through ART. Of 48,756 infants born through ART, 51% were born in multiple-birth deliveries. The multiple-birth risk was highest for women who underwent ART transfer procedures using freshly fertilized embryos from either donor eggs (40%) or their own eggs (34%). Number of embryos transferred, embryo availability (an indicator of embryo quality), and patient's age were also strong predictors of multiple-birth risk. Approximately 1% of U.S. infants born in 2003 were conceived through ART. Those infants accounted for 18% of multiple births nationwide. The percentage of ART infants who were low birthweight ranged from 9% among singletons to 94% among triplets or higher order multiples. The percentage of ART infants born preterm ranged from 15% among singletons to 97% 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, and embryo availability (an indicator of embryo quality).

Public Health Actions: ART-related multiple births represent a sizable proportion of all multiple births nationwide and in selected states. Efforts should be made to limit the number of embryos transferred for patients undergoing ART. In addition, adverse infant health outcomes (e.g., low birthweight and preterm delivery) should be considered when assessing the efficacy and safety of ART.

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Introduction

For more than 2 decades, assisted reproductive technologies (ARTs) have been used to overcome infertility. ARTs include those infertility treatments in which both eggs and sperm are handled in the laboratory for the purpose of establishing a pregnancy (i.e., in vitro fertilization 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 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 has also used this surveillance data file to perform more in-depth analyses of infant outcomes (e.g., multiple births) (*3–9*). 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. In the United States, ART has been associated with a substantial risk for multiple gestation pregnancy and multiple birth (*3–9*). In addition to the multiple-birth risks, recent studies suggest an increased risk for low birthweight among singleton infants conceived through ART (*10,11*). This report is based on ART surveillance data provided to CDC's National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), Division of Reproductive Health, regarding procedures performed in 2003. 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 presenting more detailed data regarding risks associated with ART (e.g., multiple birth, low birthweight, and preterm delivery).

Methods

The Society for Assisted Reproductive Technology (SART), an organization of ART providers affiliated with the American Society for Reproductive Medicine (ASRM), has collected data regarding ART procedures from medical centers performing ART in the United States and its territories and has provided these data to CDC by contract. A full description of the ART data reporting system has been previously published (*12*). 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, certain centers (<10%/year) have not reported their data; the majority of these centers are believed to be smaller-than-average practices. For this report, data pertaining to ART procedures initiated January 1–December 31, 2003, are presented.

ART data and outcomes from ART procedures are presented by patient's state of residence at time of treatment. In cases of missing residency data (<9%), 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 are also 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 exist. A typical ART procedure begins when a woman starts taking drugs to stimulate egg production or begins having 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 cycle 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. A live-birth delivery 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.

* 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, 2003, estimates from the U.S. Census Bureau (*13*).

Variations in a typical ART procedure are noteworthy. Although a typical ART procedure includes in vitro fertilization (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 a day or two 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 injected directly into the egg. This technique was originally developed for couples with male factor infertility but is now commonly used for an array of diagnostic groups.

Data are presented 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 in this report 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, 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 were grouped into five categories: aged <35 years, 35–37 years, 38–40 years, 41–42 years, and >42 years. Diagnoses ranged from one factor in one partner to multiple factors in one or both partners and were categorized as

- 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 factors included

- 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 woman other than the patient (a surrogate) received the transferred embryos with the expectation of gestating the pregnancy (i.e., a gestational carrier).

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 by 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, 3 and 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 diagnosed with male factor (the original indication for ICSI treatment) or couples not diagnosed with male factor.

Chi-square tests were run separately to evaluate differences in live-birth rates by select patient and treatment factors within each age group. Multivariable logistic regression was also performed to evaluate the independent effects of patient factors — diagnosis, number of previous ART procedures, and number of previous births — on chance to have a live birth as a result of an ART treatment. Because the patient's age is known to be a strong predictor for live birth, separate models were constructed for each of the five age groups such that 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 between different treatment factors and live birth.

In addition to presenting live-birth rates as a measure of success a second measure of success based on singleton live births is also presented according to treatment group and 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 was also assessed. Multiple birth 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 in which at least one was live-born. The multiple-birth risk was thus calculated as the proportion of multiple-birth deliveries among total live-birth deliveries. Multiple birth was also 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) was then calculated.[§] Each of these measures represents a different focus. The multiple-birth risk, based on 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 treatments on children in the population. Both measures are presented by type of ART treatment and by maternal age for births conceived with the patient's eggs. Multiple-birth risk is further presented by 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 have added predictive value independent of the number of embryos transferred (*3,6*). Proportion of infants born in a multiple-birth delivery is presented separately by patient's state of residency at time of ART treatment.

To assess the impact of ART on total births in the United States in 2003, additional analyses including all ART infants born in 2003 are presented. Because the goal of the analysis was to assess the effect of ART on the 2003 U.S. birth cohort and the Assisted Reproductive Technology 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 2002 and born in 2003 (approximately 2/3 of live-birth deliveries reported to the ART Surveillance System for 2002); and 2) infants conceived from ART procedures performed in 2003 and born in 2003 (approximately 1/3 of live-birth deliveries reported to the ART Surveillance System for 2003). Data regarding the total number of live births and multiple births in the United States in 2003 were obtained from birth certificate data (U.S. natality files) from CDC's National Center for Heath Statistics (*14*). These data represent 100% of births registered in the United States in 2003. Data are presented in relation to the total number of infants born in the United States in 2003 by plurality of birth.

Adverse infant health outcomes, including low birthweight, very low birthweight, and preterm delivery were also 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 (83%) or their obstetric providers (17%). 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 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 2003 are presented by plurality of birth. In addition, data for each of the five outcomes are presented for ART singletons born in 2003 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 are also presented according to maternal age, maternal race/ethnicity, 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, maternal race/ethnicity, and number of previous births. All analyses were performed by using the SAS® software system (*15*).

[§] 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 would still be counted as triplets.

Results

Of 437 medical centers in the United States and surrounding territories that performed ART in 2003, a total of 399 (91%) provided data to CDC (Figure 1). The majority of medical centers that provided ART services were located in the eastern United States, in or near major cities. Within states, the number of medical centers performing ART was variable. States with the largest number of ART centers that reported data in 2003 were California (57), New York (32), Florida (29), Texas (29), and Illinois (23). Four states and two U.S. territories had no ART medical centers (Alaska, Guam, Maine, Montana, U.S. Virgin Islands, and Wyoming).

Number and Type of ART Procedures

Overall, 122,872 ART procedures performed in 2003 were reported to CDC (Table 1). This number excludes less than 1% (n = 163) of ART procedures performed in 2003 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 (91,032; [74%]). Of the 122,872 procedures started, 103,017 (84%) progressed to embryo transfer. Overall, 42% of ART procedures that progressed to the transfer stage resulted in a pregnancy; 35% 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 using 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 (34% pregnancy rate, 27% live-birth rate, and 20% singleton live-birth rate).

In all, the 35,785 live-birth deliveries from ART procedures resulted in 48,756 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 23,748 singleton infants were born as a result of ART. The largest proportion of infants born (72%; n = 35,321) were from ART procedures in which patients used freshly fertilized embryos from their own eggs.

The number of ART procedures performed among residents of each state approximately paralleled the data by medical center location (Table 2). The greatest numbers of ART procedures reported in 2003 were performed among residents of California (15,911), New York (15,534), Massachusetts (8,813), Illinois (8,676), and New Jersey (8,299). The five states with the largest number of ART procedures performed also ranked highest in terms of numbers of live-birth deliveries and infants born. ART was used by residents of certain states and territories without an ART medical center (Alaska, Guam, Maine, Montana, U.S. Virgin Islands, and Wyoming); 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 million population ranged from 50 in Arkansas to 1,373 in Massachusetts, with a national average of 412 ART procedures started per 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 using freshly fertilized embryos from the patient's eggs were performed on women aged <35 years; 22% 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). The most common infertility diagnoses reported among couples in which the woman was aged <41 years were male factor and tubal factor; however, diagnoses varied overall. Tubal factor and male factor were more commonly reported among younger women than women in older age categories. In contrast, diminished ovarian reserve was reported for only 2% of women aged <35 years; it was reported for 17% of women aged 41–42 years and 27% of women aged >42 years. Among all women, 10%–13% were reported as having unexplained infertility; 10%–16% were reported as having multiple female factors; and 17%–19% were reported as having 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. Although 21% of women aged <35 years reported at least one previous birth, this increased steadily with age: 36% 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.,

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

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 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.

Although limited variation existed by age, the majority of ART procedures involved transfer of more than one embryo. Among women aged <35 years, 95% of procedures involved transfer of two or more embryos, and 46% involved transfer of three or more embryos. For women aged >42 years, 83% involved transfer of two or more embryos, and 63% 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 approximately 43% of women aged <35 years, whereas only 5% 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 using 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 35%, 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 diagnosis of infertility was classified as ovulatory dysfunction, male factor infertility, or unexplained infertility usually 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. The average live-birth rate for women aged 41–42 years was 15%; however, in this age category, women with an infertility diagnosis of endometriosis or uterine factor experience higher live-birth rates: 19% and 20%, respectively. The variation in success rates across diagnostic categories was not statistically significant for this age group, nor for the oldest age group (women aged >42 years). Other than women aged 41–42 years, women who had undergone a previous ART procedure had lower live-birth rates than women undergoing their first ART procedure. However, the number of previous ART procedures cannot be subdivided by whether they were successful or not because data are not available. Women in all age groups who had had one or more previous births had equal or higher live-birth rates than those with no previous births. However, the difference in live-birth rates for the number of previous births did not reach statistical significance for women aged >42 years. Multivariable adjustment for patient factors within each age strata demonstrated similar patterns to those observed in Table 4 (data not presented).

In all age groups, live-birth rates were higher among ART procedures that used IVF-ET without ICSI, in comparison with procedures that used ICSI, whether or not male factor was reported (Table 4). Among women aged ≤40 years, live-birth rates were particularly low among couples who used ICSI in the absence of male factor infertility. 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. 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 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. These groups included women with previous failed ART cycles, women diagnosed with diminished ovarian reserve, and women with a low number of eggs retrieved (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, women who used IVF with ICSI had lower success rates compared with women who used IVF without ICSI (data not presented). Thus, the pattern of results remained consistent with the findings presented (Table 4). To address concerns that extended (i.e., day 5) embryo culture might be used preferentially for women with a presumed better prognosis, data regarding women deemed to have a higher likelihood of success were evaluated separately; these subgroups included women with >10 eggs retrieved, women with diagnoses other than diminished ovarian reserve, and women with extra embryos cryopreserved for future use. Again, within each of these subgroups, women who used IVF with ICSI had lower success rates compared with women who used IVF without

ICSI (Table 4) (data not presented). Finally, analyses were conducted in which the data were stratified by patient age, number of embryos transferred, 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. Total live-birth rates ranged from 43% among women aged <35 years to 6% among women aged >42 years, and singleton live-birth rates ranged from 27% among women aged <35 years to 5% among women aged>42 years.

Multiple-Birth Risks Associated with ART

Of 12,037 multiple-birth deliveries, 8,812 (73%) were from pregnancies conceived with freshly fertilized embryos from the patient's eggs; 1,075 (9%) were from thawed embryos from the patient's eggs; 1,836 (15%) were from freshly fertilized embryos from a donor's eggs; and 314 (3%) were from thawed embryos from a donor's eggs (Table 5). In comparison with ART procedures using 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 (i.e., multiple-birth delivery rate) for ART procedures in which freshly fertilized embryos from the patient's eggs were used was 34%. This rate varied from 38% among women aged <35 years to 10% among women aged >42 years.

Of 48,756 infants born through ART, 51% (25,008) 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.

