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Assisted Reproductive Technology Surveillance — United States, 2002

Malaria Surveillance — United States, 2003

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Assisted Reproductive Technology Surveillance — United States, 2002

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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: 2002.

Description of System: CDC contracts 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 2002, a total of 115,392 ART procedures were reported to CDC. These procedures resulted in 33,141 live-birth deliveries and 45,751 infants. Nationally, 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 3% used thawed embryos from donor eggs. Overall, 42% of ART transfer procedures resulted in a pregnancy, and 34% resulted in a live-birth delivery (delivery of one or more live-born infants). The highest live-birth rates were observed among ART procedures using freshly fertilized embryos from donor eggs (50%). The highest numbers of ART procedures were performed among residents of California (15,117), New York (13,276), Massachusetts (8,631), New Jersey (7,744), and Illinois (7,492). These five states also reported the highest number of infants conceived through ART. Of 45,751 infants born through ART, 53% 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 (42%) or their own eggs (35%). 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 2002 were conceived through ART. Those infants accounted for 17% of multiple births nationally. The percentage of ART infants who were low birth rate ranged from 9% among singletons to 95% 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 nationally 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.

The material in this report originated in the National Center for Chronic Disease Prevention and Health Promotion, George A. Mensah, MD, Acting Director; and the Division of Reproductive Health, John R. Lehnherr, Acting Director.
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Introduction

For ≥2 decades, assisted reproductive technologies (ARTs) have been used by couples 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) (*3–8*). 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 (*3–8*). In addition to the multiple-birth risks, recent studies suggest an increased risk for low birthweight among singleton infants conceived through ART (*9,10*). 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 2002. 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

Each year, the Society for Assisted Reproductive Technology (SART), an organization of ART providers affiliated with the American Society for Reproductive Medicine, collects data regarding ART procedures from medical centers performing ART in the United States and its territories and provides these data to CDC by contract. A full description of the ART data reporting system has been previously published (*11*). 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 are believed to be smaller-than-average practices. For this report, data pertaining to ART procedures initiated January 1–December 31, 2002, are presented.

ART data and outcomes from ART procedures are presented by patient's state of residence at time of ART 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 or not 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 treatments 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

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

† Data regarding population size are based on July 1, 2002, estimates from the U.S. Census Bureau (*12,13*).

discontinued at any step for medical reasons or by the patient's choice.

Variations in a typical ART procedure are noteworthy. Although a typical ART procedure includes 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. Detailed data are additionally 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 1–6. 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 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 be-

cause of multicolinearity 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 2002, additional analyses including all ART infants born in 2002 are presented. Because the goal of the analysis was to assess the effect of ART on the 2002 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 2001 and born in 2002 (approximately 2/3 of live-birth deliveries reported to the ART Surveillance System for 2001); and 2) infants conceived from ART procedures performed in 2002 and born in 2002 (approximately 1/3 of live-birth deliveries reported to the ART Surveillance System for 2002). Data regarding the total number of live births and multiple births in the United States in 2002 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 2002. Data are presented in relation to the total number of infants born in the United States in 2002 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 2002 are presented by plurality of birth. Data for each of the five outcomes are additionally presented for ART singletons born in 2002 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 additionally 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 428 medical centers in the United States and surrounding territories that performed ART in 2002, a total of 391 (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 2002 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, the U.S. Virgin Islands, and Wyoming).

Number and Type of ART Procedures

Overall, 115,392 ART procedures performed in 2002 were reported to CDC (Table 1). This number excludes less than 1% (n = 146) of ART procedures performed in 2002 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 (85,826; 74%). Of the 115,392 procedures started, 96,325 (83%) progressed to embryo transfer. Overall, 42% of ART procedures that progressed to the transfer stage resulted in a pregnancy; 34% resulted in a live-birth delivery; and 22% 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 (58% pregnancy rate, 50% live-birth rate, and 29% singleton live-birth rate). The lowest rates were observed among procedures using the patient's eggs and thawed embryos (31% pregnancy rate, 25% live-birth rate, and 19% singleton live-birth rate).

In all, the 33,141 live-birth deliveries from ART procedures resulted in 45,751 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 21,597 singleton infants were born as a result of ART. The largest proportion of infants born (74%; n = 33,776) 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 2002 were performed among residents of California (15,117), New York (13,276), Massachusetts (8,631), New Jersey (7,744), and Illinois (7,492). 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 <2% of ART procedures, live-birth deliveries, and infants born. The ratio of number of ART procedures per million population ranged from 82 in Puerto Rico to 1,344 in Massachusetts, with a national average of 395 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; 23% on women aged 35–37 years; 19% on women aged 38–40 years; 8% on women aged 41–42 years; and 4% on women aged >42 years. Patient and treatment characteristics of these women varied by age (Table 3). 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, male factor, and endometriosis were more commonly reported among younger women than women in older age categories. In contrast, diminished ovarian reserve was reported for only 1% of women aged <35 years; it was reported for 15% of women aged 41–42 years and 24% of women aged >42 years. Among all women, 10%–13% were reported as having unexplained infertility; 10%–17% were reported as having multiple female factors; and 18%–21% were reported as having both male and female factors.

Approximately 62% 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 20% 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

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

all age groups, the total proportion of ICSI use (i.e., combined ICSI for male factor and ICSI for other diagnoses) was greater than the proportion of in vitro fertilization with transcervical embryo transfer (IVF-ET) without ICSI.

Among all age groups, the majority of procedures included embryo culture for 3 days; the next most common procedure 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 53% involved transfer of three or more embryos. For women aged >42 years, 85% involved transfer of two or more embryos, and 65% 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 7% among women aged >42 years. Women aged ≤40 years who had an infertility diagnosis of tubal factor, ovulatory dysfunction, endometriosis, male factor, or had unexplained infertility tended to have higher than average live-birth rates. Women aged ≤40 years with an infertility diagnosis of diminished ovarian reserve or uterine factor tended to have lower than average live-birth rates. The average live-birth rate for women aged 41–42 years was 15%; however, the average live-birth rate for women in this age category with a diagnosis of uterine factor or endometriosis was >19%. The variation in success rates across diagnostic categories was not statistically significant for the oldest age group (women aged >42 years). Across all age groups, 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 higher live-birth rates than those with no previous births. However, the difference in live-birth rates for both the number of previous ART procedures and the number of previous births did not reach statistical significance for the two oldest age groups (women aged 41–42 years and 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. Although live-birth rates also appeared to increase when a gestational carrier was used, these results reached statistical significance in only one age group (women aged 41–42 years). 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 absences 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 7% among women aged >42 years, and singleton live-birth rates ranged from 26% among women aged <35 years to 6% among women age >42 years.

Multiple-Birth Risks Associated with ART

Of 11,544 multiple-birth deliveries, 8,601 (75%) were from pregnancies conceived with freshly fertilized embryos from the patient's eggs; 890 (8%) were from thawed embryos from the patient's eggs; 1,779 (15%) were from freshly fertilized embryos from a donor's eggs; and 274 (2%) 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 procedure in which freshly fertilized embryos from the patient's eggs were used was 35%. This rate varied from 39% among women aged <35 years to 7% among women aged >42 years.

Of 45,751 infants born through ART, 53% (24,154) 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 (Figures 3–6). 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 ≤40 years (Figures 3–5), 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 (Figures 3 and 4). For women aged 38–40 years (Figure 5), 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 years (Figure 6), both the live-birth delivery rate and the multiple-birth risk increased steadily with an increased number of embryos having been transferred. 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.

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 (Figures 7–10). 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 (Figure 7), live-birth rates were >47% when only one embryo was transferred. Moreover, limited variation existed in live-birth rates by number of embryos transferred. For example, only a slight difference in live-birth rates was noted among patients with single versus double elective embryo transfers (47% versus 52%). 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 (47%–50%) and a substantial risk for higher-order multiple births (8%–10%). For women with elective embryo transfer who were aged 35–37 and 38–40 years, live-birth rates were high (48% and 43%, respectively) when only two embryos were transferred (Figures 8 and 9). Live-birth rates were also high (30%) among women aged 35–37 years with elective embryo transfer of a single embryo (Figure 8). 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 these age groups. 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 (Table 6). 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 (3,189), New York (2,448), New Jersey (1,614), Massachusetts (1,489), Texas (1,408), and Illinois (1,352). Nationally, the percentage of infants born in multiple-birth deliveries after ART was used was 53%; the percentage of twins and triplets or higher order multiples were 45% and 8%, 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 New Mexico (64%), Maine (64%), Wyoming (63%), Idaho (60%), Kentucky (60%), North Carolina (60%), and Vermont (60%); 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 2002 is presented (Table 7). Of 4,021,726 total infants born in the United States in 2002, a total of 42,483 (1%) were conceived by ART. Infants conceived with ART accounted for 0.5% of singleton births and 17% of multiple births nationally. 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 2002 that were low birthweight, very low birthweight, preterm, preterm low birthweight, and term low birthweight are presented by plurality of birth (Table 8). The percentage of infants with low birthweight varied from 9% among singletons to 95% among triplets or higher order multiples. The percentages of very low birthweight, preterm, and preterm low birthweight followed similar patterns.

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 9). 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, preterm 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 1995 National Survey of Family Growth, 15% of women of reproductive age (aged 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 has resulted in dramatic increases in the number of children conceived through ART each year. From 1996 (i.e., the first full year for which CDC collected data) through 2002, the number of ART procedures performed increased 78%, from 64,681 to 115,392 (*1*). Additionally, during 1996–2002, 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 2002. The number of infants conceived through ART increased 120%, from 20,840 infants

** 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 (Figures 3–10).

conceived through ART procedures performed in 1996 to 45,751 infants conceived through ART procedures performed in 2002.

This report documents that in 2002, ART use varied according to patient's state of residency. Residents of California, New York, Massachusetts, New Jersey, and Illinois reported the highest number of ART procedures. These states also reported the highest number of infants conceived through ART. In 2002, ART use by state of residency was not completely in line with expectations based on the total population within states (*12,13*). Whereas Massachusetts had the third highest number of ART procedures performed, it ranked thirteenth in terms of total population size.[††] Likewise, residents of Maryland, New Jersey, and Rhode Island underwent more ART procedures than would have been expected based on their population sizes. As a result, state-specific ratios of ART procedures by population varied according to state of residency. States with the highest ratio of number of ART procedures among state residents per million population were Massachusetts (1,344), New Jersey (903), the District of Columbia (857), Maryland (771), and Rhode Island (710). This divergence is not unexpected, because in 2002, Massachusetts, Maryland, New Jersey, and Rhode Island 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).

Patients with different characteristics used ART services. Among ART treatments in which freshly fertilized embryos from the patient's eggs were used (i.e., the most frequent type of ART treatment), substantial variation was observed in patient age, infertility diagnoses, history of previous ART procedures, and previous births.

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. Thus, 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, 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. Thus, CDC also closely monitors multiple births conceived through 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 2002 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 2002, the proportion of twins and triplets or higher order multiples attributed to ART were 16% and 44%, respectively.

In certain states, such infertility treatments as ART might not be covered by insurance carriers, and patients might feel pressure to maximize the opportunity for live-birth delivery. Additionally, 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 (*25*). Indeed, in the United States, high-order embryo transfer is still common practice. In 2002, approximately 62% of ART cycles that used fresh, nondonor eggs or embryos and progressed to the embryo-transfer stage involved the transfer of three or more

[††] Data regarding population size are based on July 1, 2002, estimates from the U.S. Census Bureau (*12,13*).

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

embryos; approximately 28% of cycles involved the transfer of four or more; and 10% of cycles involved the transfer of five or more embryos (*1*). Recent reports published in the scientific literature have advocated for the presentation of singleton live-birth rates as a distinct indicator of ART success (*26–31*).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 that 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 2002 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, nationally 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.

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 (*32*). Monozygotic twins are at increased risk for adverse outcomes in comparison with dizygotic twins (*33*).

This analysis was subject to certain limitations. First, ART surveillance data are 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. Additionally, 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 2002; therefore, success rates do not represent all couples with infertility who were potential ART users in 2002. Third, approximately 9% of medical centers that performed ART in 2002 did not report their data to CDC as required.