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 according to patient age (Table 6). Among all age groups, transfer of two or more embryos resulted in increased live-birth delivery rates. However, the multiple-birth risk was also substantially increased. Among women aged ≤38 years, the percentage of multiple-birth deliveries increased with increasing number of embryos transferred from two to five or more. As a result, if success were evaluated in terms of singleton live-birth deliveries rather than total live-birth deliveries, the two youngest age groups had lower singleton success rates when three or more embryos were transferred than when two embryos were transferred. For women aged 38–40 years, transfer of three or more embryos offered a certain advantage in terms of live-birth delivery rates. However, as among younger age groups, the percentage of twin deliveries and triplets or higher order multiple-birth deliveries were increased with three or more embryos having been transferred compared with two. For women aged 41–42 and >42 years, the multiple-birth deliveries did not demonstrate a trend by number of embryos (two or more) having been transferred.

A further assessment of multiple-birth risk among patients who used freshly fertilized embryos from their own eggs and set aside extra embryos for future use is also presented (Table 6). This group can be thought of as those with elective embryo transfer because they are known to have chosen to transfer fewer embryos than the total number available. For women with elective embryo transfer who were aged <35 years, live-birth rates were >39% when only one embryo was transferred and >53% when two embryos were transferred. Whereas an increase in live-birth rates was noted among patients with single versus double elective embryo transfers, transferring two embryos posed a substantial multiple-birth risk (approximately 40%) for this group. Transferring three or more embryos posed a substantial total multiple-birth risk (46%–57%) and a substantial risk for higher order multiple births (8%–10%). For women with elective embryo transfer who were aged 35–37 years, live-birth rates were high (approximately 55%) with elective embryo transfer of a single embryo. Live-birth rates also were high (45%) among women aged 41–42 years when only two embryos were transferred. The number of cases of elective transfer of one embryo among women aged 38–40 and 41–42 years was too limited to allow adequate evaluation. Live-birth rates with elective transfer of two to five or more embryos demonstrated limited variation for women aged 38–40 years. Data are not provided for women aged >42 years, because in this age group, limited sample size precluded analysis for all number of embryos transferred categories.**

The total number and percentage of infants born in multiple-birth deliveries by maternal state of residence is presented

** 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 (Table 6).

(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. These include California (3,199), New York (2,940), New Jersey (1,716), Texas (1,493), Illinois (1,482), and Massachusetts (1,295). Nationwide, the percentage of infants born in multiple-birth deliveries after ART treatment was 51%; the percentage of twins and triplets or higher order multiples were 45% and 6%, respectively. 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 Puerto Rico (60%), Oregon (59%), Arizona (59%), Tennessee (58%), Louisiana (58%), North Dakota (58%), Alaska (58%), and South Dakota (58%); however, these findings should be interpreted with care because of an overall low number of live births resulting from ART in certain states.

The contribution of ART infants to the total number of U.S. infants born in 2003 is presented (Table 8). Of 4,089,950 total infants born in the United States in 2003, a total of 46,830 (1%) were conceived by ART. Infants conceived with ART accounted for 0.6% of singleton births and 18% of multiple births nationwide. Sixteen percent of all twins and 44% of infants born in triplets or higher order multiples were conceived with ART.

Perinatal Risks Associated with ART

The proportion of ART infants born in 2003 that were low birthweight, very low birthweight, preterm, preterm low birthweight, and term low birthweight are presented by plurality of birth (Table 9). The percentage of infants with low birthweight varied from 9% among singletons to 94% among triplets or higher order multiples. The percentages of very low birthweight, preterm, and preterm low birthweight followed similar patterns.

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 10). In comparison with singletons born after procedures using freshly fertilized embryos derived from the patient's eggs, singletons born after procedures using freshly fertilized embryos derived from donor eggs were at increased risk for four perinatal outcomes — low birthweight, very low birthweight, preterm delivery, and preterm low birthweight. Singletons born after procedures using thawed embryos were at decreased risks for low birthweight, very low birthweight, and term low birthweight; however, they were at increased risk for preterm delivery overall. The variation in risk across procedure types did not reach statistical significance for very low birthweight.

More detailed analysis of maternal factors among singletons born after procedures using freshly fertilized embryos derived from the patient's eggs indicated limited variation in risk for any outcome according to maternal age. Lower risks were observed with a maternal race/ethnicity of non-Hispanic white. Lower risks were also observed among mother-infant pairs with one previous birth, although the difference did not reach statistical significance for very low birthweight and term low birthweight.

Discussion

According to the latest estimates of infertility in the United States from the 2002 National Survey of Family Growth, 10% of women of reproductive age (18–44 years) reported a previous infertility-associated health-care visit, and 2% reported a visit in the previous year (*16*). 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 ART, 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 1997, CDC has been monitoring ART procedures performed in the United States. During that time, a notable and consistent increase in the use of ART has occurred. The increased use of ART coupled with higher ART success rates have 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 2003, the number of ART procedures performed increased 90%, from 64,681 to 122,872 (*1*). In addition, during 1996–2003, live-birth rates for all types of ART procedures increased substantially. For the most common type of ART procedure, using freshly fertilized embryos from the patient's eggs, live-birth rates increased from 28% in 1996 to 35% in 2003. The number of infants conceived through ART procedures performed in 2003 (48,756) was more than two times higher than in 1996 (20,840).

This report documents that in 2003, ART use varied according to 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 2003, ART use by state of residency was not completely in line with expectations based on the total population within states (*13*). Whereas Massachusetts had the third highest number of ART procedures performed, it ranked thirteenth

in terms of total population size.[††] Likewise, residents of District of Columbia, New Jersey, and Connecticut 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. States with the highest ratio of number of ART procedures among state residents per million population were Massachusetts (1,373), District of Columbia (990), New Jersey (961), New York (808), and Connecticut (771). This divergence is not unexpected because, in 2003, Massachusetts and New Jersey had statewide mandates for insurance coverage for ART procedures. The state variation might also be related to availability of ART services within each state. However, the relation between demand for services and availability cannot be disentangled (i.e., 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 was diagnosed with male factor infertility declined with the age of the woman, while the proportion of procedures in which the couple was diagnosed with 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, while the proportion of procedures in which three or more embryos were transferred increased steadily with age.

Success rates from ART use are affected by numerous patient and treatment factors; hence, considering one single measure of success in evaluating ART efficacy is not informative. At a minimum, ART treatments need to be subdivided into categories 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 treatment, 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 (surrogate). Variation exists in success rates according to each of these factors.

CDC's primary focus in collecting ART data has been 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 clinic. 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 (*17,18*).[§§] However, success-rate data should also be balanced with consideration of effects on maternal and infant health. The data reported to CDC include information on pregnancy outcomes of public health significance and allow for monitoring of multiple-birth rates, preterm delivery, and low birthweight associated with ART.

Multiple births are associated with an increased health risk for both mothers and infants (*19–21*). 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 health risks associated with multiple births have also contributed to rising health-care costs. The estimated costs per live birth in 2003 ranged from $39,688–$87,788 (*18*).

In the United States, multiple births have increased substantially during the previous 2 decades (*14,22*). The rise in multiple births has been attributed to an increased use of ART and delayed childbearing (*5,23,24*). Although infants conceived with ART accounted for 1% of the total births in the United States in 2003, the proportion of twins and triplets or higher order multiples attributed to ART were 16% and 44%, respectively. To respond to these concerns, SART and ASRM issued voluntary guidelines on the number of embryos transferred in 1999 and recently revised them in 2004 (*25*).

In certain states infertility treatments (e.g., ART) might not be covered by insurance carriers, and patients might feel pressure to maximize the opportunity for live-birth delivery. In addition, anecdotal evidence suggests that certain ART providers might feel pressure to maximize their publicly reported success rates, if defined solely as total live-birth delivery, by transferring multiple embryos (*26*). Indeed, in the United States, high-order embryo transfer was still common practice in 2003; approximately 56% of ART cycles that used fresh,

[††] Data regarding population size are based on July 1, 2003, estimates from the U.S. Census Bureau (*13*).

[§§] Estimated cost for one cycle of IVF averages $12,400 (*17*).

nondonor eggs or embryos and progressed to the embryo-transfer stage involved the transfer of three or more embryos; approximately 23% of cycles involved the transfer of four or more; and 18% of cycles involved the transfer of five or more embryos (*1*). Among women aged <35 years, the proportions of ART cycles involving four or more embryos or five or more embryos were 12% and 3 %, respectively, as women in this age category generally experience higher success rates with fewer embryos transferred. Various reports published in the scientific literature have advocated for the presentation of singleton live-birth rates as a distinct indicator of ART success (*27–32*). This report includes this measure 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 50% for twins, and the risk for very low birthweight is 10% (*14*). In addition, twins are at substantially increased risk for perinatal and infant mortality (*14,20,24*). Thus, presentation of singleton live-birth rates is warranted.

Data regarding multiple-birth deliveries and proportion of multiple-birth infants as distinct outcomes are also provided. Data in this report indicate that 53% of infants born through ART in 2003 were multiple births; this compares with 3% in the general U.S. population during the same period (*14*). The twin rate was 45%, approximately 15 times higher than in the general U.S. population (3%); the triplet and higher order multiples rate was 8%, approximately 42 times higher than the general U.S. population (0.2%). Regarding the specific type of ART treatment, multiple-birth rates were among the highest for women who underwent ART procedures using freshly fertilized embryos from their own eggs (53%) or from donor eggs (60%).

In the majority of states, >50% of infants conceived through ART were born in multiple-birth deliveries. Idaho, Kentucky, Maine, New Mexico, North Carolina, Vermont, and Wyoming reported ART-associated multiple-birth rates ≥60%. 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 (two or more). However, embryo availability (an indicator of embryo quality) was also a strong predictor of multiple-birth risk and had added predictive value beyond the number of embryos transferred. When patient age, number of embryos transferred, and embryo availability were jointly considered, high live-birth rates and singleton live-birth rates were achieved, which was particularly evident among younger women as transfer of a single embryo was efficacious. Among the majority of groups, multiple-birth risk can be minimized by limiting the number of embryos transferred without compromising success rates.

In addition to the known multiple-birth risks associated with ART, singleton infants conceived from ART are at increased risk for low birthweight and preterm delivery. In this report, 9% of singleton infants conceived with ART were low birthweight, compared with 6% in the general U.S. population during the same period (*14*). The percentage of singleton infants conceived from ART that were very low birthweight (2%) was twice that of singletons conceived in the general U.S. population (1%), and the percentage of ART singletons born preterm (15%) was also higher than the general U.S. population (10%). Thus, adverse infant health outcomes among singletons (e.g., low birthweight and preterm delivery) should also be considered when assessing the efficacy and safety of ART. Although separating the effect of ART from the possible influence of the underlying infertility is difficult, increased ART-related risk for low birthweight among singletons has been reported in multiple subgroups of patients with different infertility patterns (*10*).

A comparison of perinatal outcomes among ART twins and triplets or higher order multiples with their counterparts in the general population is inadvisable. 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 16% of twins and 44% of triplets or higher order multiples in the United States. 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 (*33*). Monozygotic twins are at increased risk for adverse outcomes in comparison with dizygotic twins (*34*).

This analysis was subject to certain 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 undergoing more than one procedure in a given year are most likely to be those who failed one or more treatments, 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

number of persons undergoing ART per population. Second, these data represent couples who sought ART services in 2003; therefore, success rates do not represent all couples with infertility who were potential ART users in 2003. Third, approximately 9% of medical centers that performed ART in 2003 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 where the patient resided. In this report, ART data are presented by the female patient's state of residence. In previous reports (*23*), ART data were not presented by state of residence because of incomplete residency data. In 2003, residency data were missing for <9% of all live-birth deliveries reported to CDC. The range of missing residency data varied by medical center. Medical centers located in 41 states had <5% missing residency data; medical centers located in three states had 5%–10% missing residency data; and medical centers located in four states (i.e., Georgia, Massachusetts, Minnesota, and New York) had >10% missing residency data. 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 these states. Concurrently, the numbers might be underestimated in states bordering 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 state in which the ART medical center was located rather than the patient's state of residence. The rankings of the states in terms of total number of infants and multiple-birth infants were similar to the rankings based on patient's state of residence (data not presented).