ART data are reported to CDC by the ART medical center where 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 2002, 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 had >10% missing residency data. These states were Georgia, Massachusetts, Minnesota, and New York. 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 concern to consider 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 (*34*). 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 2002, a total of 739 (0.6%) ART procedures were performed in four military medical centers. These medical centers were located in California, the 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, the District of Columbia, Georgia, Guam, Hawaii, Maryland, Maine, North Carolina, North Dakota, New Mexico, South Carolina, South Dakota, Texas, Virginia, the U.S. Virgin Islands, and Wyoming. States for which >5% of ART procedures among state residents were performed in a military medical center were the District of Columbia, Guam, Virginia, and the U.S. Virgin Islands.

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. Additionally, 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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TABLE 1. Outcomes of assisted reproductive technology (ART), by procedure type — United States, 2002

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 procedure (%)	Total no. of live-born infants
Patient's eggs used										
Freshly fertilized embryos	85,826	74,519	69,857	29,423	42.1	24,324	34.8	15,723	22.5	33,776
Thawed embryos	16,383	N/A*	14,598	4,562	31.3	3,620	24.8	2,730	18.7	4,592
Donor eggs used										
Freshly fertilized embryos	9,261	8,647	8,394	4,854	57.8	4,195	50.0	2,416	28.8	6,088
Thawed embryos	3,922	N/A	3,476	1,207	34.7	1,002	28.8	728	20.9	1,295
Total	**115,392†**	**N/A**	**96,325**	**40,046**	**41.6**	**33,141**	**34.4**	**21,597**	**22.4**	**45,751**

* Not applicable.
† This number does not include 146 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, 2002

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	549	471	210	181	258	122.6
Alaska§	94	74	32	29	41	146.5
Arizona	1,661	1,404	561	463	668	305.3
Arkansas	407	343	136	118	161	150.4
California	15,117	13,039	5,258	4,344	6,001	431.9
Colorado	1,624	1,420	783	681	973	360.8
Connecticut	1,656	1,293	553	460	625	478.8
Delaware	414	317	131	114	154	513.7
District of Columbia§	488	409	167	138	177	857.4
Florida	4,999	4,151	1,751	1,469	2,020	299.5
Georgia§	2,553	2,099	922	768	1,082	298.8
Guam§	¶	¶	¶	¶	¶	¶
Hawaii§	775	647	203	167	233	624.7
Idaho	371	317	164	140	203	276.2
Illinois	7,492	6,113	2,368	1,891	2,598	595.2
Indiana	1,871	1,531	575	470	668	303.9
Iowa	998	796	376	309	422	339.9
Kansas	706	584	252	221	317	260.3
Kentucky	868	727	343	306	450	212.2
Louisiana	605	490	206	173	231	135.2
Maine§	176	144	68	56	84	135.9
Maryland§	4,200	3,374	1,327	1,062	1,423	770.6
Massachusetts	8,631	7,282	2,807	2,318	3,086	1,344.0
Michigan	3,288	2,720	1,089	931	1,282	327.4
Minnesota	2,211	1,920	860	714	942	440.0
Mississippi	370	314	122	101	145	129.1
Missouri	1,260	1,030	508	423	608	222.2
Montana	111	95	44	39	55	121.9
Nebraska	675	562	223	190	260	390.7
Nevada	603	492	223	175	251	278.2
New Hampshire	512	446	162	137	191	401.8
New Jersey	7,744	6,215	2,805	2,266	3,106	903.1
New Mexico§	223	201	121	99	149	120.4
New York	13,276	10,942	4,358	3,471	4,742	693.8
North Carolina§	1,947	1,658	691	612	896	234.4
North Dakota§	207	178	66	61	85	326.5
Ohio	3,411	2,863	1,193	1,033	1,457	299.0
Oklahoma	535	463	238	203	280	153.3
Oregon	815	694	353	300	425	231.5
Pennsylvania	4,329	3,427	1,264	1,045	1,449	351.1
Puerto Rico	318	291	110	83	119	82.4
Rhode Island	759	671	257	216	285	710.5
South Carolina§	772	656	324	265	362	188.1
South Dakota§	146	127	47	45	59	192.0
Tennessee	787	647	302	249	366	135.9
Texas§	5,716	4,827	2,159	1,828	2,559	263.0
Utah	574	483	207	183	258	247.5
Vermont	175	151	75	65	95	283.9
Virgin Islands, U.S. §	¶	¶	¶	¶	¶	¶
Virginia§	3,364	2,874	1,227	994	1,324	461.6
Washington	2,101	1,797	803	677	931	346.3
West Virginia	172	143	61	54	75	95.3
Wisconsin	1,231	1,087	397	337	478	226.3
Wyoming§	68	65	39	33	48	136.3
Non-U.S. resident	1,414	1,243	520	429	589	N/A
Total	**115,392**	**96,325**	**40,046**	**33,141**	**45,751**	**395.0****

* 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 four states had missing residency data for <10% of ART infants. Medical centers located in Georgia, Massachusetts, Minnesota, and New York had >10% missing residency data.

† **Source of population size:** July 1, 2002, 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, the 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, the District of Columbia, Georgia, Guam, Hawaii, Maine, Maryland, New Mexico, North Carolina, North Dakota, South Carolina, South Dakota, Texas, the U.S. Virgin Islands, Virginia, and Wyoming. States and territories for which >5% of ART procedures among state residents were performed in a military medical center were the District of Columbia, Guam, the U.S. Virgin Islands, and Virginia.

¶ 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, 2002

	Patient age (yrs)				
	<35 (n = 32,288) (%)	35–37 (n = 15,781) (%)	38–40 (n = 13,571) (%)	41–42 (n = 5,660) (%)	>42 (n = 2,557) (%)
Patient factors					
Diagnosis					
Tubal factor	14.3	15.4	14.4	9.7	7.3
Ovulatory dysfunction	8.2	5.2	4.0	3.0	3.1
Diminished ovarian reserve	1.4	2.9	7.0	14.8	24.3
Endometriosis	8.2	7.6	5.2	3.1	2.2
Uterine factor	0.9	1.5	1.8	1.9	1.8
Male factor	23.9	19.7	16.1	10.1	7.0
Other causes	4.3	5.2	6.5	7.9	8.6
Unexplained cause	10.4	12.7	12.4	12.2	10.0
Multiple factors, female only	10.2	11.5	14.0	16.2	16.5
Multiple factors, female and male	18.1	18.3	18.6	21.1	19.2
Number of previous ART procedures					
0	62.2	52.5	48.7	43.8	41.9
≥1	37.5	47.1	51.0	55.9	57.8
Number of previous births					
0	79.8	69.1	66.1	65.4	63.6
≥1	19.8	30.5	33.5	33.8	35.6
Treatment factors					
Method of embryo fertilization and transfer†					
IVF-ET without ICSI	36.3	38.1	39.3	40.1	42.6
IVF-ET with ICSI	62.9	61.2	59.9	58.7	56.0
IVF-ET with ICSI among couples diagnosed with male factor infertility	38.2	34.1	31.1	27.5	22.3
IVF-ET with ICSI among couples not diagnosed with male factor infertility	24.7	27.1	28.8	31.2	33.7
GIFT	0.2	0.2	0.3	0.3	0.6
ZIFT	0.5	0.4	0.5	0.7	0.6
Combination	0.1	0.1	0.1	0.2	0.3
No. of days of embryo culture§					
1	0.4	0.3	0.4	0.4	0.5
2	4.9	4.6	4.7	4.7	4.9
3	70.6	75.1	79.4	81.8	81.9
4	2.6	2.9	3.0	3.7	4.5
5	18.6	14.5	10.4	7.8	6.1
6	1.9	1.6	1.0	0.8	0.6
Number of embryos transferred					
1	4.6	6.4	8.3	12.0	15.3
2	42.8	27.3	18.8	16.6	19.6
3	36.9	36.6	29.7	22.2	19.3
4	11.5	21.7	27.2	22.6	18.1
≥5	4.2	8.1	15.9	26.5	27.6
Extra embryo(s) available and cryopreserved					
Yes	42.7	30.7	18.6	8.9	4.6
No	57.3	69.3	81.4	91.2	95.4
Use of gestational carrier					
Yes	0.7	1.1	1.2	1.2	1.1
No	99.3	98.9	98.8	98.8	98.9

* N = 69,857.
† 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, 2002

	Patient age (yrs)				
	<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	**43.0**	**37.1**	**26.4**	**14.7**	**6.6**
Patient factors					
Diagnosis					
Tubal factor	43.4*	37.2*	28.3*	14.5*	6.4
Ovulatory dysfunction	45.0	40.5	27.3	15.3	6.3
Diminished ovarian reserve	35.7	29.2	21.7	16.5	7.1
Endometriosis	43.9	37.4	31.6	20.3	7.0
Uterine factor	37.2	30.0	24.7	19.4	6.7
Male factor	45.2	39.2	28.2	15.4	4.4
Other causes	40.9	40.1	28.3	16.9	6.3
Unexplained cause	43.1	39.6	28.6	15.3	8.6
Multiple factors, female only	41.0	32.7	23.5	12.7	6.7
Multiple factors, female and male	40.9	35.7	23.9	12.1	5.9
Number of previous ART procedures					
0	45.2*	39.2*	28.1*	15.1	6.1
≥1	39.4	34.8	24.9	14.3	7.0
Number of previous births					
0	41.6*	35.6*	25.2*	14.0	6.4
≥1	48.5	40.3	28.7	15.9	7.0
Treatment factors					
Method of embryo fertilization and transfer†					
IVF-ET without ICSI	45.3*	39.9*	28.2*	17.2*	8.2*
IVF-ET with ICSI among couples diagnosed with male factor infertility	43.2	37.1	25.9	12.6	5.1
IVF-ET with ICSI among couples not diagnosed with male factor infertility	39.5	33.6	24.5	13.6	5.5
Number of days of embryo culture§					
3	41.9*	36.8*	25.7*	14.5*	6.3*
5	49.7	42.7	35.1	20.9	14.8
Number of embryos transferred					
1	20.8*	14.6*	10.4*	3.5*	1.0*
2	46.3	37.7	23.3	10.4	5.0
3	43.6	39.6	28.9	13.5	5.9
4	39.0	38.4	29.9	16.6	8.4
≥5	39.2	38.1	28.1	21.8	10.2
Extra embryo(s) available and cryopreserved					
Yes	50.4*	46.7*	38.1*	24.4*	15.3*
No	37.5	32.9	23.8	13.7	6.2
Use of gestational carrier					
Yes	49.2	43.7	27.8	24.2*	11.1
No	42.9	37.0	26.4	14.6	6.6

* 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 GIFT, 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 limited proportion of procedures.
§ Limited to 3 and 5 days to embryo culture. ART procedures including 1, 2, 4, and 6 days to embryo culture were not included because each of these accounted for a limited proportion of procedures.

TABLE 5. Multiple-birth risk, by type of assisted reproductive technology (ART) transfer procedure performed — United States, 2002

	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	24,324	8,601	35.4	33,776	18,053	53.4
	<35	13,882	5,399	38.9	19,842	11,359	57.2
	35–37	5,856	2,072	35.4	8,132	4,348	53.5
	38–40	3,587	965	26.9	4,628	2,006	43.3
	41–42	830	154	18.6	995	319	32.1
	>42	169	11	6.5	179	21	11.7
Thawed embryos	All ages	3,620	890	24.6	4,592	1,862	40.5
	<35	2,145	563	26.2	2,767	1,185	42.8
	35–37	836	189	22.6	1,043	396	38.0
	38–40	466	92	19.7	563	189	33.6
	41–42	116	30	25.9	145	59	40.7
	>42	57	16	28.1	74	33	44.6
Donor's eggs used†							
Freshly fertilized embryos	All ages	4,195	1,779	42.4	6,088	3,672	60.3
Thawed embryos	All ages	1,002	274	27.3	1,295	567	43.8
Total	**All ages**	**33,141**	**11,544**	**34.8**	**45,751**	**24,154**	**52.8**

* 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. 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, 2002

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 higher order deliveries (%)
Alabama	258	144	55.8	42.6	13.2
Alaska§	41	23	56.1	48.8	7.3
Arizona	668	381	57.0	44.6	12.4
Arkansas	161	82	50.9	42.2	8.7
California	6,001	3,189	53.1	46.5	6.7
Colorado	973	556	57.1	47.6	9.6
Connecticut	625	319	51.0	45.3	5.8
Delaware	154	75	48.7	40.3	8.4
District of Columbia§	177	75	42.4	37.3	5.1
Florida	2,020	1,055	52.2	45.0	7.3
Georgia§	1,082	590	54.5	43.3	11.2
Guam§	¶	¶	¶	¶	¶
Hawaii§	233	124	53.2	42.9	10.3
Idaho	203	121	59.6	52.2	7.4
Illinois	2,598	1,352	52.0	44.8	7.3
Indiana	668	368	55.1	41.6	13.5
Iowa	422	220	52.1	47.9	4.3
Kansas	317	187	59.0	51.4	7.6
Kentucky	450	268	59.6	45.6	14.0
Louisiana	231	110	47.6	38.5	9.1
Maine§	84	54	64.3	57.1	7.1
Maryland§	1,423	702	49.3	45.0	4.4
Massachusetts	3,086	1,489	48.3	43.1	5.2
Michigan	1,282	675	52.7	45.9	6.7
Minnesota	942	440	46.7	40.7	6.1
Mississippi	145	78	53.8	31.0	22.8
Missouri	608	353	58.1	48.7	9.4
Montana	55	30	54.5	43.6	10.9
Nebraska	260	132	50.8	40.8	10.0
Nevada	251	148	59.0	50.2	8.8
New Hampshire	191	104	54.5	48.2	6.3
New Jersey	3,106	1,614	52.0	45.2	6.7
New Mexico§	149	96	64.4	56.4	8.1
New York	4,742	2,448	51.6	45.2	6.4
North Carolina§	896	540	60.3	51.1	9.2
North Dakota§	85	46	54.1	44.7	9.4
Ohio	1,457	803	55.1	45.8	9.3
Oklahoma§	280	147	52.5	40.7	11.8
Oregon	425	241	56.7	50.6	6.1
Pennsylvania	1,449	764	52.7	43.7	9.0
Puerto Rico	119	65	54.6	36.1	18.5
Rhode Island	285	141	49.5	47.4	2.1
South Carolina§	362	189	52.2	43.9	8.3
South Dakota§	59	26	44.1	28.8	15.3
Tennessee	366	213	58.2	41.0	17.2
Texas§	2,559	1,408	55.0	48.5	6.6
Utah	258	143	55.4	47.3	8.1
Vermont	95	57	60.0	50.5	9.5
Virgin Islands, U.S.§	¶	¶	¶	¶	¶
Virginia§	1,324	629	47.5	40.2	7.3
Washington	931	492	52.8	47.0	5.8
West Virginia	75	40	53.3	45.3	8.0
Wisconsin	478	272	56.9	49.2	7.7
Wyoming§	48	30	62.5	62.5	0.0
Non-U.S. resident	589	306	52.0	45.5	6.5
Total	**45,751**	**24,154**	**52.8**	**45.3**	**7.5**

* 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 four states had missing residency for <10% of ART infants. Medical centers located in Georgia, Massachusetts, Minnesota, and New York had >10% missing residency data.

† Numbers might not sum to total because of rounding.

§ 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, the District of Columbia, Georgia, Guam, Hawaii, Maine, Maryland, New Mexico, North Carolina, North Dakota, South Carolina, South Dakota, Texas, the U.S. Virgin Islands, Virginia, and Wyoming. States and territories for which >5% of ART procedures among state residents were performed in a military medical center were the District of Columbia, Guam, the U.S. Virgin Islands, and Virginia.

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

TABLE 7. Effect of assisted reproductive technology (ART) on the total live-born infants in the United States, by plurality — United States, 2002

Plurality	Number of ART infants*† (% of total)	Number of total U.S. infants§ (% of total)	Contribution of ART to total infants born in the United States (%)
Infants born in singleton deliveries	19,829 (46.7%)	3,889,191 (96.7%)	0.5
Infants born in multiple-birth deliveries	22,654 (53.3%)	132,535 (3.3%)	17.1
Twin deliveries	19,409 (45.7%)	125,134 (3.1%)	15.5
Triplets or higher-order deliveries	3,245 (7.6%)	7,401 (0.2%)	43.8
Total number of infants	**42,483**	**4,021,726**	**1.1**

* **Source:** Assisted Reproductive Technology Surveillance System.
† Includes infants conceived from ART procedures performed in 2001 and born in 2002 and infants conceived from ART procedures performed in 2002 and born in 2002.
§ **Source:** U.S. natality file, CDC, National Center for Health Statistics.

TABLE 8. Percentage of adverse perinatal outcomes* among assisted reproductive technology (ART) infants born in 2002, by plurality — United States†

Plurality	LBW (%)	VLBW (%)	Preterm (%)	Preterm LBW (%)	Term LBW (%)
ART singletons (n = 19,829)	9.1	1.9	14.5	7.1	2.1
ART twins (n = 19,409)	54.3	8.8	61.7	44.9	9.5
ART triplets or higher-order multiples (n = 3,245)	94.8	30.7	97.2	92.6	§

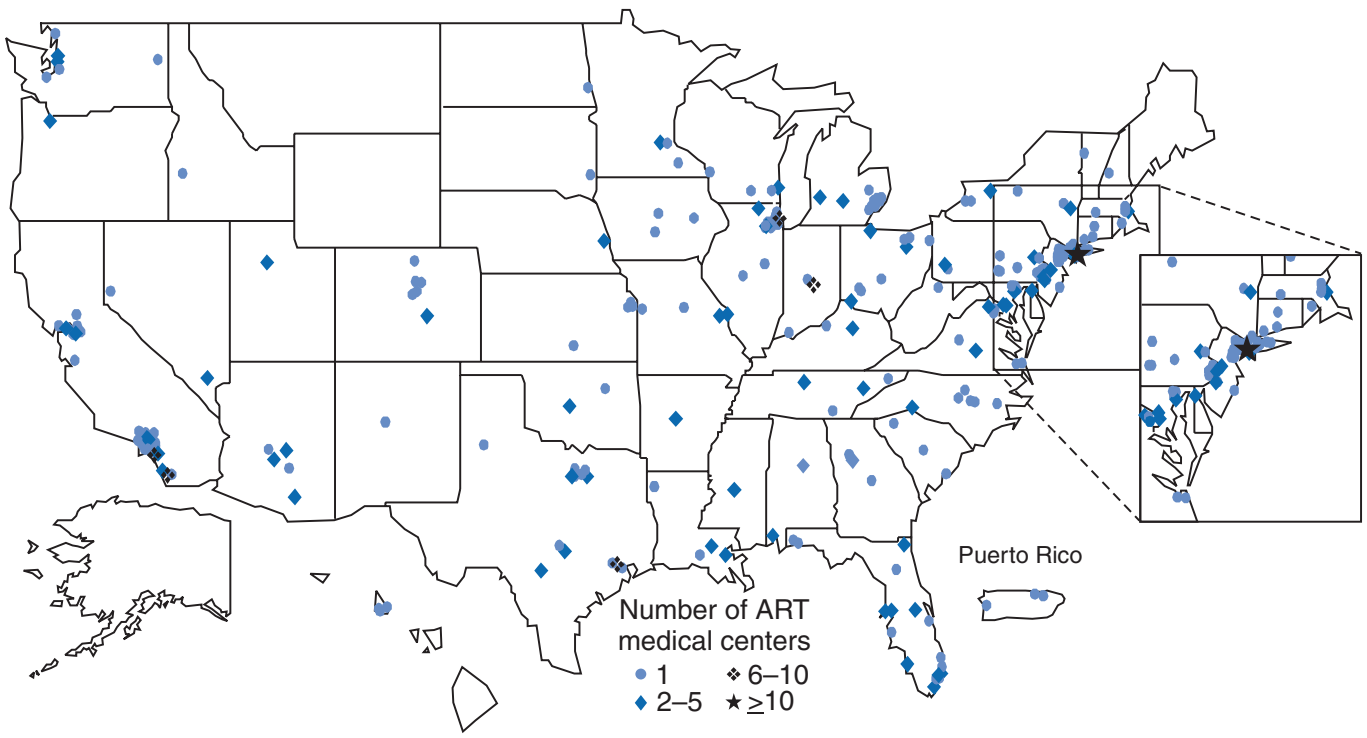
* LBW = low birthweight (<2,500 g); VLBW = very low birthweight (<1,500 g); preterm = gestational age <37 weeks; preterm LBW = gestational age <37 weeks and low birthweight (<2,500 g); and term LBW = gestational age ≥37 weeks and low birthweight (<2,500 g).
† Includes infants conceived from ART procedures performed in 2001 and born in 2002 and infants conceived from ART procedures performed in 2002 and born in 2002. Samples for calculation 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 9. Adverse perinatal outcomes* among assisted reproductive technology (ART) singleton infants born in 2002, by procedure type and selected maternal factors — United States†

Procedure type/Maternal factor	LBW (%)	VLBW (%)	Preterm (%)	Preterm LBW (%)	Term LBW (%)
Freshly fertilized embryos, patient eggs (n = 14,615)	**9.3§**	**1.9**	**13.3§**	**7.0§**	**2.3§**
Maternal age (yrs)					
<35	9.3	1.8	13.5	7.0	2.3
35–37	9.1	2.1	13.0	7.0	2.1
38–40	9.6	1.9	13.4	7.2	2.4
41–42	10.0	2.5	13.7	7.5	2.4
>42	7.0	¶	9.5	¶	¶
Maternal race/ethnicity**					
Non-Hispanic white	9.2††	1.7††	13.5††	6.9††	2.2
Non-Hispanic black	18.2	5.1	21.9	14.3	4.0
Hispanic	12.7	2.3	15.7	10.0	2.7
Asian	11.0	2.5	12.3	7.5	3.3
Number of previous births§§					
0	9.8††	2.0	13.2††	7.3††	2.5
1	7.5	1.4	12.4	5.7	1.7
≥2	10.0	2.2	16.7	7.8	2.3
Freshly fertilized embryos, donors eggs (n = 2,199)	**10.7**	**2.1**	**16.3**	**9.0**	**1.8**
Thawed embryos¶¶ (n = 3,015)	**7.2**	**1.6**	**18.9**	**6.0**	**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 2001 and born in 2002 and infants conceived from ART procedues performed in 2002 and born in 2002. 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.
¶ Risk for outcome not provided if number of cases in a given subgroup is <10.
** Analysis did not include 43% of ART singletons for whom data on maternal race/ethnicity were missing. Analysis did not include 0.1% of ART singletons with mothers whose race/ethnicity was Native American or Other because of limited sample size and ensuing unstable estimates for perinatal outcomes.
†† P<0.01; chi-square to test for variations in adverse perinatal outcomes across maternal factor categories.
§§ Analysis did not include 0.4% of ART singletons for whom maternal data on number of previous births were missing.
¶¶ Includes cycles in which thawed embryos were used from patient eggs and donor eggs.