A further consideration in reviewing the state-based statistics in this report is that 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. Data from the U.S. Census Bureau demonstrate that annually, approximately 3% of the U.S. population move between states (*35*). This rate is even higher for persons aged 20–34 years.

One group with a recognized high potential for migration is members of the U.S. armed forces. Therefore, ART procedures performed among patients who attended military medical centers were evaluated separately. In 2003, a total of 739 (0.6%) ART procedures were performed in four military medical centers. These medical centers were located in California, District of Columbia, Hawaii, and Texas. In certain of these 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 state residents were performed in a military medical center were Alaska, District of Columbia, Georgia, Guam, Hawaii, Maryland, Maine, North Carolina, North Dakota, New Mexico, South Carolina, South Dakota, Texas, Virginia, U.S. Virgin Islands, and Wyoming. States for which >5% of ART procedures among state residents were performed in a military medical center were District of Columbia, Guam, Virginia, and U.S. Virgin Islands. Finally, data on race/ethnicity were missing in a large proportion of procedures. Therefore, no firm conclusions can be drawn on differences between such groups.

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. First, ART surveillance data can be used to monitor trends in ART use and outcomes from ART procedures. Second, data from ART surveillance can be used to assess patient and treatment factors that contribute to higher success rates. Third, ongoing surveillance data can be used to assess the risk for multiple births and adverse perinatal outcomes among singleton births. Fourth, surveillance data provide information to assess changes in clinical practice related to ART treatment.

Multiple births are one of the most important public health concerns associated with using ART. Increased use of ART treatments and the widespread practice of transferring multiple embryos during ART treatments have led to a substantial increase in multiple-birth rates in the United States (*5,14,22*). Balancing the chance of success with ART against the risk for multiple births is difficult in certain cases. 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 will ultimately require ART patients and providers to view treatment success in terms of singleton pregnancies and births. In addition, continued research is critical to understanding the effect 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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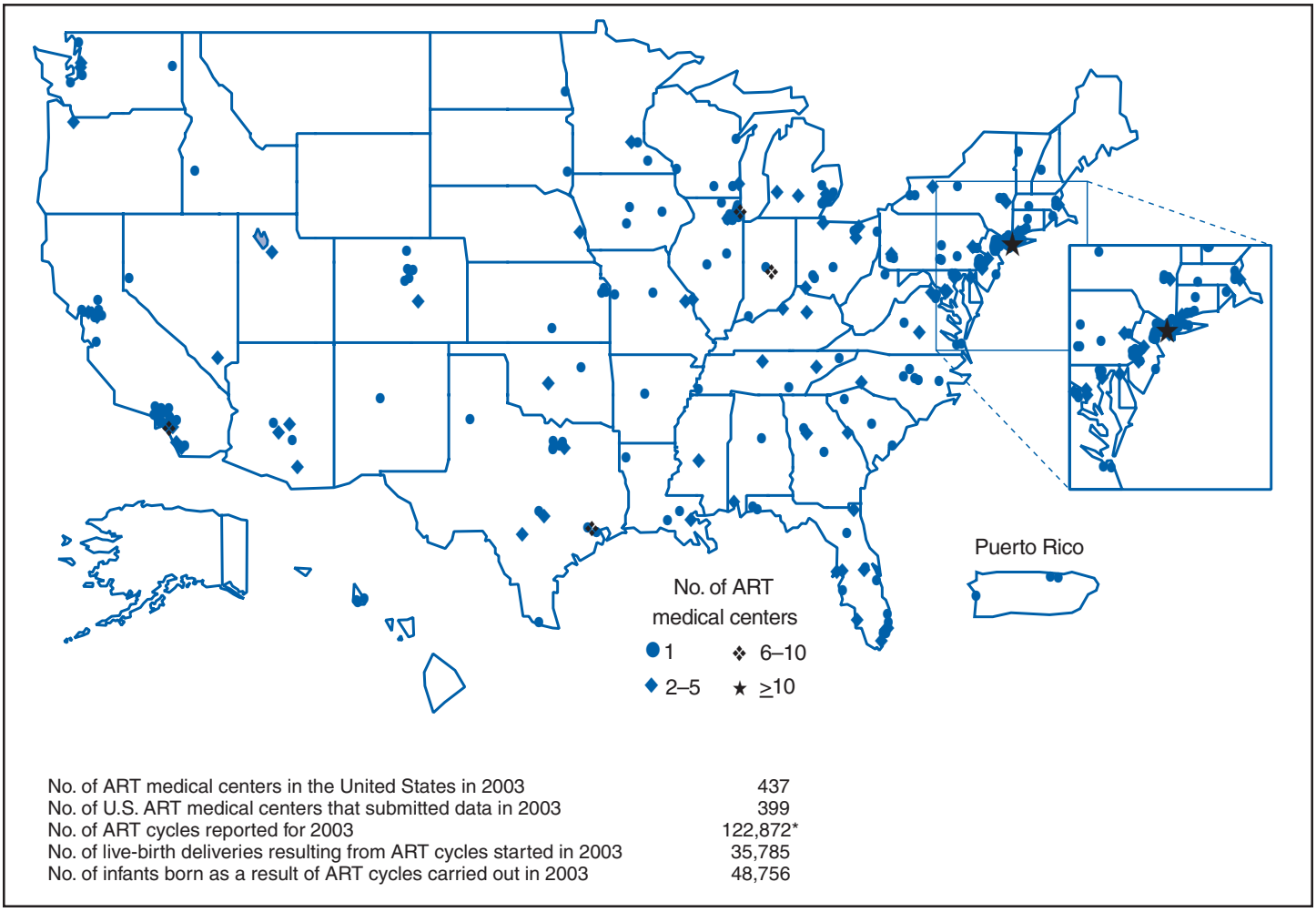
FIGURE 1. Location of assisted reproductive technology (ART) medical centers — United States and Puerto Rico, 2003



No. of ART medical centers in the United States in 2003	437
No. of U.S. ART medical centers that submitted data in 2003	399
No. of ART cycles reported for 2003	122,872*
No. of live-birth deliveries resulting from ART cycles started in 2003	35,785
No. of infants born as a result of ART cycles carried out in 2003	48,756

*This number does not include 163 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 — United States, 2003

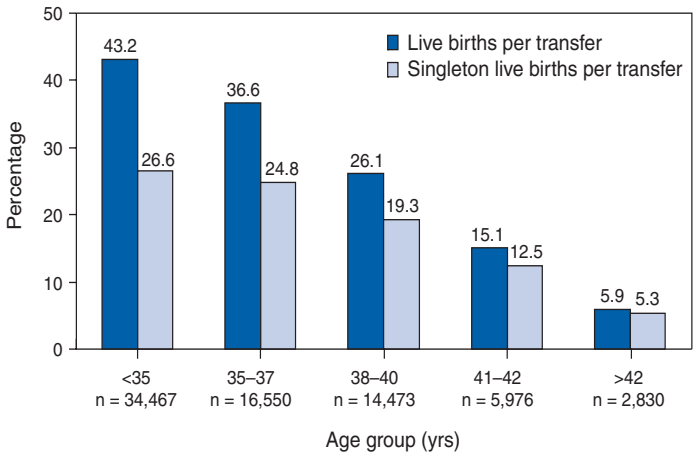


TABLE 1. Number and outcomes of assisted reproductive technology (ART), by procedure type — United States, 2003

ART procedure type	No. of ART procedures started	No. of procedures progressing to retrievals	No. of procedures progressing to transfers	No. of pregnancies	Pregnancies per transfer procedure (%)	No. of live-birth deliveries	Live-birth deliveries per transfer procedure (%)	No. of singleton live births	Singleton live births per transfer (%)	No. of infants born
Patient's eggs used										
Freshly fertilized embryos	91,032	79,602	74,296	31,348	42.2	25,775	34.7	16,963	22.8	**35,321**
Thawed embryos	17,517	N/A*	15,725	5,381	34.2	4,246	27.0	3,171	20.2	**5,393**
Donor eggs used										
Freshly fertilized embryos	9,859	9,272	8,970	5,271	58.8	4,554	50.8	2,718	30.3	**6,506**
Thawed embryos	4,464	N/A	4,026	1,503	37.3	1,210	30.1	896	22.3	**1,536**
Total	**122,872†**	**N/A**	**103,017**	**43,503**	**42.2**	**35,785**	**34.7**	**23,748**	**23.1**	**48,756**

* Not applicable.
† This number does not include 163 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, and number of live-birth deliveries, by patient's state/territory of residence* at time of treatment — United States, 2003

Patient's state/ territory of residence	No. of ART procedures started	No. of transfer procedures	No. of pregnancies	No. of live-birth deliveries	No. of infants born	Ratio of no. of ART procedures started/population (million)†
Alabama	461	379	154	113	157	102.4
Alaska§	110	97	45	36	52	169.6
Arizona	1,754	1,473	714	589	862	314.5
Arkansas	135	115	53	47	63	49.5
California	15,911	13,668	5,481	4,552	6,199	448.7
Colorado	1,580	1,393	758	634	883	347.4
Connecticut	2,689	2,218	919	754	1,003	771.4
Delaware§	460	369	157	130	181	562.5
District of Columbia	552	443	166	129	171	989.5
Florida	5,101	4,228	1,815	1,512	2,054	300.2
Georgia	2,767	2,223	1,030	861	1,183	316.3
Guam	¶	¶	¶	¶	¶	¶
Hawaii§	645	548	156	140	191	516.7
Idaho	352	319	162	146	207	257.3
Illinois	8,676	7,001	2,710	2,194	2,957	685.9
Indiana	1,935	1,607	623	523	737	312.3
Iowa	1,026	827	408	360	492	348.8
Kansas	746	608	284	247	335	273.8
Kentucky	924	815	378	329	466	224.4
Louisiana	656	529	214	166	238	146.1
Maine	175	131	57	45	61	133.8
Maryland§	3,963	3,275	1,298	1,041	1,380	718.9
Massachusetts	8,813	7,526	2,786	2,248	2,912	1373.3
Michigan	3,232	2,654	1,120	961	1,356	320.7
Minnesota	2,138	1,886	884	740	971	422.4
Mississippi	452	384	168	145	206	156.9
Missouri	1,304	1,081	493	411	555	228.0
Montana	118	104	61	52	72	128.6
Nebraska	783	621	241	209	294	450.5
Nevada	623	514	232	191	265	277.9
New Hampshire	637	554	217	174	226	494.7
New Jersey	8,299	6,686	3,114	2,498	3,379	960.5
New Mexico	203	186	113	90	120	108.0
New York	15,534	13,020	5,437	4,294	5,823	807.9
North Carolina§	2,161	1,815	774	668	930	256.6
North Dakota	191	162	72	66	95	301.7
Ohio	3,394	2,832	1,158	1,016	1,398	296.9
Oklahoma§	570	495	425	195	269	162.6
Oregon	781	684	337	288	413	219.2
Pennsylvania	4,653	3,770	1,413	1,167	1,575	376.3
Puerto Rico	345	294	95	78	116	89.0
Rhode Island	771	684	257	213	285	716.7
South Carolina§	899	766	382	321	435	216.8
South Dakota	166	151	57	52	73	217.1
Tennessee	959	808	375	325	466	164.2
Texas§	5,843	5,033	2,345	1,954	2,731	264.4
Utah	555	479	242	221	305	233.3
Vermont	160	134	59	43	57	258.4
U.S. Virgin Islands	¶	¶	¶	¶	¶	¶
Virginia§	3,631	3,060	1,282	1,012	1,359	491.8
Washington	2,057	1,765	829	683	914	335.5
West Virginia	284	245	125	94	126	156.9
Wisconsin	1,323	1,163	454	379	531	241.8
Wyoming	40	36	25	21	29	79.7
Non-U.S. resident	1,317	1,143	522	421	590	N/A
Total	**122,872**	**103,017**	**43,503**	**35,785**	**48,756**	**412.1****

* In cases of missing residency data, the patient's state of residency was assigned as the state in which the ART procedure was performed. Medical centers in all but five states had missing residency for <10% of ART infants. Medical centers located in Georgia, Massachusetts, Minnesota, New York, and Pennsylvania had >10% missing residency data.