FIGURE 1. Location of assisted reproductive technology (ART) medical centers — United States and Puerto Rico, 2002



Number of ART medical centers in the United States in 2002	428
Number of U.S. ART medical centers that submitted data in 2002	391
Number of ART cycles reported for 2002	115,392*
Number of live-birth deliveries resulting from ART cycles started in 2002	33,141
Number of infants born as a result of ART cycles carried out in 2002	45,751

* This number does not include 146 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, 2002

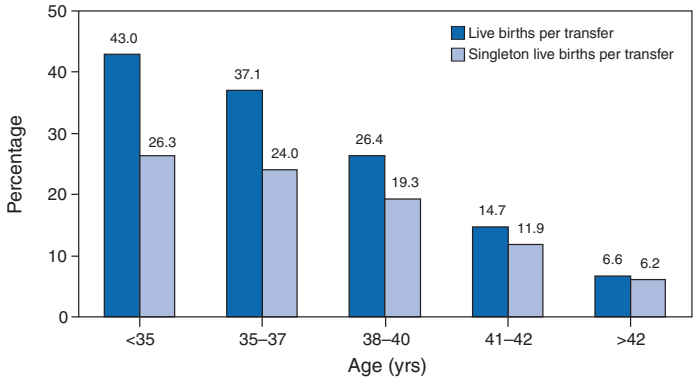
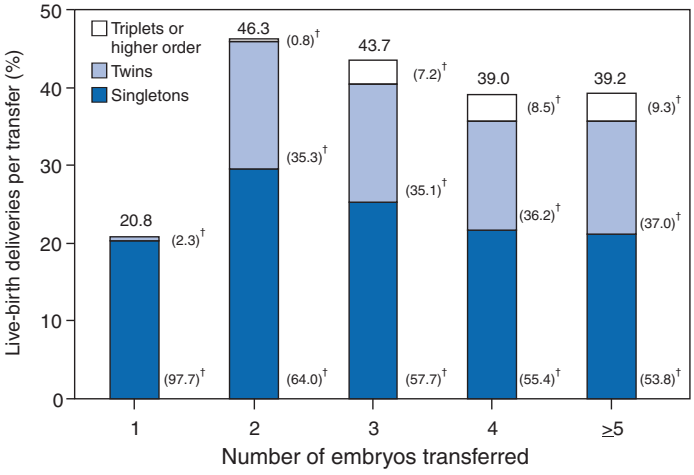


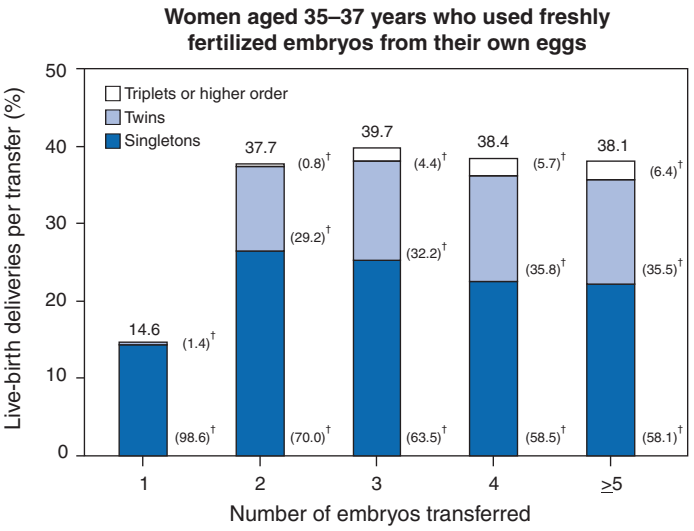
FIGURE 3. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2002*

Women aged <35 years who used freshly fertilized embryos from their own eggs



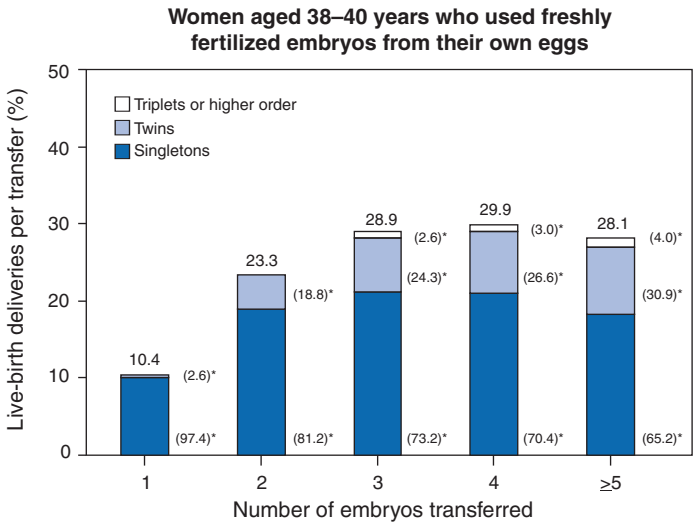
* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

FIGURE 4. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2002*



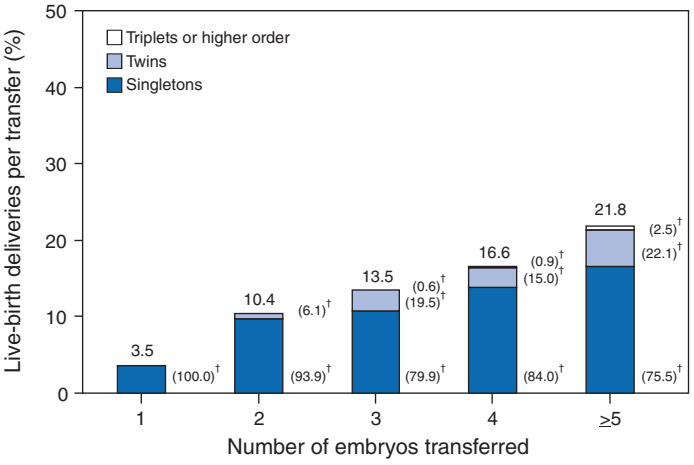
* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

FIGURE 5. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2002



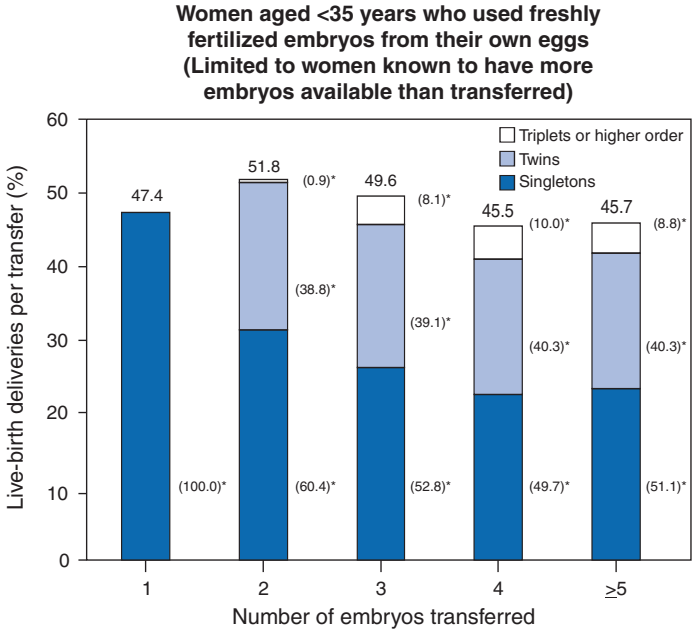
* Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

FIGURE 6. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2002*



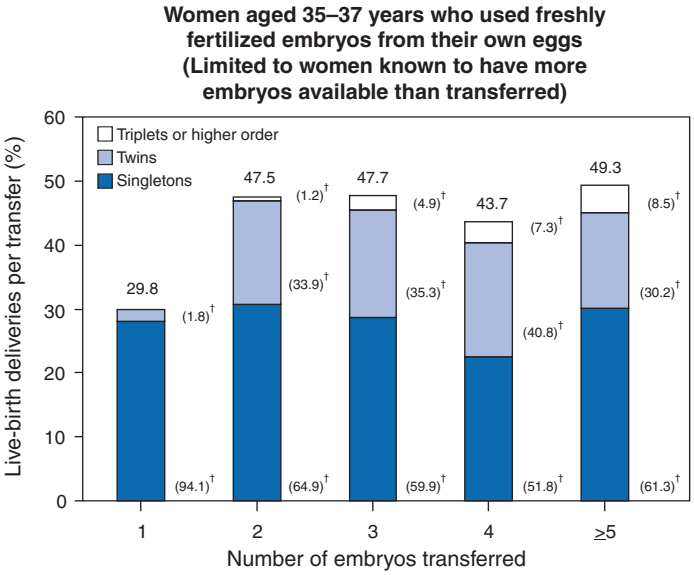
* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

FIGURE 7. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2002



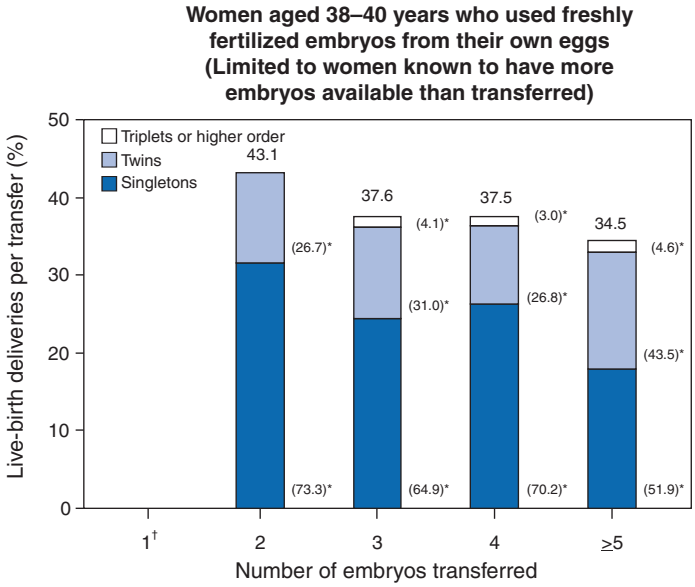
* Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

Figure 8. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2002*



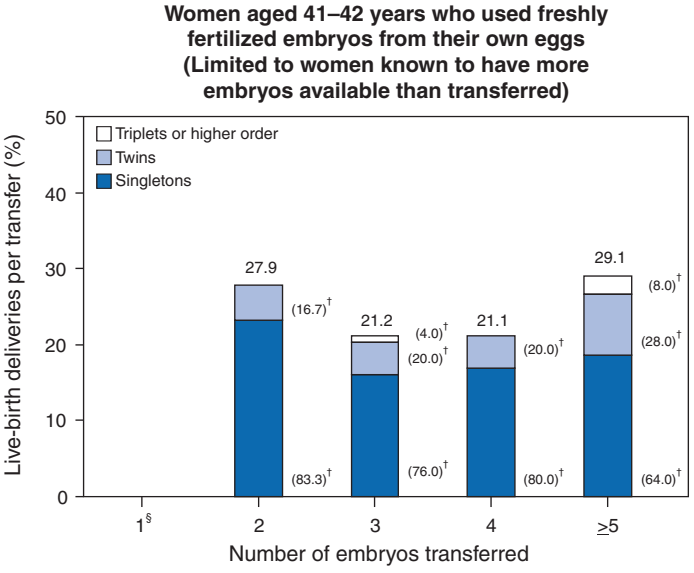
* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

Figure 9. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2002



* Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.
† Statistics are not provided in cases where the denominator is <10.

Figure 10. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2002*



* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.
§ Statistics are not provided in cases where the denominator is <10.

Malaria Surveillance — United States, 2003

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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 transmission. In the United States, cases can also occur through exposure to infected blood products, by congenital transmission, or by local mosquitoborne transmission. Malaria surveillance is conducted to identify episodes of local transmission and to guide prevention recommendations for travelers.

Period Covered: This report covers cases with onset of illness in 2003, and summarizes trends over 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 1,278 cases of malaria with an onset of symptoms in 2003, including seven fatal cases, among persons in the United States or one of its territories. This number represents a decrease of 4.4% from the 1,337 cases reported for 2002. *P. falciparum, P. vivax, P. malariae, and P. ovale* were identified in 53.3%, 22.9%, 3.6%, and 2.6% of cases, respectively. Twelve patients (0.9% of total) were infected by two or more species. The infecting species was unreported or undetermined in 212 (16.6%) cases. Compared with 2002, the number of reported malaria cases acquired in Asia (n = 177) and the Americas (n = 147) increased by 3.5% and 4.3% respectively, whereas the number of cases acquired in Africa (n = 840) decreased by 7.0%. Of 762 U.S. civilians who acquired malaria abroad, 132 (17.3%) reported that they had followed a chemoprophylactic drug regimen recommended by CDC for the area to which they had traveled. Ten patients became infected in the United States, including one probable transfusion-related, one in which epidemiologic investigations failed to identify any apparent mode of acquisition, and eight which were introduced cases as a result of local mosquitoborne transmission. Of the seven deaths attributed to malaria, five were caused by *P. falciparum*, and a species was not identified in the other two.

Interpretation: The 4.4% decrease in malaria cases in 2003, compared with 2002, resulted primarily from a decrease in cases acquired in Africa, but this decrease was offset by an increase in the number of cases acquired in the Americas and Asia. This small decrease probably represents year-to-year variation in malaria cases, but also could have resulted from local changes in disease transmission, decreased travel to malaria-endemic regions, or fluctuation in reporting to state and local health departments. In the majority of reported cases, U.S. civilians who acquired infection abroad were not on an appropriate chemoprophylaxis regimen for the country in which they acquired malaria.

Public Health Actions: Additional information was obtained concerning the seven fatal cases and the 10 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 travelers should use personal protection measures to prevent mosquito bites. Any person who has been to a malarious area and who subsequently experiences 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 by calling the Malaria Hotline at 770-488-7788 or by accessing CDC's Internet site at http://www.cdc.gov/travel. Recommendations concerning diagnosis of malaria and its treatment can be obtained by calling the Malaria Hotline or accessing CDC's Internet site at http://www.cdc.gov/malaria/diagnosis_treatment/treatment.htm.

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Introduction

Malaria 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 infection remains a devastating global problem, with an estimated 300–500 million cases occurring annually (*1*). Forty-one percent of the world's population lives in areas where malaria is transmitted (e.g., parts of Africa, Asia, the Middle East, Central and South America, Hispaniola, and Oceania) (*1*), and 700,000–2.7 million persons die of malaria each year, 75% of them African children (*2*). Before the 1950s, malaria was endemic throughout the southeastern United States; an estimated 600,000 cases occurred in 1914 (*3*). 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 antimalarial drug resistance. Anopheline mosquitos remain seasonally present in all states and territories except Guam and Hawaii.

The majority of reported cases of malaria each year diagnosed in the United States have been imported from regions of the world 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 (*4*), typically <1% per year.

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 (*5*).

The signs and symptoms of malaria illness are varied, but the majority of patients experience fever. Other common symptoms include headache, back pain, chills, sweating, myalgia, nausea, vomiting, diarrhea, and cough. The diagnosis of malaria should be considered for persons who experience these symptoms and who have traveled to an area with known malaria transmission. Malaria should also be considered in the differential diagnoses of persons who experience fevers of unknown origin, regardless of their travel history. Untreated *P. falciparum* infections can rapidly progress to coma, renal failure, pulmonary edema, and death. Asymptomatic parasitemia can occur, most commonly among persons who have been long-term residents of areas where malaria is endemic. This report summarizes malaria cases reported to CDC with onset of symptoms in 2003.

Methods

Data Sources

Malaria case data are reported to the National Malaria Surveillance System (NMSS) and the National Notifiable Diseases Surveillance System (*6*). 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 about each case (e.g., information about the area to which the infected person has traveled). This report presents only data about cases reported to NMSS.

Cases of blood-film–confirmed malaria among civilians and military personnel are identified by health-care providers or laboratories. Each slide-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. Cases reported directly to CDC are 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. U.S. military and civilian cases diagnosed outside of the United States and its territories are not reported through this system and are not included in this report.

Definitions

The following definitions are used in this report:

- **Laboratory criteria for diagnosis:** Demonstration of malaria parasites on blood film.
- **Confirmed case:** Symptomatic or asymptomatic infection that occurs in a person in the United States who has microscopically confirmed malaria parasitemia, regardless of whether the person had previous episodes of malaria while in other countries. A subsequent episode of

malaria is counted as an additional case if the indicated *Plasmodium* sp. differs from the initially identified species. A subsequent episode of malaria occurring in a person while in the United States could indicate a relapsing infection or treatment failure resulting from drug resistance if the indicated *Plasmodium* sp. is the same species identified previously.

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

- **Autochthonous malaria:**
  - — **Indigenous.** Mosquitoborne transmission of malaria in a geographic area where malaria occurs regularly.
  - — **Introduced.** Mosquitoborne transmission of malaria from 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 (Puerto Rico, Guam, 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., clinical symptoms or parasitemia) of malarial infection that is 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 where epidemiologic investigations fail to identify a plausible mode of acquisition (this term applies mainly to cases identified in countries where malaria is not endemic).

Microscopic 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 an area where malaria is endemic. 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).

* 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 2003, CDC received 1,278 malaria case reports occurring among persons in the United States and its territories, representing a 4.4% decrease from the 1,337 cases reported with a date of onset in 2002 (*8*) (Table 1). In 2003, a total of 767 cases occurred among U.S. civilians and 306 cases among foreign civilians (Table 1). In recent years, cases among U.S. civilians have increased and cases among foreign-born civilians have decreased (Figure 1). These trends are probably a result of increased travel among U.S. citizens and decreased immigration since 2001.

TABLE 1. Number of malaria cases* among U.S. and foreign civilians and U.S. military personnel — United States, 1973–2003

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**

* A case was defined as symptomatic or asymptomatic illness that occurs in the United States in a person who has microscopy-confirmed 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 occurred in the 1990s might be attributed to a change in the surveillance form.

Plasmodium Species

The infecting species of *Plasmodium* was identified in 1,066 (83.4%) of the cases reported in 2003. *P. falciparum* and *P. vivax* were identified in blood films from 53.4% and 22.9% of infected persons, respectively (Table 2). The 682 *P. falciparum* cases reported for 2003 represented a 2.4% decrease from the 699 cases in 2002, and the number of *P. vivax* infections decreased by 13.6% (from 339 in 2002 to 293 in 2003). Among 1,015 cases in which both the region of acquisition and the infecting species were known, 83.5 % of infections acquired in Africa were attributed to *P. falciparum*; 7.0% were attributed to *P. vivax*. The converse was true of infections acquired in the Americas and Asia: 62.9% and 80.4% were attributed to *P. vivax*, and 31.5% and 12.0% were attributed to *P. falciparum*, respectively.

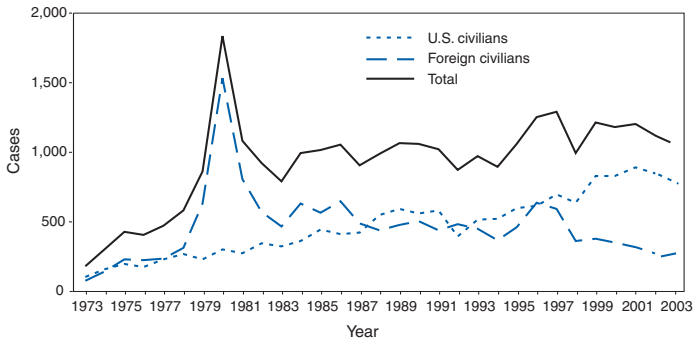
Region of Acquisition and Diagnosis

All but 10 reported cases (n = 1,268) were imported. Of 1,201 imported cases in which the region of acquisition was known, the majority (70.0%; n = 840) were acquired in Africa; 14.7 % (n = 177) and 12.3% (n = 147) were acquired in Asia and the Americas, respectively (Table 3). A limited number of imported cases were acquired in Oceania (3.1%; n = 37). The highest concentration of cases acquired in Africa came from countries in West Africa (67.5%; n = 567); a substantial percentage of cases acquired in Asia came from the Indian subcontinent (56.5%; n = 100). From within the Americas, the majority of cases were acquired in Central America and the Caribbean (63.9%; n = 94), followed by South America (21.8%; n = 32) and Mexico (14.3% n=21). Information about region of acquisition was missing for 67 (5.3%) of the imported cases.

Compared with 2002, the number of reported malaria cases acquired in Asia and the Americas increased by 3.5% and 4.3% respectively, and the number of cases acquired in Africa decreased 7.0%.

In the United States, the six health departments reporting the highest number of malaria cases were New York City (n = 191), California (n = 155), Florida (n = 86), Maryland (n = 73), Georgia (n = 68), and New York State (n = 68) (Figure 2). The majority of these health departments reported a decrease in cases compared with 2002, consistent with the overall decrease in cases occurring nationwide. This decrease probably represents year-to-year variation in malaria cases rather than a trend, but could also have resulted from local changes in disease transmission abroad, decreased travel to malaria-endemic regions, or fluctuation in reporting to state and local health departments.

FIGURE 1. Number of malaria cases among U.S. and foreign civilains, by year — United States,* 1973–2003†



* Includes Puerto Rico, Guam, 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.

Interval Between Arrival and Illness

The interval between date of arrival in the United States and onset of illness and the infecting *Plasmodium* species was known for 640 (50.5 %) of the imported malaria cases (Table 4). Symptoms began before arrival in the United States for 77 (12.0%) persons, and symptoms began after arrival in the United States for 563 (88.0%) persons. Clinical malaria occurred within 1 month after arrival in 363 (79.4%) of the 457 persons with *P. falciparum* cases and in 57 (42.2%) of the 135 persons with *P. vivax* cases (Table 4). Only five (0.8%) of the 640 persons became ill >1 year after returning to the United States.

TABLE 2. Number of malaria cases, by *Plasmodium* species — United States, 2001, 2002, and 2003

Plasmodium species	2001		2002		2003	
	No.	(%)	No.	(%)	No.	(%)
P. falciparum	693	(50.1)	699	(52.3)	682	(53.4)
P. vivax	385	(27.8)	339	(25.4)	293	(22.9)
P. malariae	62	(4.5)	38	(2.8)	46	(3.6)
P. ovale	50	(3.6)	37	(2.8)	33	(2.6)
Mixed	14	(1.0)	11	(0.8)	12	(0.9)
Undetermined	179	(12.9)	213	(15.9)	212	(16.6)
Total	**1,383**	**(100.0)**	**1,337**	**(100.0)**	**1,278**	**(100.0)**

TABLE 3. Imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2003

Country of acquisition	*Plasmodium* species						
	P. falciparum	*P. vivax*	*P. malariae*	*P. ovale*	Unknown	Mixed	Total
Africa	**587**	**49**	**31**	**29**	**137**	**7**	**840**
Angola	2	0	0	0	1	0	3
Benin	1	0	0	0	0	1	2
Burkina Faso	2	0	0	0	0	0	2
Burundi	0	0	0	0	0	0	0
Cameroon	29	3	2	2	5	0	41
Central African Republic	1	0	0	0	0	0	1
Chad	2	0	0	0	0	0	2
Comoros	0	0	0	0	1	0	1
Congo	9	2	3	0	1	1	16
Cote d'Ivoire	16	0	0	1	1	0	18
Democratic Republic of Congo	1	0	0	0	0	0	1
Equatorial Guinea	2	0	0	0	1	0	3
Eritrea	0	1	0	0	0	0	1
Ethiopia	3	5	0	1	3	0	12
Gabon	2	0	0	0	0	1	3
Gambia	15	0	2	0	3	0	20
Ghana	93	4	4	2	18	1	122
Guinea	11	1	2	3	5	1	23
Kenya	37	8	1	3	10	0	59
Liberia	16	1	0	0	5	0	22
Malagasy Republic	1	0	0	0	0	0	1
Malawi	3	0	0	1	0	0	4
Mali	11	0	0	0	0	0	11
Mauritania	0	2	0	0	0	0	2
Morocco	1	0	0	0	0	0	1
Mozambique	4	0	1	0	0	0	5
Niger	3	0	0	0	1	0	4
Nigeria	182	6	5	6	39	2	240
Rwanda	0	0	0	0	0	0	0
Senegal	27	1	1	0	5	0	34
Sierra Leone	30	0	1	2	9	0	42
Somalia	1	0	0	0	0	0	1
South Africa	6	2	1	0	0	0	9
Sudan	2	2	0	0	2	0	6
Tanzania	4	1	1	0	2	0	8
Togo	4	0	0	0	1	0	5
Tunisia	0	0	0	0	0	0	0
Uganda	14	4	4	4	12	0	38
Zambia	4	0	0	0	0	0	4
Zimbabwe	4	0	0	0	0	0	4
West Africa, unspecified	15	0	1	2	3	0	21
Central Africa, unspecified	0	0	0	0	0	0	0
East Africa, unspecified	0	0	0	0	0	0	0
Africa, unspecified	29	6	2	2	9	0	48
Asia	**19**	**127**	**7**	**3**	**19**	**2**	**177**
Afghanistan	1	10	0	0	2	0	13
Cambodia	0	2	0	0	0	0	2
China	0	1	0	0	0	0	1
India	12	76	3	2	7	0	100
Indonesia	1	6	0	1	1	0	9
Iraq	0	7	0	0	1	0	8
Korea (South)	0	7	1	0	0	0	8
Lao PDR	1	0	0	0	0	0	1
Malaysia	0	0	0	0	1	0	1
Nepal	0	0	0	0	1	0	1
Pakistan	2	15	3	0	2	1	23
Philippines	0	0	0	0	1	0	1
Thailand	0	2	0	0	1	1	4
United Arab Emirates	0	0	0	0	0	0	0
Vietnam	1	1	0	0	0	0	2
Yemen	1	0	0	0	1	0	2
Asia, unspecified	0	0	0	0	0	0	0
Southeast Asia, unspecified	0	0	0	0	1	0	1

TABLE 3. (*Continued*) Imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2003