† **Source of population size:** July 1, 2003, state population estimates. Population Division, U.S. Census Bureau.

§ A total of 0.6% of ART procedures were reported from military medical centers located 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 were Alaska, Delaware, District of Columbia, Hawaii, Maryland, North Carolina, Oklahoma, South Carolina, Texas, and Virginia. States and territories for which >5% of ART procedures among state residents were performed in a military medical center were Alaska and the District of Columbia.

¶ Data not indicated to preserve confidentiality but included in totals.

** Non-U.S. residents excluded.

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 age — United States, 2003

Patient/Treatment factors	Patient age (yrs) <35 (n = 34,467) (%)	35–37 (n = 16,550) (%)	38–40 (n = 14,473) (%)	41–42 (n = 5,976) (%)	>42 (n = 2,830) (%)
Patient factors					
Diagnosis					
Tubal factor	12.8	14.5	12.9	9.1	7.0
Ovulatory dysfunction	8.7	5.0	3.5	2.6	2.5
Diminished ovarian reserve	1.6	3.8	8.2	17.3	27.0
Endometriosis	8.3	7.2	5.2	2.8	1.9
Uterine factor	0.9	1.6	1.9	2.0	1.3
Male factor	24.5	20.6	15.1	9.9	7.5
Other causes	5.2	5.8	7.3	9.4	10.2
Unexplained cause	11.2	13.4	13.1	12.2	9.6
Multiple factors, female only	9.8	10.9	13.8	15.5	16.2
Multiple factors, female and male	17.2	17.3	19.1	19.2	16.9
No. of previous ART procedures					
0	63.5	53.5	49.4	45.4	41.5
≥1	36.5	46.5	50.6	54.6	58.5
No. of previous births					
0	79.5	68.7	66.3	65.5	64.2
≥1	20.6	31.3	33.7	34.5	35.8
Treatment factors					
Method of embryo fertilization and transfer*					
IVF-ET without ICSI	33.9	35.2	36.5	39.0	39.1
IVF-ET with ICSI	65.6	64.2	62.8	60.1	60.0
IVF-ET with ICSI among couples diagnosed with male factor infertility	38.1	34.2	30.4	25.4	21.8
IVF-ET with ICSI among couples not diagnosed with male factor infertility	27.5	30.0	32.4	34.7	38.2
GIFT	0.1	0.1	0.1	0.2	0.3
ZIFT	0.4	0.5	0.5	0.5	0.4
Combination	0.1	0.1	0.1	0.1	0.2
No. of days of embryo culture†					
1	0.3	0.3	0.5	0.5	0.5
2	4.1	4.1	4.3	4.9	4.5
3	67.6	72.7	76.1	78.6	80.0
4	3.2	3.7	4.0	4.7	6.0
5	21.9	16.7	12.8	9.4	6.9
6	2.0	1.6	1.2	1.0	0.7
No. of embryos transferred					
1	5.2	7.1	9.6	12.1	16.9
2	48.8	32.0	21.6	18.2	20.3
3	34.1	36.9	31.5	22.7	19.8
4	9.0	18.4	24.5	22.9	18.1
≥5	2.9	5.6	12.7	24.1	24.8
Extra embryo(s) available and cryopreserved					
Yes	43.0	30.1	18.5	8.7	4.8
No	57.0	69.9	81.6	91.3	95.2
Use of gestational carrier					
Yes	0.7	0.8	1.0	0.7	0.7
No	99.3	99.2	99.0	99.3	99.3

* 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 age and selected patient and treatment factors — United States, 2003

	Patient age (yrs)				
Patient/Treatment factors	**<35 Live births per transfer procedure (%)**	**35–37 Live births per transfer procedure (%)**	**38–40 Live births per transfer procedure (%)**	**41–42 Live births per transfer procedure (%)**	**>42 Live births per transfer procedure (%)**
Total	**43.2**	**36.6**	**26.1**	**15.1**	**5.9**
Patient factors					
Diagnosis					
Tubal factor	42.7*	37.0*	26.8*	16.0	3.5
Ovulatory dysfunction	45.5	38.9	29.6	10.4	7.1
Diminished ovarian reserve	38.2	30.9	24.7	13.5	5.1
Endometriosis	43.4	37.0	27.8	19.3	11.3
Uterine factor	43.5	39.8	24.9	20.2	8.3
Male factor	45.0	37.7	28.2	15.7	4.7
Other causes	40.9	36.9	28.7	16.8	8.3
Unexplained cause	43.9	38.5	27.2	17.4	8.1
Multiple factors, female only	39.8	32.9	22.8	13.5	6.1
Multiple factors, female and male	42.2	35.8	24.1	14.3	4.8
No. of previous ART procedures					
0	45.2*	38.8*	27.1*	14.5	6.1
≥1	39.6	34.0	25.0	15.6	5.7
No. of previous births					
0	42.1*	35.0*	24.8*	14.1*	5.9
≥1	47.4	40.0	28.6	16.9	5.9
Treatment factors					
Method of embryo fertilization and transfer†					
IVF-ET without ICSI	45.3*	38.7*	28.5*	17.3*	7.1
IVF-ET with ICSI among couples diagnosed with male factor infertility	43.7	36.7	25.7	14.7	4.7
IVF-ET with ICSI among couples NOT diagnosed with male factor infertility	40.0	34.2	23.8	12.7	5.4
No. of days of embryo culture§					
3	42.1*	35.3*	25.5*	14.8*	6.1
5	49.6	45.0	32.2	20.5	6.7
No. of embryos transferred					
1	20.7*	16.9*	9.0*	5.4*	0.8*
2	46.8	39.1	23.1	10.5	5.1
3	43.1	38.3	28.7	16.1	6.6
4	39.2	37.6	30.0	17.8	6.2
≥5	36.5	32.3	30.1	19.9	9.3
Extra embryos available and cryopreserved					
Yes	51.4*	46.3*	37.2*	29.0*	14.0*
No	37.0	32.4	23.5	13.8	5.5
Use of gestational carrier					
Yes	50.6*	44.5	21.9	20.5	14.3
No	43.1	36.5	26.1	15.0	5.8

* $p<0.05$; 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 small proportion of procedures.

TABLE 5. Multiple-birth risk, by type of assisted reproductive technology transfer procedure performed — United States, 2003

Procedure type	Patient age (yrs)	No. of live-birth deliveries	No. of multiple-birth deliveries	Multiple-birth deliveries (%)*	No. of infants born	No. of infants born in multiple-birth deliveries	Infants born in multiple-birth deliveries (%)
Patient's eggs used							
Freshly fertilized embryos	All ages	25,775	8,812	34.2	35,321	18,358	52.0
	<35	14,881	5,709	38.4	21,070	11,898	56.5
	35–37	6,053	1,943	32.1	8,163	4,053	49.7
	38–40	3,773	986	26.1	4,838	2,051	42.4
	41–42	901	157	17.4	1,067	323	30.3
	>42	167	17	10.2	183	33	18.0
Thawed embryos	All ages	4,246	1,075	25.3	5,393	2,222	41.2
	<35	2,457	635	25.8	3,140	1,317	42.0
	35–37	1,039	273	26.3	1,329	563	42.4
	38–40	555	123	22.2	684	252	36.8
	41–42	120	22	18.3	142	44	31.0
	>42	75	22	29.3	98	45	45.9
Donor's eggs used†							
Freshly fertilized embryos	All ages	4,554	1,836	40.3	6,506	3,788	58.2
Thawed embryos	All ages	1,210	314	26.0	1,536	640	41.7
Total	All ages	35,785	12,037	33.6	48,756	25,008	51.3

* 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 multiple-birth risk for assisted reproductive technology (ART) transfer procedures, by patient age and number of embryos transferred — United States, 2003*

	ART transfer procedures using freshly fertilized embryo from the patient's eggs (n = 74,242)				ART transfer procedures using freshly fertilized embryos from the patient's eggs (limited to women known to have more embryos available than transferred) (n = 23,135)			
Patient age (yrs)	**Live births per transfer (%)**	**Singletons† (%)**	**Twins† (%)**	**Triplets or higher order deliveries† (%)**	**Live births per transfer (%)**	**Singletons† (%)**	**Twins† (%)**	**Triplets or higher order deliveries† (%)**
<35								
No. of embryos transferred								
1	**20.7**	99.2	0.8	0.0	**39.5**	99.0	1.0	0.0
2	**46.8**	63.9	35.2	0.9	**53.3**	60.4	38.6	0.9
3	**43.2**	57.7	35.6	6.7	**49.2**	53.9	37.8	8.3
4	**39.2**	53.3	39.2	7.5	**45.9**	43.5	46.7	9.9
≥5	**36.5**	56.5	34.6	8.9	**48.2**	48.2	41.7	10.2
35–37								
No. of embryos transferred								
1	**16.9**	98.0	2.0	0.0	**54.6**	100.0	0.0	0.0
2	**39.1**	72.5	26.6	0.9	**47.9**	66.3	32.9	0.9
3	**38.3**	64.8	31.3	3.9	**45.2**	61.5	34.3	4.2
4	**37.6**	63.4	31.7	4.9	**44.8**	57.2	36.8	5.9
≥5	**32.3**	58.0	37.0	5.0	**42.8**	52.5	40.7	6.8
38–40								
No. of embryos transferred								
1	**9.0**	94.4	5.6	0.0	§	§	§	§
2	**23.1**	82.4	16.3	1.3	**37.9**	73.5	24.9	1.6
3	**28.7**	74.2	23.2	2.6	**36.6**	68.6	26.2	5.2
4	**30.0**	67.9	29.2	2.9	**37.6**	66.0	32.1	1.9
≥5	**30.1**	68.6	28.5	2.9	**38.5**	58.7	38.0	3.3
41–42								
No. of embryos transferred								
1	**5.4**	92.4	7.6	0.0	§	§	§	§
2	**10.5**	85.1	14.9	0.0	**45.0**	77.8	22.2	0.0
3	**16.1**	88.1	11.9	0.0	**27.9**	86.8	13.2	0.0
4	**17.8**	82.4	16.0	1.6	**28.7**	80.9	17.0	2.1
≥5	**19.9**	76.2	21.3	2.5	**25.2**	68.4	29.0	2.6
>42								
No. of embryos transferred								
1	§	§	§	§	§	§	§	§
2	**5.1**	93.1	6.9	0.4	§	§	§	§
3	**6.6**	86.4	13.5	0.9	§	§	§	§
4	**6.2**	90.5	9.3	0.6	§	§	§	§
≥5	**9.3**	89.2	10.8	1.0	§	§	§	§

* Analysis did not include 54 (0.07%) ART transfer procedures in which data on number of embryos transferred were missing.
† Percentages of live births that were singletons, twins, and triplets or higher order multiples.
§ Statistics are not provided in cases where the denominator is <10.