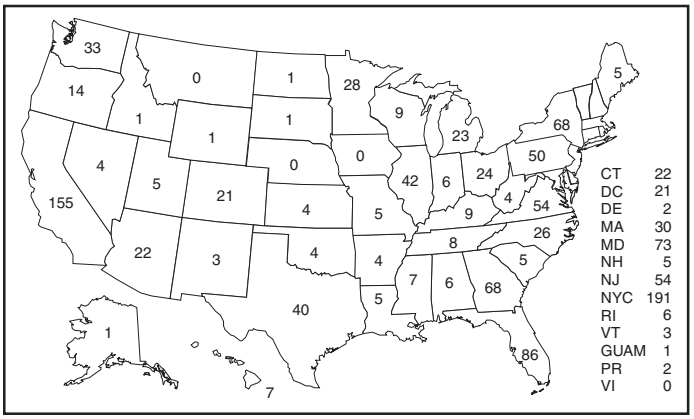
Country of acquisition	*Plasmodium* species						
	P. falciparum	*P. vivax*	*P. malariae*	*P. ovale*	Unknown	Mixed	Total
Central America and the Caribbean	**28**	**45**	**2**	**0**	**18**	**1**	**94**
Belize	0	1	0	0	0	0	1
Costa Rica	1	0	0	0	2	0	3
Dominican Republic	0	1	0	0	0	0	1
El Salvador	1	3	0	0	0	0	4
Guatemala	1	12	0	0	2	1	16
Haiti	17	1	0	0	5	0	23
Honduras	8	24	1	0	9	0	42
Nicaragua	0	1	1	0	0	0	2
Panama	0	1	0	0	0	0	1
Central America, unspecified	0	1	0	0	0	0	1
North America	**5**	**14**	**1**	**0**	**1**	**0**	**21**
Mexico	5	14	1	0	1	0	21
South America	**6**	**17**	**1**	**0**	**6**	**2**	**32**
Bolivia	0	0	0	0	1	0	1
Brazil	1	5	0	0	1	0	7
Ecuador	0	3	1	0	1	0	5
Guyana	3	3	0	0	0	1	7
Peru	2	4	0	0	1	1	8
Venezuela	0	0	0	0	1	0	1
South America, unspecified	0	2	0	0	1	0	3
Oceania	**2**	**24**	**3**	**1**	**7**	**0**	**37**
Marshall Islands	0	0	1	0	0	0	1
Papua New Guinea	2	20	1	0	6	0	29
Solomon Islands	0	1	0	0	0	0	1
Vanuatu	0	2	0	0	1	0	3
Oceania unspecified	0	1	1	1	0	0	3
Europe/Newly Independent States	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Unknown	**33**	**10**	**1**	**0**	**23**	**0**	**67**
Total	**680**	**286**	**46**	**33**	**211**	**12**	**1268**

Imported Malaria Cases

Imported Malaria Among U.S. Military Personnel

In 2003, a total of 36 cases of imported malaria was reported among U.S. military personnel. These cases were reported by state health departments. Of these, 28 (77.8%) had been acquired in Asia, five (13.9%) in the Americas, two (5.6%) in Africa, and one (2.8%) in Oceania. This is similar to the distribution of cases in 2002.

FIGURE 2. Number of malaria cases, by state in which the disease was diagnosed — United States, 2003



Imported Malaria Among Civilians

A total of 1,066 imported malaria cases were reported among civilians. Of these, 761 (71.4%) occurred among U.S. residents, and 305 (28.6%) cases occurred among residents of other countries (Table 5). Of the 761 imported malaria cases among U.S. civilians, 561 (73.7%) had been acquired in Africa, a decrease of 12.5% from cases reported in 2002. Asia accounted for 83 (10.9%) cases of imported malaria among U.S. civilians, and travel to the Central American and Caribbean regions accounted for 59 (7.6%) cases. Of the 305 imported cases among foreign civilians, the majority of cases were acquired in Africa (n = 202; 66.2%).

Antimalarial Chemoprophylaxis Use

Chemoprophylaxis Use Among U.S. Military Personnel

Information about chemoprophylaxis use and travel area was known for 33 (91.7%) of the 36 U.S. military personnel who had imported malaria. Of these 33 persons, eight (24.2%)

TABLE 4. Number of imported malaria cases, by interval between date of arrival in the country and onset of illness and *Plasmodium* species* — United States, 2003

	P. falciparum		*P. vivax*		*P. malariae*		*P. ovale*		Mixed		Total	
Interval (days)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<<0†	59	(12.9)	15	(11.1)	1	(4.3)	0	0	2	(22.2)	**77**	**(12.0)**
0–29	363	(79.4)	57	(42.2)	13	(60.0)	6	(37.5)	4	(44.4)	**443**	**(69.2)**
30–89	28	(6.1)	27	(20.0)	4	(17.4)	3	(18.8)	1	(11.1)	**63**	**(9.8)**
90–179	2	(0.4)	19	(14.1)	4	(17.4)	4	(25.0)	2	(22.2)	**31**	**(4.8)**
180–364	2	(0.4)	16	(11.9)	1	(4.3)	2	(12.5)	0	0	**21**	**(3.3)**
≥365	3	(0.7)	1	(0.7)	0	0	1	(6.3)	0	0	**5**	**(0.8)**
Total	**457**	**(100.0)**	**135**	**(100.0)**	**23**	**(100.0)**	**16**	**(100.0)**	**9**	**(100.0)**	**640**	**(100.0)**

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

were not using any chemoprophylaxis, two (6.1%) had not taken a CDC-recommended drug for the area visited, and 23 (69.7%) took a CDC-recommended medication. Of the 23 U.S. military personnel who took a CDC-recommended medication for the area visited, 10 (43.5%) reported taking doxycycline daily, two of those in combination with primaquine for terminal prophylaxis; seven (30.4%) had taken mefloquine weekly, one in combination with primaquine; four (17.4%) who had traveled to areas where chloroquine-resistant malaria has not been documented had taken chloroquine weekly, three in combination with primaquine; none had taken atovaquone-proguanil; and two (8.7%) had taken a combination of drugs that included more than one CDC-recommended medication for the travel region.

Chemoprophylaxis Use Among U.S. Civilians

Information about chemoprophylaxis use and travel area was known for 709 (93.2%) of the 761 U.S. civilians who had imported malaria. Of these 709 persons, 445 (62.8%) had not taken any chemoprophylaxis, and 111 (15.7%) had not taken a CDC-recommended drug for the area visited (*9*). Only 132 (18.6%) U.S. civilians had taken a CDC-recommended medication (*9*). Data for the specific drug taken were missing for the remaining 21 (3.0%) travelers. A total of 85 (64.4%) patients on CDC-recommended prophylaxis had reported taking mefloquine weekly; 35 (26.5%) had taken doxycycline daily; none had taken atovaquone-proguanil daily; and five (3.8%) who had traveled only in areas where chloroquine-resistant malaria has not been documented had taken chloroquine weekly. Information about adherence to the drug regimen for these persons is presented in the following section. Seven patients (5.3%) had taken combinations of drugs that included one or more CDC-recommended drug for the travel region. Of the 111 patients taking a nonrecommended drug, 47 (42.3%) 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 167 patients (132 U.S. civilians, 23 persons in the U.S. military, six foreign civilians, and six persons whose information about their status was missing) contracted malaria after taking a recommended antimalarial drug for chemoprophylaxis. Of these, 58 (34.7%) reported compliance with the regimen, 79 (47.3%) reported noncompliance, and compliance was unknown for the remaining 30 (18.0%). Infor-

TABLE 5. Number of imported malaria cases among U.S. and foreign civilians, by region of acquisition — United States, 2003*

	United States		Foreign		Total	
Area or region	No.	(%)	No.	(%)	No.	(%)
Africa	561	(73.7)	202	(66.2)	763	(71.6)
Asia	83	(10.9)	54	(17.7)	137	(12.9)
Central America and the Caribbean	59	(7.6)	24	(7.9)	83	(7.8)
South America	21	(2.8)	8	(2.6)	29	(2.7)
North America	6	(0.8)	12	(3.9)	18	(1.7)
Oceania	26	(3.4)	4	(1.1)	30	(2.8)
Europe/Newly Independent States	0	(0)	0	(0)	0	(0)
Unknown†	5	(0.7)	1	(0.3)	6	(0.6)
Total	**761**	**(100.0)**	**305**	**(100.0)**	**1,066**	**(100.0)**

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

mation about infecting species was available for 131 (78.4%) patients taking a recommended antimalarial drug; the infecting species was undetermined for the remaining 36.

Cases of *P. vivax* or *P. ovale* After Recommended Prophylaxis Use. Of the 167 patients who had malaria diagnosed after recommended chemoprophylaxis use, 65 (38.9 %) had cases that were caused by *P. vivax* and three (1.8%) by *P. ovale*.

A total of 18 (26.5%) cases of *P. vivax* or *P. ovale* 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 about symptom onset or return date to assess whether 34 cases were relapsing infections. Sixteen cases, 15 by *P. vivax* and one by *P. ovale*, occurred <45 days after the patient returned to the United States. Nine of the 16 patients were known to be noncompliant with their antimalarial chemoprophylaxis regimen. Four patients reported compliance with an antimalarial chemoprophylaxis regimen. Of these four, one had traveled to Asia, one to sub-Saharan Africa, and two to South America. One of these patients reported taking mefloquine and three reported using doxycycline. Blood samples for serum drug levels were not available for these four patients. The possible explanations for these cases include inappropriate dosing, noncompliance that was not reported, malabsorption of the drug, or emerging parasite resistance. For the remaining three patients, no information was available about compliance. The region of acquisition varied for these three patients (one from Ethiopia, one from Mexico, and one from Papua New Guinea).

Cases of *P. falciparum* and *P. malariae* after Recommended Prophylaxis Use. The remaining 99 cases of malaria reported among persons who had taken a recommended antimalarial drug for chemoprophylaxis include 54 cases of *P. falciparum*, six cases of *P. malariae*, three cases of mixed infection, and 36 cases in which the infecting species was unidentified.

A total of 52 of the 54 *P. falciparum* cases among those who reported taking a recommended antimalarial drug were acquired in Africa and two in South America. In 33 (61.1%) of these 54 cases, noncompliance with antimalarials was reported. In 14 (26.0%) of these 54 cases, patients reported compliance with antimalarial chemoprophylaxis. All 14 of these patients had traveled to Africa. Thirteen had reported taking mefloquine, and one had reported taking doxycycline for malaria chemoprophylaxis. Blood samples were not available for the 14 patients who reported compliance with a recommended regimen. Seven cases of *P. falciparum* were identified for which patient compliance was unknown.

Five of the six *P. malariae* cases among those who reported taking a recommended antimalarial drug were acquired in Africa. Two (40.0%) of these patients reported noncompliance with antimalarials, and two (40.0%) patients reported compliance with a recommended chemoprophylaxis regimen. One of the compliant patients had used doxycycline and the other one used mefloquine; one had traveled to Africa and one to Asia and blood samples were not available.

Purpose of Travel

Purpose of travel to malaria-endemic areas was reported for 692 (90.9%) of the 761 U.S. civilians with imported malaria (Table 6). Certain cases reported more than one purpose of travel. Of the U.S. civilians with malaria, the largest proportion (53.9%) was persons who had visited friends or relatives in malarious areas; the second and third highest proportion, 12.5% and 9.2%, had traveled for tourism and to do missionary work, respectively.

Malaria During Pregnancy

A total of 31 cases of malaria were reported among pregnant women in 2003, representing 7.0% of cases among women. Eighteen of the 31 (58.1%) were among U.S. civilians; all 18 had traveled to Africa and 14 of the 18 women had traveled to visit friends and relatives. Of the remaining 13, a total of 12 were foreign civilians. Approximately 13% of pregnant women and 28.2% of nonpregnant women reported taking malaria chemoprophylaxis.

Malaria Acquired in the United States

Cryptic Malaria

One case of cryptic malaria was reported in 2003 and is described in the following case report:

TABLE 6. Number of imported malaria cases among U.S. civilians, by purpose of travel at the time of acquisition* — United States, 2003

	Imported cases	
Category	**No.**	**(%)**
Visiting friends/relatives	422	(53.9)
Tourism	98	(12.5)
Missionary or dependent	72	(9.2)
Business representative	59	(7.5)
Student/teacher	30	(3.8)
Peace Corps volunteer	11	(1.4)
Refugee/immigrant	4	(0.5)
Air crew/sailor	2	(0.3)
Other	16	(2.0)
Unknown	69	(8.8)
Total	**783**	**(100.0)**

* In several cases, more than one purpose of travel was specified.