TABLE 7. Number and percentage of infants born in multiple-birth deliveries, by patient's state/territory of residence* at time of assisted reproductive technology (ART) treatment — United States, 2003

Patient's state of residency	No. of infants born	No. of infants born in multiple-birth deliveries	Infants born in multiple-birth deliveries† (%)	Infants born in twin deliveries (%)	Infants born in triplet or more deliveries (%)
Alabama	157	83	52.9	43.3	9.6
Alaska§	52	30	57.7	46.2	11.5
Arizona	862	507	58.8	44.2	14.6
Arkansas	63	32	50.8	50.8	0.0
California	6,199	3,199	51.6	46.3	5.3
Colorado	883	486	55.0	51.2	3.9
Connecticut	1,003	484	48.3	44.1	4.2
Delaware§	181	97	53.6	46.4	7.2
District of Columbia§	171	80	46.8	38.6	8.2
Florida	2,054	1,047	51.0	45.0	6.0
Georgia	1,183	624	52.7	47.2	5.6
Guam	¶	¶	¶	¶	¶
Hawaii§	191	101	52.9	49.7	3.1
Idaho	207	114	55.1	43.0	12.1
Illinois	2,957	1,482	50.1	45.0	5.1
Indiana	737	404	54.8	43.8	11.0
Iowa	492	259	52.6	49.6	3.0
Kansas	335	169	50.4	44.2	6.3
Kentucky	466	262	56.2	46.8	9.4
Louisiana	238	138	58.0	47.9	10.1
Maine	61	32	52.5	52.5	0.0
Maryland§	1,380	657	47.6	42.5	5.1
Massachusetts	2,912	1,295	44.5	41.0	3.4
Michigan	1,356	744	54.9	44.6	10.3
Minnesota	971	448	46.1	41.2	4.9
Mississippi	206	115	55.8	45.6	10.2
Missouri	555	271	48.8	39.6	9.2
Montana	72	39	54.2	50.0	4.2
Nebraska	294	157	53.4	39.8	13.6
Nevada	265	143	54.0	46.8	7.2
New Hampshire	226	104	46.0	43.4	2.7
New Jersey	3,379	1,716	50.8	45.6	5.2
New Mexico	120	60	50.0	45.0	5.0
New York	5,823	2,940	50.5	44.2	6.3
North Carolina§	930	497	53.4	44.4	9.0
North Dakota	95	55	57.9	48.8	9.5
Ohio	1,398	724	51.8	42.8	9.0
Oklahoma§	269	143	53.2	46.1	7.1
Oregon	413	245	59.3	53.8	5.6
Pennsylvania	1,575	783	49.7	42.5	7.2
Puerto Rico	116	70	60.3	42.2	18.1
Rhode Island	285	144	50.5	47.7	2.8
South Carolina§	435	219	50.3	43.4	6.9
South Dakota	73	42	57.5	57.5	0.0
Tennessee	466	271	58.2	51.1	7.1
Texas§	2,731	1,493	54.7	47.3	7.4
Utah	305	160	52.5	44.6	7.9
Vermont	57	27	47.4	42.1	5.3
U.S. Virgin Islands	¶	¶	¶	¶	¶
Virginia§	1,359	676	49.7	45.3	4.4
Washington	914	448	49.0	43.8	5.3
West Virginia	126	65	51.6	49.2	2.4
Wisconsin	531	285	53.7	42.0	11.7
Wyoming	29	16	55.2	55.2	0.0
Non-U.S. resident	590	324	54.9	46.9	8.0
Total	**48,756**	**25,008**	**51.3**	**44.9**	**6.4**

* In cases of missing residency data, the patient's state of residency was assigned as the state in which the ART procedure was performed. Medical centers in all but five states had missing residency for <10% of ART infants. Medical centers located in Georgia, Massachusetts, Minnesota, New York, and Pennsylvania had >10% missing residency data.

† **Source of population size:** July 1, 2003, state population estimates. Population Division, U.S. Census Bureau.

§ A total of 0.6% of ART procedures were reported from military medical centers located 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 were Alaska, Delaware, District of Columbia, Hawaii, Maryland, North Carolina, Oklahoma, South Carolina, Texas, and Virginia. States and territories for which >5% of ART procedures among state residents were performed in a military medical center were Alaska and the District of Columbia.

¶ Data not indicated to preserve confidentiality but included in totals.

TABLE 8. Effect of assisted reproductive technology (ART) on the total number of infants born in the United States, by plurality — United States, 2003

Plurality	No. of ART infants*†	(%) of total	No. of total U.S. infants§	(%) of total	Contribution of ART to total births in the United States (%)
Infants born in singleton deliveries	22,383	(47.8)	3,953,622	(96.7)	0.6
Infants born in multiple-birth deliveries	24,447	(52.2)	136,328	(3.3)	17.9
Twins	21,057	(45.0)	128,665	(3.1)	16.4
Triplets or higher order	3,390	(7.2)	7,663	(0.2)	44.2
Total no. of infants	**46,830**		**4,089,950**		**1.1**

* **SOURCE:** Assisted Reproductive Technology Surveillance System.
† Includes infants conceived from ART procedures performed in 2002 and born in 2003 and infants conceived from ART procedures performed in 2003 and born in 2003.
§ **SOURCE:** U.S. natality file, CDC, National Center for Health Statistics.

TABLE 9. Percentage of adverse perinatal outcomes* among assisted reproductive technology (ART) infants born in 2003, by plurality — United States†

Plurality	LBW (%)	VLBW (%)	Preterm (%)	Preterm LBW (%)	Term LBW (%)
ART singletons (n = 22,383)	9.3	1.9	14.7	7.1	2.2
ART twins (n = 21,057)	56.0	8.4	64.0	46.9	9.0
ART triplets or higher-order multiples (n = 3,390)	93.7	32.4	97.0	91.5	§

* 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 (<2,500 g); and term LBW = gestational age ≥37 weeks and low birthweight (<2,500 g).
† Includes infants conceived from ART procedures performed in 2002 and born in 2003 and infants conceived from ART procedures performed in 2003 and born in 2003. Samples for calculations of percentages of outcomes were reduced from totals because of missing values for birthweight and gestational age.
§ Data not provided because of limited numbers.

TABLE 10. Adverse perinatal outcomes* among assisted reproductive technology (ART) singleton infants born in 2003, by procedure type and selected maternal factors — United States†

Procedure type/Medical factor	LBW (%)	VLBW (%)	Preterm (%)	Preterm LBW (%)	Term LBW (%)
Freshly fertilized embryos, patient's eggs (n = 16,082)	**9.3§**	**1.9**	**13.4§**	**6.9§**	**2.4§**
Maternal age (yrs)					
<35	9.6	1.9	14.1¶	7.1	2.5
35–37	9.6	1.9	13.2	7.3	2.2
38–40	8.6	1.7	12.0	6.1	2.4
41–42	7.5	1.7	10.2	5.2	2.3
>42	8.7	**	11.3	6.7	**
Maternal race/ethnicity††					
White, non-Hispanic	7.0	1.4	11.7	5.3	1.8
Black, non-Hispanic	16.0	5.2	17.7	11.5	**
Hispanic	12.1	**	16.2	7.7	4.6
Asian	13.0	**	10.0	7.4	5.7
No. of previous births§§					
0	10.0¶	2.0	13.4	7.3¶	2.7¶
1	7.3	1.6	12.6	5.6	1.7
≥2	8.1	1.9	15.4	6.7	1.4
Freshly fertilized embryos, donor's eggs (n = 2,507)	11.2	2.3	17.6	9.1	2.1
Thawed embryos¶¶ (n = 3,653)	**8.1**	**1.6**	**18.4**	**6.8**	**1.2**

* 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 (<2,500 g); and term LBW = gestational age ≥37 weeks and low birthweight (<2,500 g).

† Includes infants conceived from ART procedures performed in 2002 and born in 2003 and infants conceived from ART procedures performed in 2003 and born in 2003. Samples for calculation of percentages of outcomes were reduced from totals because of missing values for birthweight and gestational age.

§ $p<0.01$; chi-square to test for variations in adverse perinatal outcomes across procedure types.

¶ $p<0.01$; chi-square to test for variations in adverse perinatal outcomes across maternal factor categories.

** Risk for outcome not provided if number of cases in a given subgroup <10.

†† Analysis did not include 68% of ART singletons who had missing data for maternal race/ethnicity or the 0.1% classified as Native American or Other. Because of the large proportion of missing data on maternal race/ethnicity, no significance testing was performed on the observed differences.

§§ Analysis did not include 0.4% of ART singletons that were missing data on number of previous births.

¶¶ Includes cycles in which thawed embryos were used from patient eggs and donor eggs.

Malaria Surveillance — United States, 2004

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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 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 2004 and summarizes trends during previous years.

Description of System: Malaria cases confirmed by blood film 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 1,324 cases of malaria, including four fatal cases, with an onset of symptoms in 2004 among persons in the United States or one of its territories. This number represents an increase of 3.6% from the 1,278 cases reported for 2003. *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 49.6%, 23.8%, 3.6%, and 2.0% of cases, respectively. Seventeen patients (1.3% of total) were infected by two or more species. The infecting species was unreported or undetermined in 262 (19.8%) cases. Compared with 2003, the number of reported malaria cases acquired in the Americas (n = 173) increased 17.7%, whereas the number of cases acquired in Asia (n = 172) and Africa (n = 809) decreased 2.8% and 3.7%, respectively. Of 775 U.S. civilians who acquired malaria abroad, only 160 (20.6%) reported that they had followed a chemoprophylactic drug regimen recommended by CDC for the area to which they had traveled. Four patients became infected in the United States; three cases were attributed to congenital transmission and one to laboratory-related mosquitoborne transmission. Four deaths were attributed to malaria, including two caused by *P. falciparum*, one by *P. vivax*, and one by a mixed infection with *P. falciparum* and *P. malariae*.

Interpretation: The 3.6% increase in malaria cases in 2004, compared with 2003, resulted primarily from an increase in the number of cases acquired in the Americas but was offset by a decrease in the number of cases acquired in Africa and Asia. This limited increase might reflect local changes in disease transmission, increased travel to regions in which malaria is endemic, or fluctuations in reporting to state and local health departments. These changes likely reflect expected variation in annual reporting and should not be interpreted as indicating a longer-term trend. 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.

Public Health Actions: Additional investigations were conducted for the four fatal cases and four 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 medical care immediately and report their travel history to the clinician; investigation should include a 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 at telephone 770-488-7788. Recommendations concerning malaria treatment can be obtained at http://www.cdc.gov/malaria/diagnosis_treatment/treatment.htm or by calling the Malaria Hotline.

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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 are imported from regions where malaria transmission is known to occur, although congenital infections and infections resulting from exposure to blood or blood products are also 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 2004.

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. A substantial difference in the data collected in these two systems 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 regarding cases reported to NMSS.

Cases of blood-film–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 acquired in the United States are investigated, including all induced and congenital cases and possible introduced or cryptic cases. Information derived from uniform case report forms is entered into a database and analyzed annually.

Definitions

The following definitions are used in this report:

- **Laboratory criteria for diagnosis:** Demonstration of malaria parasites on blood film or by polymerase chain reaction (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 (*6*). 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 is generally reserved for cases for which blood-film diagnosis of malaria or species determination is inadequate.

* 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 Infectious Diseases, Division of Parasitic Diseases, Malaria Branch at 770-488-7788.

Results

General Surveillance

For 2004, CDC received 1,324 reports concerning cases of malaria occurring among persons in the United States and its territories, representing a 3.6% increase from the 1,278 cases reported with a date of onset in 2003 (*7*) (Table 1). In 2004, a total of 775 cases occurred among U.S. civilians and 282 cases among foreign civilians (Table 1). In recent years, cases have increased among U.S. civilians and decreased among foreign-born civilians (Figure 1).