- **Case 1.** On August 7, 2003, a female aged 14 years from Maryland with a history of cerebral palsy was admitted for 4 days to a local hospital for work up of fever. No source was identified, and the patient was discharged but returned to another hospital the following day with persistent fever and was admitted. Six days after admission, the patient had a peripheral blood smear that was positive for *P. falciparum* with a 12% parisitemia. The patient was anemic and thrombocytopenic. She was treated successfully with intravenous (IV) quinidine and doxycycline. The patient had no history of recent travel or transfusion, but had been hospitalized during July 14–August 1, 2003, for placement of a surgical feeding tube. During that hospital stay, she shared a pediatric intensive care unit room with a boy aged 9 years who was being treated for *P. falciparum*, presumably acquired on a recent trip to Gambia. They shared the room for <24 hours on July 22, 2003. No needle-stick injuries, transfusions, or common infusions were reported.

Induced Malaria

One case of induced malaria, caused by blood transfusion, was reported in 2003 and is described in the following case report:

- **Case 1.** On March 31, 2003, a man aged 69 years from Texas was admitted to a local hospital with severe hypertension and acute renal failure. Three days after admission, the patient had upper gastrointestinal bleeding (hemoglobin: 6.9 mg/dL) and was transfused with two units of packed red blood cells (PRBCs). The patient reported having had no other blood transfusions during the 12 months preceding hospitalization. The patient was started on hemodialysis and discharged on April 12. On April 19, the patient experienced fever, diarrhea, and mental confusion. He went to the emergency department 3 days later with fever (101.4°F [38.5°C]), lethargy, and altered mental status, and was admitted to the intensive care unit (ICU). Blood cultures and cerebrospinal fluid testing did not reveal the presence of a bacterial pathogen. Blood smears demonstrated *P. falciparum*. The patient was started on IV quinidine and doxycycline and discharged after 21 days. The patient was retired, spent the majority of his time indoors, denied IV drug use, and last traveled outside of his home town in 1995 to Laredo, Texas. The Texas Department of Health, in collaboration with CDC and the local blood collection center, conducted a donor traceback investigation of the two units of PRBCs used for the patient's transfusions. The investigation determined that one donor was a Ghanian man aged 18 years who had immigrated to Houston in May 2002. His mother reported that her son had been treated for malaria in Ghana 2 years earlier. Blood smear examination and polymerase chain reaction (PCR) performed on the specimen from the Ghanaian donor were negative for the presence of malaria parasites or parasite DNA. However, serology using indirect immunofluoresence antibody (IFA) testing demonstrated elevated titers of antibodies to malaria (1:256 for *P. falciparum*, 1:64 for *P. malariae*, 1:64 for *P. ovale*, and 1:64 for *P. vivax*), indicating previous malaria infection at an indeterminate time.

Introduced Malaria

Eight cases of introduced malaria were reported in 2003 (*10*). The cases occurred in Palm Beach County, Florida, and PCR demonstrated the same strain for all eight cases. They are described in the following case reports:

- **Case 1.** On July 22, a man aged 46 years reported to the emergency department (ED) of hospital A with a 3-day history of fever, headache, chills, anorexia, nausea, vomiting, dehydration, and malaise. He was treated with IV fluids and discharged on levofloxacin. On July 24, he returned to the ED with worsening symptoms and was admitted with a diagnosis of pneumonia. On July 25, *P. vivax* was identified on a blood smear, which was later confirmed by PCR. The patient recovered after treatment with doxycycline, quinine, and primaquine. The patient denied blood transfusion, IV drug use, or travel to any malarious regions during the preceding 12 months. The patient is a construction worker who reported working outside.
- **Case 2.** On July 24, a man aged 37 years was admitted to hospital A with a 6-day history of fever, chills, headache, anorexia, and vomiting. On July 25, *P. vivax* was identified on a blood smear, which was confirmed by PCR. The patient recovered after treatment with doxycycline, quinine, and primaquine. The patient had no history of blood transfusions or IV drug use, and his only travel during the preceding 12 months had been to the Bahamas during June 28–July 2, 2003. The patient is a plumber who reported working outside during the day but who stayed indoors at night.
- **Case 3.** On August 15, a man aged 32 years was admitted to hospital A with a 33-day history of fever, chills, headache, vomiting, and intermittent sweating. He had consulted multiple physicians for his symptoms and had been treated unsuccessfully with azithromycin and prednisone. On the day of admission, *P. vivax* was identified on a blood smear, which was later confirmed by PCR. The patient fully recovered after treatment with doxycycline, quinine, and primaquine. The patient denied blood trans-

fusions or IV drug use, and his only other travel during the preceding 12 months was to the Bahamas in May 2003. He reported having played golf and tennis in the evenings.

- **Case 4.** On August 19, a man aged 45 years visited the ED of hospital A with a 2-day history of fever, chills, anorexia, arthralgias, and diarrhea and was discharged on ibuprofen. The patient returned to the ED on August 21 for these same symptoms, was evaluated, and discharged. On August 22, he returned again with worsening symptoms and mental confusion and was admitted. A blood smear demonstrated the presence of *P. vivax*, which was later confirmed with PCR. The patient was treated with chloroquine and primaquine and recovered. The patient denied ever having traveled to a malarious area, IV drug use, or history of blood transfusion during the preceding 12 months. The patient slept in a homeless camp in a wooded area near a canal.
- **Case 5.** On August 24, a man aged 23 years was admitted to hospital A with a 12-day history of fever, chills, arthralgias, diarrhea, and vomiting. A blood smear demonstrated the presence of *P. vivax*, which was later confirmed with PCR. He had visited the ED previously with the same complaints and had been treated with antibiotics for a respiratory infection. The patient recovered after treatment with chloroquine and primaquine. The patient denied ever having traveled to a malarious area, IV drug use, or history of blood transfusion during the preceding 12 months. He reported fishing at a community pond in the evenings.
- **Case 6.** On August 25, a male aged 17 years was admitted to hospital B with an 8-day history of fever, chills, and headaches. A blood smear from August 26 identified *P. vivax*, which was later confirmed with PCR. Treatment was started with doxycycline, quinine, and primaquine, and the patient made a full recovery. The patient denied having ever traveled to a malarious area or using IV drugs and had no history of blood transfusion. He reported playing basketball outside around dusk at his house and spending time at a pond near the house.
- **Case 7.** On August 26, a man aged 48 years was admitted to hospital C with a 7-day history of fever and chills. He had self-treated earlier that week with antibiotics. A blood smear identified *P. vivax* on the day of admission, which was later confirmed with PCR. He recovered after treatment with chloroquine and primaquine. The patient denied blood transfusions or IV drug use during the preceding 12 months. He had resided in Colombia, but had last been there in 2001. The patient is a carpenter and works until 8 p.m. in an open warehouse.
- **Case 8.** On September 14, 2003, a man aged 27 years was admitted to hospital C after experiencing fever, nausea, and vomiting. A blood smear identified *P. vivax*, which was later confirmed with PCR. He recovered after treatment with quinine, doxycycline, and primaquine. The patient was originally from Mexico, but had not traveled there in 5 years. He denied having had malaria since living in the United States, but was unsure of malaria infection before that time. He denied any history of blood transfusions during the preceding 12 months. The patient was a construction worker and was frequently outdoors.

Deaths Attributed to Malaria

Seven deaths attributable to malaria were reported in 2003 and are described in the following case reports:

- **Case 1.** On January 3, 2003, a female aged 57 years from Yemen who had arrived in the United States on December 30, 2002, went to a local outpatient clinic. She had complaints of right hip pain, headache, and loss of appetite for 2 days, nausea and vomiting for 2 weeks, and subjective fevers of unknown duration. She was neutropenic and sent to a local hospital ED. The patient had cervical cancer and had been treated with both radiation and chemotherapy, the most recent course of therapy on December 12, 2002. In the ED, the patient was afebrile, dehydrated, and had an absolute neutrophil count of 0.79 x 109 cells/L and a hemoglobin of 8.2 g/dL. The patient was admitted for further evaluation of her hip pain and for blood transfusion. The patient was transfused on January 1, 2003, and on January 5 the patient experienced a fever and was empirically started on ciprofloxacin and piperacillin/tazobactam. Urine and blood cultures did not demonstrate bacterial pathogens and chest radiograph did not show any indication of pneumonia. The patient experienced acute renal failure. On January 10, the patient's mental status deteriorated, and an infectious disease consultant recommended adding vancomycin and cefipime, checking a peripheral smear, and performing a lumbar puncture. The patient's mental status continued to deteriorate. She died later that day. Blood cultures later grew gram positive cocci in clusters, and the blood smear demonstrated *Plasmodium*, although no species was reported.
- **Case 2.** On April 1, 2003, a man aged 47 years in Florida went to his primary care physician with a 2-day history of fever, chills, vomiting, headache, low back pain, and myalgias and was referred to the ED. The patient had returned approximately 2 weeks prior from a 1-week

vacation in rural Haiti where he had visited family. The patient's initial laboratory studies were significant for thrombocytopenia (115,000/uL), large numbers of immature leukocytes (31% bands), and hypoxemia (PO_2 60.9 mm/Hg). The patient's chest radiograph was normal. He was admitted with a presumptive diagnosis of pneumonia and started on intravenous ceftriaxone, azithromycin, and trimethoprim/sulfamethaxzole. On April 3, a peripheral blood smear demonstrated the presence of *P. falciparum* with a parasite density of 0.4%. The patient was started on oral chloroquine, and repeat blood smear on April 4 demonstrated a decreasing parasitemia (<0.1%). Nonetheless, the patient experienced shortness of breath with worsening hypoxemia and anemia (hemoglobin: 9.2 g/dL) and on April 5, was intubated and admitted to ICU on mechanical ventilation. The patient was transfused with PRBCs and fresh frozen plasma and continued on chloroquine and antibiotics. On April 8, the patient experienced asystole, and resuscitative efforts were unsuccessful.

- **Case 3.** On April 26, 2003, a man aged 67 years in Louisiana went to a local ED with complaints of fever and chills for 3 days. The patient had returned 13 days previously from a 2-week trip in Zimbabwe and reported taking chloroquine as prophylaxis. The patient was admitted for presumed malaria, and a peripheral blood smear demonstrated the presence of *P. falciparum* with a parasite density of 5%–10%. The patient was started on oral quinine and IV doxycycline. On hospital day 2, his parasitemia had dropped to 1%, but the patient had a focal seizure, became obtunded, and required endotracheal intubation with mechanical ventilation. His renal function deteriorated, necessitating dialysis, and the patient was switched to IV quinidine and doxycycline. The IV quinidine was discontinued on hospital day 3 because of EKG abnormalities, and the patient was switched to quinine by nasogastric tube. Vasopressors became necessary to maintain adequate systolic blood pressure. On hospital day 5, the patient had markedly elevated liver enzymes, fixed and dilated pupils, and an EEG revealing minimal activity although parasitemia had cleared. Later that day, the patient experienced cardiac arrest, and resuscitative measures were unsuccessful.
- **Case 4.** On October 29, 2003, a man aged 54 years in Florida went to a local hospital with mental confusion. The patient was visiting from England. He arrived in the United States in October of 2003, and previous travel history was unknown. The patient was anemic and confused and was admitted to the hospital. He died on November 11. Postmortem examination demonstrated the presence of *plasmodium* parasites. No species was identified.
- **Case 5.** On November 23, 2003, a man aged 40 years in Texas returned from a 16-day trip to Zambia. The patient had been prescribed chloroquine prophylaxis but only had taken a few doses. On the return flight home, the patient reported having fever, nausea, and myalgias, but did not seek medical care on arrival because the symptoms had dissipated. On December 5, the patient went to a local outpatient clinic with fever, chills, nausea, and vomiting, was sent home, and then went to an ED. At that time, he had fever but his physical examination was otherwise normal. A thin smear demonstrated plasmodium parasites, later determined to be *P. falciparum*, with a parasite density of 17%. Other laboratory abnormalities included a hemotocrit of 33%, creatinine of 3.6 mg/dL, and a total bilirubin of 11.0 mg/dL. The patient was admitted to ICU and started on oral quinine and doxycycline. An exchange transfusion was planned. While preparing for the transfusion, the patient became hypotensive, requiring dopamine to maintain a systolic blood pressure between 60–70 mm/Hg. During the transfusion, the patient became increasingly tachypnic and experienced atrial flutter with worsening hypotension. Cardioversion was attempted, but the patient subsequently experienced asystole. Resuscitative efforts were unsuccessful, and the patient died 6 hours after admission.
- **Case 6.** On December 21, 2003, a man aged 56 years in Louisiana was brought to an ED by his family because he had a seizure and fever. The patient was an engineer and spent 28-day rotations in Nigeria. He had last returned on December 4 and was not taking prophylaxis. The patient experienced fever, cough, and myalgias before returning to the United States. On arrival, he began treating himself with over-the-counter medications. The patient did not seek medical care. The patient's symptoms worsened 2 days before admission, and he was found at home on December 21 unresponsive with urinary incontinence. On arrival at the ED, the patient was confused and afebrile. While in the ED, he experienced a fever (temperature of 103.9°F [40°C]) and had a seizure. *Plasmodium* parasites were identified on blood smear, but the species was not identified. Other laboratory abnormalities included leukocytosis with large numbers of immature neutrophils (white blood cell count: 16,000/uL, 38% bands), anemia (Hgb: 9.0 g/dL), thrombocytopenia (platelets: 49,000/uL), hyponatremia (sodium: 112 mmol/L), acute renal insufficiency (creatinine: 1.9 mg/