Plasmodium Species

Of the 1,324 cases reported in 2004, the infecting species of *Plasmodium* was identified in 1,062 (80.2%) cases. *P. falciparum* and *P. vivax* were identified in blood films from 49.5% and 23.8% of infected persons, respectively (Table 2). The number of reported cases of *P. falciparum* decreased 3.8%, from 682 in 2003 to 656 in 2004, and the number of *P. vivax* infections increased 7.5%, from 293 to 315. Among 964 cases for which both the region of acquisition and the infecting species were known, 81.1% of infections acquired in Africa were attributed to *P. falciparum* and 10.3% to *P. vivax*. The converse was true for infections acquired in the Americas and Asia; 56.1% and 81.3%, respectively, were attributed to *P. vivax* and 35.3% and 11.1% to *P. falciparum*.

Region of Acquisition and Diagnosis

All but four reported cases (n = 1,320) were imported. Of 1,190 imported cases for which the region of acquisition was known, 809 (68.0%) were acquired in Africa, 172 (14.5%) in Asia, and 173 (14.5%) in the Americas (Table 3). A total of 368 (3.0%) imported cases were acquired in Oceania. West Africa accounted for 598 (73.9%) cases acquired in Africa, and India accounted for 113 (65.7%) cases acquired in Asia. In the Americas, 121 (69.9%) cases were acquired in Central America and the Caribbean, followed by 34 (19.7%) cases in South America and 18 (10.4%) cases in Mexico. Information regarding region of acquisition was missing for 130 (9.8%) imported cases. Compared with 2003, the number of reported malaria cases acquired in the Americas increased 17.7%, and the number of cases acquired in Asia and Africa decreased 2.8% and 3.7%, respectively.

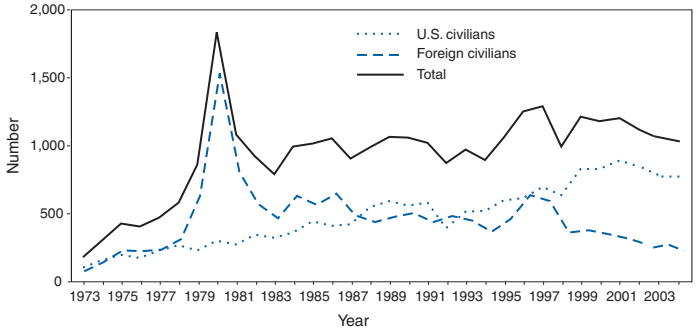
TABLE 1. Number of malaria cases* among U.S. and foreign civilians and U.S. military personnel — United States, 1973–2004

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**

* A case was defined as symptomatic or asymptomatic illness that occurs in the United States or one of its territories in a person who has 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.

FIGURE 1. Number of malaria cases among U.S. and foreign civilians, by year — United States,* 1973–2004†



* 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.

In the United States, the six health departments reporting the highest number of malaria cases were New York City (n = 214), California (n = 130), Texas (n = 123), New Jersey (n = 75), Maryland (n = 70), and Georgia (n = 65) (Figure 2). Of these, three health departments (New Jersey, New York City, and Texas) reported an increase in cases compared with 2003, and three (California, Georgia, and Maryland) reported a decrease.

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 617 (46.7%) of the imported malaria cases (Table 4). Symptoms began before arrival in the United States for 75 (12.2%) persons and after arrival for 542 (87.8%) persons. Clinical malaria occurred ≤1 month after arrival in 344 (80.9%) of the 425 *P. falciparum* cases and in 64 (43.0%) of the 149 *P. vivax* cases (Table 4). Nine (1.5%) of 617 persons became ill >1 year after returning to the United States.

TABLE 2. Number and percentage of malaria cases, by *Plasmodium* species — United States, 2002–2004

Plasmodium species	2002		2003		2004	
	No.	(%)	No.	(%)	No.	(%)
P. falciparum	699	(52.3)	682	(53.4)	656	(49.5)
P. vivax	339	(25.4)	293	(22.9)	315	(23.8)
P. malariae	38	(2.8)	46	(3.6)	47	(3.5)
P. ovale	37	(2.8)	33	(2.6)	27	(2.0)
Mixed	11	(0.8)	12	(0.9)	17	(1.3)
Undetermined	213	(15.9)	212	(16.6)	262	(19.8)
Total	**1,337**		**1,278**		**1,324**	

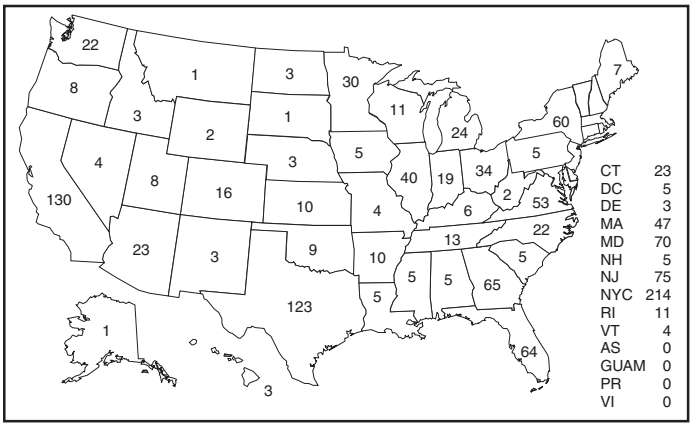
TABLE 3. Imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2004

Country of acquisition	*Plasmodium* species						
	P. falciparum	*P. vivax*	*P. malariae*	*P. ovale*	Unknown	Mixed	Total
Africa	**529**	**67**	**27**	**21**	**157**	**8**	**809**
Algeria	1	0	0	0	0	0	**1**
Angola	0	0	0	0	2	0	**2**
Benin	3	0	0	0	0	0	**3**
Burkina Faso	3	0	0	0	3	0	**6**
Burundi	3	0	0	0	0	0	**3**
Cameroon	25	3	2	1	5	0	**36**
Chad	2	0	0	0	0	0	**2**
Congo	8	0	0	0	2	1	**11**
Cote d'Ivoire	18	2	1	0	4	1	**26**
Democratic Republic of the Congo	2	0	0	0	0	0	**2**
Djibouti	0	3	0	0	0	1	**4**
Ethiopia	0	12	0	0	3	0	**15**
Gambia	3	1	0	1	1	0	**6**
Ghana	63	8	6	5	12	1	**95**
Guinea	13	0	0	0	2	0	**15**
Guinea-Bissau	1	0	0	0	0	0	**1**
Kenya	24	1	4	3	7	1	**40**
Liberia	17	1	0	0	9	0	**27**
Malagasy Republic	1	3	1	0	0	0	**5**
Malawi	2	0	0	0	0	0	**2**
Mali	5	0	0	0	3	0	**8**
Mauritania	1	0	0	0	0	0	**1**
Mozambique	3	0	0	0	2	1	**6**
Niger	3	0	1	0	2	0	**6**
Nigeria	209	14	9	5	39	2	**278**
Rwanda	2	1	0	0	1	0	**4**
Senegal	12	0	0	0	2	0	**14**
Sierra Leone	29	3	0	0	19	0	**51**
Somalia	0	1	0	0	0	0	**1**
South Africa	7	2	0	0	1	0	**10**
Sudan	3	0	0	1	1	0	**5**
Tanzania	3	0	0	0	2	0	**5**
Togo	6	0	0	0	2	0	**8**
Uganda	19	2	1	2	13	0	**37**
Zambia	3	1	0	1	3	0	**8**
Zimbabwe	3	0	0	0	0	0	**3**
West Africa, unspecified	8	3	0	0	7	0	**18**
Central Africa, unspecified	0	0	0	0	1	0	**1**
East Africa, unspecified	0	0	0	0	0	0	**0**
South Africa, unspecified	0	0	0	0	1	0	**1**
Africa, unspecified	24	6	2	2	8	0	**42**
Asia	**16**	**117**	**7**	**1**	**28**	**3**	**172**
Afghanistan	0	13	0	0	0	0	**13**
Burma (Myanmar)	0	1	0	0	0	0	**1**
Cambodia	0	1	0	0	0	0	**1**
China	0	0	0	0	1	0	**1**
India	12	73	5	0	21	2	**113**
Indonesia	1	3	0	0	1	0	**5**
Korea (South)	0	7	1	0	1	0	**9**
Laos	1	0	0	0	0	0	**1**
Nepal	0	1	0	0	0	0	**1**
Pakistan	1	17	1	0	2	0	**21**
Philippines	0	1	0	0	0	0	**1**
Saudi Arabia	0	0	0	1	0	0	**1**
Sri Lanka (Ceylon)	0	0	0	0	1	0	**1**
Vietnam	0	0	0	0	0	1	**1**
Yemen	0	0	0	0	1	0	**1**
Asia, unspecified	1	0	0	0	0	0	**1**

TABLE 3. (*Continued*) Imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2004

Country of acquisition	*Plasmodium* species						
	P. falciparum	*P. vivax*	*P. malariae*	*P. ovale*	Unknown	Mixed	Total
Central America and the Caribbean	**41**	**49**	**6**	**1**	**22**	**2**	**121**
Belize	0	2	0	1	0	0	**3**
Costa Rica	3	1	0	0	3	0	**7**
Dominican Republic	4	0	0	0	0	0	**4**
El Salvador	1	4	0	0	3	0	**8**
Guatemala	2	16	2	0	3	0	**23**
Haiti	22	0	2	0	2	0	**26**
Honduras	8	24	2	0	9	2	**45**
Nicaragua	0	0	0	0	1	0	**1**
Central America, unspecified	1	2	0	0	1	0	**4**
North America	**0**	**12**	**1**	**0**	**5**	**0**	**18**
Mexico	0	12	1	0	5	0	**18**
South America	**8**	**17**	**1**	**0**	**7**	**1**	**34**
Brazil	1	5	1	0	1	1	**9**
Colombia	1	0	0	0	2	0	**3**
Ecuador	0	3	0	0	1	0	**4**
Guyana	4	5	0	0	2	0	**11**
Peru	2	4	0	0	0	0	**6**
South America, unspecified	0	0	0	0	1	0	**1**
Oceania	**3**	**22**	**2**	**2**	**7**	**0**	**36**
Papua New Guinea	3	17	2	2	6	0	**30**
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**	**28**	**3**	**2**	**36**	**3**	**130**
Total	**655**	**312**	**47**	**27**	**262**	**17**	**1,320**

FIGURE 2. Number of malaria cases, by state in which the disease was diagnosed — United States, 2004



Imported Malaria Cases

Imported Malaria Among U.S. Military Personnel

In 2004, a total of 32 cases of imported malaria were reported among U.S. military personnel. 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 26 patients for whom information regarding chemoprophylaxis use was available, six (23.1%) were not using any chemoprophylaxis, and two (7.7%) had adhered to an incorrect regimen.

Imported Malaria Among Civilians

Of 1,057 imported malaria cases reported among civilians, 775 (73.3%) occurred among U.S. residents and 282 (26.7%) among residents of other countries (Table 5). Of the 775 imported malaria cases among U.S. civilians, 548 (70.7%) were acquired in Africa, a decrease of 2.3% compared with 2003. Asia accounted for 91 (11.7%) cases of imported malaria among U.S. civilians, and travel to the Central American and Caribbean regions accounted for 73 (9.4%) cases. Of the 282 imported cases among foreign civilians, 177 (62.8%) were acquired in Africa.

Antimalarial Chemoprophylaxis Use

Chemoprophylaxis Use Among U.S. Civilians

Information concerning chemoprophylaxis use and travel area was known for 694 (89.5%) of the 775 U.S. civilians who had imported malaria. Of these 694 persons, 452 (65.1%) had not taken any chemoprophylaxis, and 72 (10.4%) had not taken a CDC-recommended drug for the area visited (*8*).

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, 2004

	P. falciparum		*P. vivax*		*P. malariae*		*P. ovale*		Mixed		Total	
Interval (days)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<0†	55	(12.9)	17	(11.4)	1	(3.7)	1	(11.1)	1	(14.3)	**75**	**(12.2)**
0–29	344	(80.9)	64	(43.0)	18	(66.7)	1	(11.1)	4	(57.1)	**431**	**(69.9)**
30–89	19	(4.5)	29	(19.5)	4	(14.8)	1	(11.1)	1	(14.3)	**54**	**(8.8)**
90–179	4	(0.9)	17	(11.4)	2	(7.4)	5	(55.6)	0		**28**	**(4.5)**
180–364	1	(0.2)	17	(11.4)	0		1	(11.1)	1	(14.3)	**20**	**(3.2)**
≥365	2	(0.5)	5	(3.4)	2	(7.4)	0		0		**9**	**(1.5)**
Total	**425**		**149**		**27**		**9**		**7**		**617**	

* 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, 2004*

	United States		Foreign		Total	
Area or region	No.	(%)	No.	(%)	No.	(%)
Africa	548	(70.7)	177	(62.8)	**725**	**(68.6)**
Asia	91	(11.7)	53	(18.8)	**144**	**(13.6)**
Central America and the Caribbean	73	(9.4)	35	(12.4)	**108**	**(10.2)**
South America	24	(3.1)	3	(1.1)	**27**	**(2.6)**
North America	6	(0.8)	11	(3.9)	**17**	**(1.6)**
Oceania	28	(3.6)	1	(0.4)	**29**	**(2.7)**
Eastern Europe	0		0		**0**	
Unknown†	5	(0.7)	2	(0.7)	**7**	**(0.7)**
Total	**775**		**282**		**1,057**	

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

Only 138 (19.9%) U.S. civilians had taken a CDC-recommended medication (*8*). Data for the specific drug taken were missing for the remaining 32 (4.6%) travelers. A total of 86 (62.3%) patients on CDC-recommended prophylaxis reported taking mefloquine weekly; 34 (24.6%) had taken doxycycline daily; none had taken atovaquone-proguanil daily; and 11 (8.0%) who had traveled only in areas where chloroquine-resistant malaria has not been documented had taken chloroquine weekly. Information on adherence to the drug regimen for these persons is presented in the following section. Seven patients (5.1%) had taken combinations of drugs that included one or more CDC-recommended drug for the travel region. Of the 72 patients taking a nonrecommended drug, 26 (36.1%) 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 160 patients (including 138 U.S. civilians, 15 persons in the U.S. military, three foreign civilians, and four persons for whom information regarding status was missing) contracted malaria after taking a recommended antimalarial drug for chemoprophylaxis. Of these, 62 (38.8%) reported complete compliance with the regimen, and 73 (45.6%) reported noncompliance; compliance was unknown for the remaining 25 (15.6%). Information regarding infecting species was available for 123 (76.9%) patients who had taken a recommended antimalarial drug and undetermined for the remaining 37.

Cases of *P. vivax* or *P. ovale* After Recommended Prophylaxis Use. Of the 160 patients who had malaria diagnosed after recommended chemoprophylaxis use, 50 (31.3%) had cases that were caused by *P. vivax*, and five (3.1%) had cases caused by *P. ovale*. Of the 55 total cases of *P. vivax* or *P. ovale*, 25 (45.5%) 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 because of missing data regarding symptom onset or return date to assess whether 19 cases were relapsing infections. Eleven cases, all caused by *P. vivax*, occurred ≤45 days after the patient returned to the United States. Five of the 11 patients were known to be noncompliant with their antimalarial chemoprophylaxis regimen. Four patients reported compliance with an antimalarial chemoprophylaxis regimen; one had traveled to Africa, one to Oceania, one to Asia, and one to South America. Two of these patients

reported taking mefloquine, one reported using doxycycline, and one reported using both doxycycline and mefloquine; 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 the remaining two patients, no information was available concerning compliance; the region of acquisition was North America for one patient and South America for the other.

Cases of *P. falciparum* and *P. malariae* After Recommended Prophylaxis Use. The remaining 105 cases of malaria reported among persons who had taken a recommended antimalarial drug for chemoprophylaxis include 58 cases of *P. falciparum*, seven of *P. malariae*, three of mixed infection, and 37 for which the infecting species was unidentified. Of the 58 *P. falciparum* cases among those who reported taking a recommended antimalarial drug, 54 were acquired in Africa, one in Oceania, one in Asia, one in Central America, and one in South America. In 41 (70.7%) of these 58 cases, noncompliance with antimalarials was reported. In 13 (22.4%) cases, patients reported compliance with antimalarial chemoprophylaxis; 11 of these patients had traveled to Africa, one to South America, and one to Papua New Guinea. Seven had reported taking mefloquine, five doxycycline, and one both atovaquone-proguanil and doxycycline for malaria chemoprophylaxis. Blood samples were not available for the 13 patients who reported compliance with a recommended regimen. Patient compliance was unknown for four persons with *P. falciparum* who reported taking a recommended antimalarial drug for prophylaxis.

Six of the seven *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 four (57.1%) reported compliance with a recommended chemoprophylaxis regimen. Three compliant patients used mefloquine, and one used doxycycline. All four 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 692 (89.3%) of the 775 U.S. civilians with imported malaria (Table 6). The largest proportion (52.6%) represented persons who had visited friends or relatives in malarious areas; the second and third highest proportions, 10.6% and 8.7%, represented persons who had traveled as missionaries or as tourists, respectively.

TABLE 6. Number and percentage of imported malaria cases among U.S. civilians, by purpose of travel at the time of acquisition — United States, 2004

	Imported cases	
Category	**No.**	**(%)**
Visiting friends/relatives	408	(52.6)
Missionary or dependent	82	(10.6)
Tourism	67	(8.7)
Business representative	50	(6.5)
Student/teacher	34	(4.4)
Peace Corps volunteer	8	(1.0)
Air crew/sailor	2	(0.3)
Refugee/immigrant	0	
Other/mixed purpose	41	(5.3)
Unknown	83	(10.7)
Total	**775**	

Malaria During Pregnancy

A total of 30 cases of malaria were reported among pregnant women in 2004, representing 6.9% of cases among women. Nine (30.0%) of the 30 cases occurred among U.S. civilians; eight women had traveled to Africa and one to Asia; five had traveled to visit friends and relatives. Approximately 10.0% of pregnant women and 23.0% of nonpregnant women reported taking malaria chemoprophylaxis. Birth outcomes were not available for any of these 30 women.

Malaria Acquired in the United States

Congenital Malaria

Three cases of congenital malaria were reported in 2004 and are described in the following case reports:

- **Case 1.** On April 27, 2004, a male infant aged 5 weeks was brought to an outpatient clinic for a posthospitalization follow-up visit. One week earlier, the infant had been admitted to a hospital for fever and decreased oral intake. During admission, blood, urine and cerebrospinal fluid cultures were obtained, and the patient was started on ampicillin and gentamicin for presumed sepsis. Laboratory studies on admission were notable for anemia (hemoglobin: 9.2 g/dL). Repeat hemoglobin level on day 2 of hospitalization was 8.0 g/dL. On day 4 of hospitalization, all cultures for bacteria continued to be negative, antibiotics were discontinued, and the patient was discharged. Three days after discharge, the patient was brought in for a follow-up outpatient appointment; during this visit, the patient was noted to be anemic (hemoglobin: 6.0 g/dL). A complete blood count demonstrated trophozoites and gametocytes consistent with *P. vivax* (<1% parasitemia). The patient was readmitted to the hospital for a blood transfusion and treatment with chloroquine. The patient tolerated therapy

and was discharged home at the completion of treatment. Repeat blood films were negative. The patient had no history of travel, blood transfusion, or organ transplant. The infant had been born through spontaneous vaginal delivery to a female who had emigrated from Guatemala 1 year earlier. During month 6 of gestation, the mother had one febrile episode lasting multiple days that resolved without treatment. A blood film was obtained from the mother after her son received a diagnosis of malaria. The blood film was negative, but further investigation revealed a positive PCR test for *P. vivax*. After testing negative for glucose-6-phosphate dehydrogenase deficiency, the mother was treated with chloroquine and primaquine.

- **Case 2.** On May 28, 2004, a female infant aged 2 weeks was admitted to a hospital with a 2-day history of fever, cough, and poor feeding. On admission, her physical examination revealed mild pallor, hepatomegaly, and a temperature of 102.0°F (38.9°C). Blood and urine cultures were obtained, and the patient was started on ampicillin and gentamicin for presumed sepsis. A blood film indicated intraerythrocytic parasites consistent with *P. vivax*. She recovered fully after treatment with intravenous quinidine and clindamycin for 2 days, 1 dose of oral quinine, and 3 days of chloroquine. The infant was a full-term female born by cesarean section because of failure to progress. The mother had recently immigrated to the United States from India and reported having one episode of clinical malaria in 2001. One day after delivery, the mother experienced fever and received a diagnosis of malaria (species not determined). She was treated with oral antimalarial medications and recovered completely.
- **Case 3.** On September 15, 2004, a male infant aged 5½ weeks was taken to an emergency department (ED) with fever and irritability for 3 days. In the ED, the infant had an unremarkable physical exam except for a fever of 102.4°F (39.1°C) and tachycardia. Initial laboratory studies demonstrated anemia (hemoglobin: 8.4 g/dL), thrombocytopenia (platelet count: 92,000/μL) and an elevated lactate dehydrogenase (512 IU/L). Blood, urine, and cerebrospinal fluid cultures were obtained, and the infant was started on ceftriaxone for presumed sepsis. A blood film indicated intraerythrocytic parasites consistent with *P. falciparum* (3% parasitemia). The patient was started on oral quinine sulfate and clindamycin. All cultures for bacteria were negative, and ceftriaxone was stopped after 2 days. The patient was discharged after 10 days. A repeat blood film at the end of his hospitalization was negative for *P. falciparum*. The infant was a full-term male born on August 3 to a Nigerian woman aged 34 years who experienced fever during delivery and who subsequently received a diagnosis of *P. falciparum* malaria. The mother was treated with oral quinine and doxycycline for 7 days. The infant had fever of 103.0°F (39.4°C) soon after birth, but the fever resolved without treatment and did not recur. Blood films obtained on the date of birth and 24 and 48 hours after birth were negative. The patient was discharged 2 days after birth and was asymptomatic until 3 days before he was taken to the ED on September 15.

Probable Laboratory-Acquired Mosquitoborne Malaria

One case of malaria attributed to laboratory-related transmission was reported in 2004 and is described in the following case report:

- **Case 1.** On August 11, 2004, a male laboratory employee had fever, shaking chills, headache, and malaise. The next day, he reported to his laboratory supervisor, and a blood film was obtained. The patient received a diagnosis of *P. vivax* malaria and was referred to the employee health clinic, where he was started on chloroquine. By day 3 of treatment, the patient's symptoms improved, and his thick blood film was negative for intraerythrocytic parasites. After testing negative for glucose-6-phosphate dehydrogenase deficiency, he was treated with primaquine. The patient had no history of travel to an area in which malaria is endemic or blood transfusion but was employed at a laboratory that worked with malaria-infected mosquitoes. The most likely explanation for his illness is that an infected mosquito escaped and infected the employee while he was in the screened-off area used for working with infected mosquitoes. All laboratory employees were notified of the incident and instructed to report to their supervisor if they had any symptoms of malaria. No other employees were infected.