dL), and hyperbilirubinemia (total bilirubin: 7.7 mg/dL). The patient was started on IV ceftriaxone, and oral doxycycline and quinine. The patient's condition deteriorated on hospital day 2, and repeat laboratory studies demonstrated a worsening anemia (Hgb: 7.1 g/dL), thrombocytopenia (platelets: 18,000/uL), and acidosis (pH: 6.7). The patient was switched to IV quinidine gluconate and transfused with 4 units of PRBCs but did not improve. Exchange transfusion was planned, but the patient died later that day.

- **Case 7.** On March 10, 2003, a man aged 57 years in Pennsylvania went to an ED with daily fevers, chills, fatigue, confusion, and myalgias. The symptoms began on February 19 when he returned from a 19-day vacation in Kenya and Tanzania. He reported taking mefloquine prophylaxis during the trip but stopped it 1 week after return. In the ED, he had a fever (103.5°F [39.5°C]), anemia (Hgb: 10.1 g/dL), mild hypotension, acute renal failure (creatinine: 2.0 mg/dL), and jaundice (total bilirubin: 4.2 mg/dL). His blood smear demonstrated *Plasmodium* parasites with high parasitemia, and he was transferred to another hospital for admission. A repeat blood smear at the admitting hospital confirmed the presence of malaria (parasite density 1.7% of RBCs infected), but no species was identified. The patient was started on IV quinidine gluconate. Despite therapy, the patient became more obtunded on hospital day 2, necessitating endotracheal intubation and mechanical ventilation. The patient experienced thrombocytopenia (platelets: 12,000/uL) with worsening renal and liver failure, and had fevers ≥106°F (≥41°C). Repeat peripheral smear demonstrated a parasitemia of >10%. The patient underwent exchange transfusion. He did not improve and died on March 12.

Discussion

A total of 1,278 cases of malaria were reported to CDC for 2003, representing a 4.4% decrease from the 1,337 cases reported for 2002. This change primarily resulted from a decrease in cases acquired in Africa. 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 decrease in cases in 2003, compared with 2002, most likely does not represent a true trend. Possible explanations for a decrease include decreased international travel or changing patterns of travel (e.g., decreased immigration from malarious areas).

One reason for conducting malaria surveillance is to monitor for prophylaxis failures that might indicate emergence of drug resistance; however, approximately 82.7% of imported malaria among U.S. civilians occurred among persons who were either not taking prophylaxis or were taking nonrecommended prophylaxis for the region to which they were traveling. Among patients for whom appropriate prophylaxis was reported and for whom adequate information was available about species and onset of symptoms to indicate that the infection was a primary one rather than a relapse, the majority reported noncompliance with recommended regimen or had 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 should contact CDC rapidly whenever they suspect chemoprophylaxis failure, thus enabling measurement of serum drug levels of the antimalarial drugs in question.

The importance of taking correct precautions and chemoprophylaxis is underscored by the seven fatal cases of malaria that occurred in the United States in 2003. 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 (*11*).

The occurrence of 18 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 (*12*). In addition, the fetus might be adversely affected (*13*). 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 eight cases of introduced malaria in Florida demonstrate the potential for reintroduction of malaria into the United States. Of the 10 species of *Anopheles* mosquitoes found in the United States, the two species that were responsible for malaria transmission before eradication (*Anopheles*

quadrimaculatus in the east and *An. freeborni* in the west) are still widely prevalent. Intensive surveillance, rapid recognition, accurate diagnosis, and appropriate case management are essential for limiting the spread of a malaria outbreak.

Signs and symptoms of malaria are often nonspecific, but fever is usually 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 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 (*14*). If the 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 usually entail the use of a drug effective against such resistant strains.

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 (770-488-7788) during regular business hours or the CDC's Emergency Operations Center (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 from CDC by telephone (877-394-8747 [toll-free voice information system] or 888-232-3299 [toll-free facsimile request line]) or on the Internet (http://www.cdc.gov/travel/diseases.htm/malaria). In addition, CDC biannually publishes recommendations in *Health Information for International Travel* (commonly referred

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 voice information system	24 hours/day	877-394-8747 (877-FYI-TRIP)
Prophylaxis	CDC's Traveler's Health fascimile information service	24 hours/day	888-232-3299
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 Public Health Publication Sales P.O. Box 753 Waldorf, MD 20604	877-252-1200 or 301-645-7773 or http://www.phf.org
Diagnosis	CDC's Division of Parasitic Diseases diagnostic Internet site (DPDx)	24 hours/day	http://www.dpd.cdc.gov/dpdx
Diagnosis	CDC's Division of Parasitic Diseases diagnostic CD-ROM (DPDx)	Order by electronic mail from CDC Division of Parasitic Diseases	dpdx@cdc.gov
Treatment*	CDC's Malaria Branch	8:00 am–4:30 pm Eastern Time, Monday–Friday	770-488-7788*
Treatment	CDC's Malaria Branch	4:30 pm–8:00 am Eastern Time, evenings, 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 Malaria Branch). http://www.cdc.gov/malaria/diagnosis_treatment/treatment.htm.

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

to as *The Yellow Book*) (*10*), which is available for purchase from the Public Health Foundation at 877-252-1200 or 301-645-7773; it is also available and updated more frequently on CDC's Internet site at http://www.cdc.gov/travel.

CDC provides technical support for health-care providers in the diagnosis of malaria through DPDx, a program that enhances diagnosis of parasitic diseases throughout the world. It includes an Internet site (http://www.dpd.cdc.gov/dpdx) that contains information about laboratory diagnosis, geographic distribution, clinical features, treatment, and life cycles of more than 100 different parasite species, including malaria parasites. The DPDx Internet site is also a portal for diagnostic assistance for health-care providers through telediagnosis. Digital images captured from diagnostic specimens are submitted for diagnostic consultation through e-mail. Because laboratories can transmit images to CDC and rapidly obtain answers to their inquiries, this system allows efficient diagnosis of difficult cases and rapid dissemination of information. Approximately 46 public health laboratories in 41 states, Puerto Rico, and Guam have or are in the process of acquiring the hardware to perform telediagnosis.

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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). 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, the diagnosis of malaria is unlikely. A useful complement to microscopy is polymerase chain reaction (e.g., when microscopy fails to determine parasite species or for confirming negative blood smears). Additional information regarding collecting and preparing 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

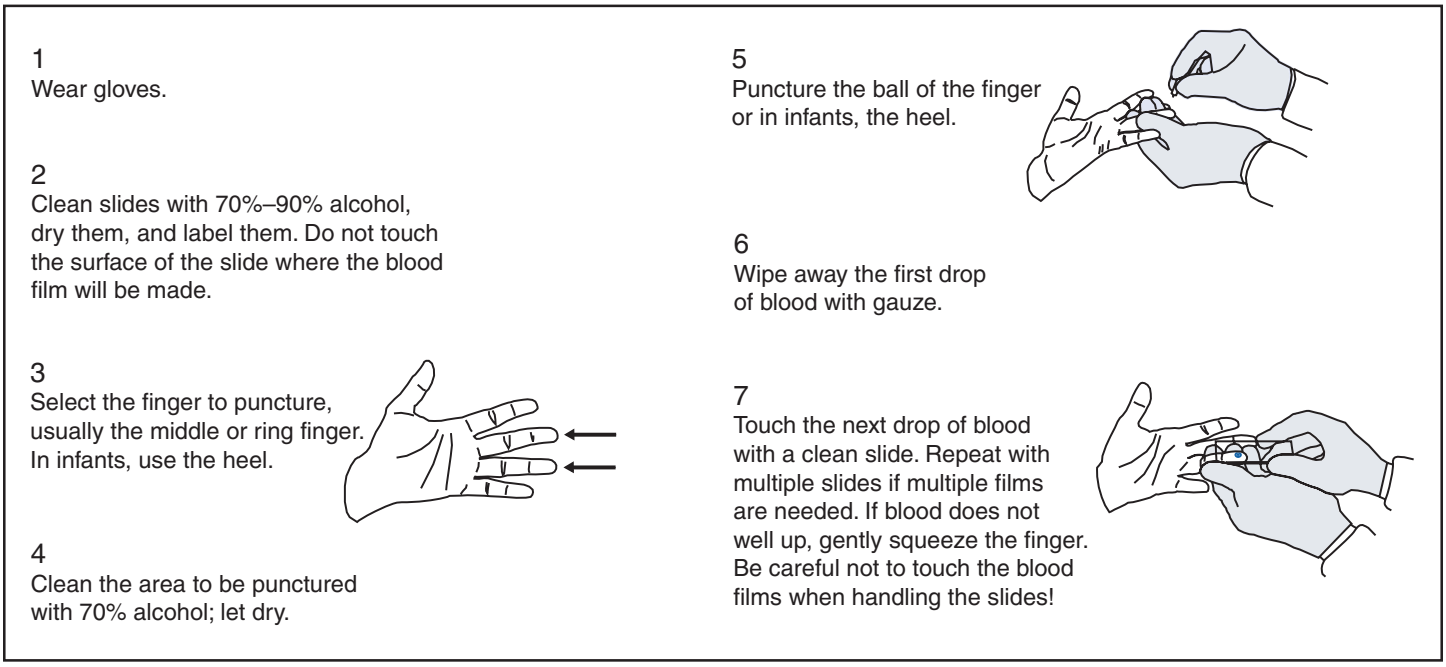
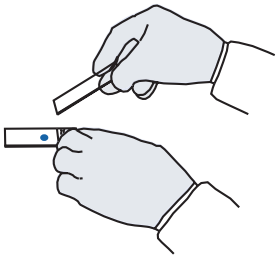


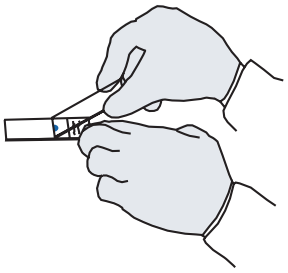
FIGURE A-2. Preparation of thin and thick blood films

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

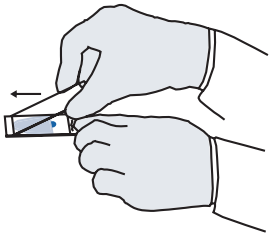
2
Thin film (a): Bring a clean spreader slide, held at a 45-deg angle, toward the drop of blood on the specimen slide.



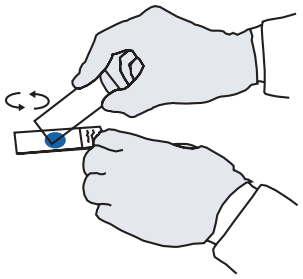
3
Thin film (b): Wait until the blood spreads along the entire width of the spreader slide.



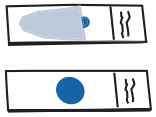
4
Thin film (c): While holding the spreader slide at the same angle, push it forward rapidly and smoothly.



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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