Deaths Attributed to Malaria

Four deaths attributable to malaria were reported in 2004 and are described in the following case reports:

- **Case 1.** On February 13, 2004, a female aged 21 years went to an ED with fever, chills, night sweats, headache, and severe prostration for 4 days. The patient had traveled to Ghana to visit relatives during December 17, 2003–January 22, 2004. The patient had taken 1 dose of mefloquine before starting her trip but had not continued using an antimalarial for chemoprophylaxis. On evaluation, the patient was noted to have intraerythrocytic parasites on thick and thin blood film consistent with *P. falciparum* (2% parasitemia). Admission laboratory tests

revealed a normal creatinine (1.2 mg/dL), mild anemia (hematocrit: 35%), and thrombocytopenia (platelet count: 98,000/μL). Despite known resistance to chloroquine in Ghana, the patient was started on a trial of chloroquine on admission to the hospital. The patient continued to have fevers and had seizures 24 hours after admission. She was then started on oral quinine and doxycycline. Thirty-six hours after admission, the patient had progressive coma consistent with cerebral malaria and was started on intravenous quinidine gluconate and doxycycline. The patient continued to deteriorate and died 48 hours after admission.

- **Case 2.** On April 5, 2004, a male aged 43 years went to an ED with a 2-day history of fevers, chills, and rigors. The patient had returned from Uganda 1 week earlier. He did not report using any antimalarial for chemoprophylaxis. On admission, the patient was noted to have intraerythrocytic parasites on blood film and received a diagnosis of *P. malariae*. He was started on chloroquine and primaquine but continued to have periodic fevers. On day 4 of hospitalization, the patient had respiratory distress and metabolic acidosis requiring endotracheal intubation and transfer to the intensive care unit. A repeat blood film revealed a mixed population of *P. malariae* and *P. falciparum*, and the patient was started on oral quinine and doxycycline. The patient had multiorgan system failure with manifestations of acute respiratory distress syndrome, renal failure, hepatic failure, and disseminated intravascular coagulation, and his condition continued to deteriorate. On April 17, he had a cardiac arrest and died.
- **Case 3.** On June 3, 2004, a male aged 20 years went to an ED with a 2-week history of right upper-quadrant abdominal pain, fevers, and chills. The patient had immigrated to the United States from Honduras 2 days earlier. On admission, the patient was noted to have intraerythrocytic parasites and received a diagnosis of *P. falciparum* (>5% parasitemia). The patient was mildly anemic (hematocrit: 37%) and was noted to have hepatosplenomegaly on abdominal computed tomography scan. Treatment was initiated with oral quinine and doxycycline. On day 2 of hospitalization, the patient had acute respiratory distress syndrome requiring emergent endotracheal intubation and transfer to the intensive care unit. Intravenous quinidine and exchange transfusion were recommended by the infectious disease specialist caring for the patient, but no intravenous quinidine was available in the hospital or surrounding area. The patient was transferred to a tertiary care center on June 5, where he was treated with intravenous quinidine and exchange transfusion. He subsequently had complications of acute respiratory distress syndrome, including bilateral pneumothoraces, *Klebsiella* sp. pneumonia, sinusitis, and deep venous thrombosis. On July 18, the patient became progressively hypoxic, had a cardiac arrest, and died.
- **Case 4.** On June 10, 2004, a male aged 69 years went to an ED with a 1-week history of fever, nausea, and fatigue. He had a long-standing history of hypertension, hypothyroidism, and type-2 diabetes mellitus with complications of retinopathy, neuropathy, and right below-the-knee amputation. He had spent 1 year in India and returned to the United States in October 2003. On admission, he received a diagnosis of *P. vivax* malaria, anemia (hematocrit: 32%), thrombocytopenia (platelet count: 71,000/μL), and renal insufficiency (creatinine: 1.5 mg/dL). He was also noted to have a non-Q-wave myocardial infarction and congestive heart failure. He was treated with chloroquine. On day 2 of hospitalization, the patient had metabolic acidosis and respiratory distress requiring transfer to the intensive care unit. He had a cardiac arrest on day 3 of hospitalization and sustained severe anoxic encephalopathy, ischemic hepatopathy, and probable aspiration pneumonia. Because of his condition, the family requested withdrawal of life-support measures, and the patient died on June 15.

Discussion

A total of 1,324 cases of malaria were reported to CDC for 2004, representing an increase of 3.6% from the 1,278 cases reported for 2003. This change primarily resulted from an increase in cases acquired in the Americas. Since 2000, CDC has routinely contacted state health departments to ask for outstanding malaria case reports from the previous reporting year or for a statement that reporting is complete. The limited increase in the number of cases in 2004, compared with 2003, might reflect increased international travel or changing patterns of travel but is more consistent with expected variation in annual reporting and should not be interpreted as representing a longer-term trend.

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 were either not taking prophylaxis or taking nonrecommended prophylaxis for the region to which they were traveling. The majority of patients for whom appropriate prophylaxis was reported and adequate information was

available regarding species and onset of symptoms 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 problems with adherence while using correct antimalarial chemoprophylaxis, malabsorption of the antimalarial drug, or 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 is impossible. 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. Health-care 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.

The four fatal cases of malaria that occurred in the United States in 2004 underscore the importance of taking correct precautions and chemoprophylaxis. An earlier review of deaths attributed to malaria in the United States indicated that failure to take or adhere to recommended antimalarial chemoprophylaxis, to promptly seek medical care for posttravel illness, and to promptly diagnose and treat suspected malaria all contributed to fatal outcomes (*9*).

Of particular note, 17 cases of malaria, three among U.S. civilians, were reported in the Dominican Republic in 2004 from urban areas in Duarte Province and resort areas in La Altagracia Province previously thought to be nonmalarious (*10*). In response to this outbreak, CDC expanded its recommendations for chloroquine prophylaxis to include the affected areas. This underscores the need for effective domestic surveillance to detect cases of malaria acquired in presumed nonmalarious areas to guide antimalarial chemoprophylaxis recommendations and better protect travelers. As of March 2006, the resort areas of La Altagracia Province, but not the urban areas of Duarte Province, remain included in the list of areas with malaria transmission in the Dominican Republic.

The occurrence of 30 cases of malaria among pregnant U.S. civilians is also cause for concern. Malaria during pregnancy among nonimmune women is more likely to result in severe disease or contribute to an adverse outcome than malaria in nonpregnant women; the fetus might be adversely affected as well (*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 three 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, strong consideration should be given to presumptive treatment of the neonate or infant with an antimalarial appropriate for the mother's infecting species and region of acquisition.

Signs and symptoms of malaria are often 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 is 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's National Center for Infectious Diseases, Division of Parasitic Diseases at telephone

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/day	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
Diagnosis*	CDC's DPD telediagnosis service (DPDx)	8:00 a.m.–4:30 p.m. Eastern Time, Monday–Friday	http://www.dpd.cdc.gov/DPDx or e-mail dpdx@cdc.gov
Treatment*	CDC's Malaria Hotline	8:00 a.m.–4:30 p.m. Eastern Time, Monday–Friday	770-488-7788*
Treatment*	CDC's Malaria Hotline	4:30 p.m.–8:00 a.m. Eastern Time on weekdays and all day weekends and holidays	770-488-7100* (This is the number for the CDC's Emergency Operations Center. Ask staff member to page person on call for the Malaria Branch). http://www.cdc.gov/malaria/diagnosis_treatment/treatment.htm

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

770-488-7788 during regular business hours or CDC's Emergency Operations Center at 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/diagnosis_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*) (*8*), which is available for purchase from Elsevier at http://www.elsevierhealth.com or telephone 1-800-545-2522; it 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 March 2006, 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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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 should also 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 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 may 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

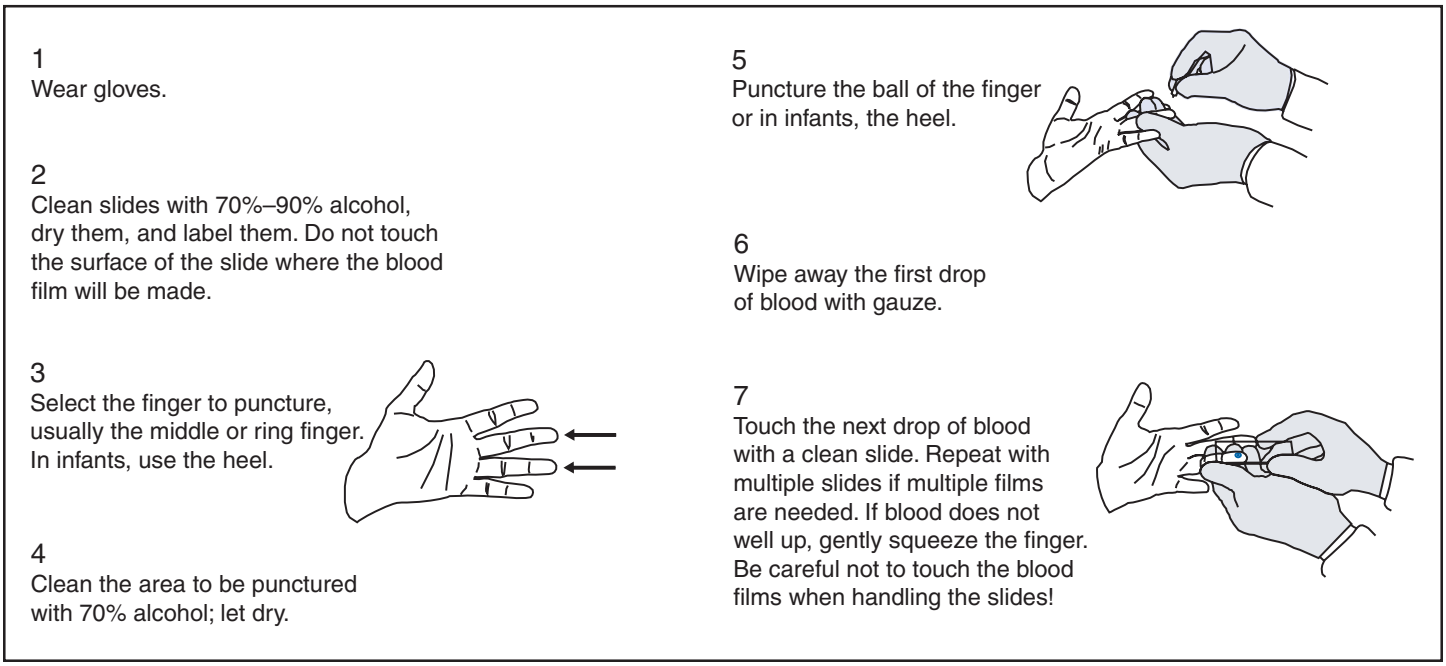
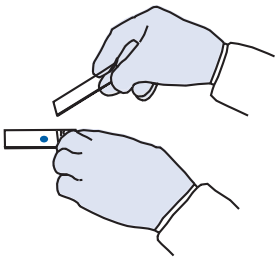


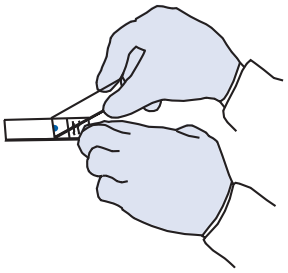
FIGURE A-2. Preparation of thin and thick blood films

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

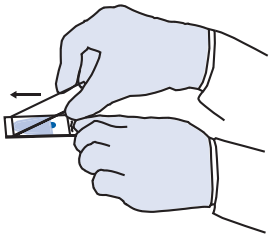
2
Thin film (a): Bring a clean spreader slide, held at a 45-degree angle, toward the drop of blood on the specimen slide.



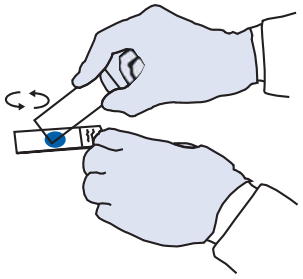
3
Thin film (b): Wait until the blood spreads along the entire width of the spreader slide.



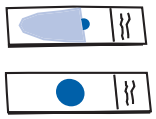
4
Thin film (c): While holding the spreader slide at the same angle, push it forward rapidly and smoothly.



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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