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Abstract

Problem/Condition: In 1996, CDC initiated data collection regarding assisted reproductive technology (ART) procedures performed in the United States to determine medical center-specific pregnancy success rates, 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: 2001.

Description of System: CDC contracts with a professional society, the Society for Assisted Reproductive Technology (SART), to obtain data from fertility medical centers located in the United States. Since 1997, CDC has compiled data related to ART procedures. The Assisted Reproductive Technology Surveillance System was initiated by CDC in collaboration with the American Society for Reproductive Medicine, the Society for Assisted Reproductive Technology, and RESOLVE: The National Infertility Association.

Results: In 2001, a total of 29,344 live-birth deliveries and 40,687 infants resulting from 107,587 ART procedures were reported from 384 medical centers in the United States and U.S. territories. Nationally, 80,864 (75%) of ART treatments used freshly fertilized embryos from the patient's eggs; 14,705 (14%) used thawed embryos from the patient's eggs; 8,592 (8%) used freshly fertilized embryos from donor eggs; and 3,426 (3%) used thawed embryos from donor eggs. Overall, 40% of ART procedures that progressed to the transfer stage resulted in a pregnancy; 33% resulted in a live-birth delivery (delivery of ≥1 infant); and 21% resulted in a singleton live birth. The highest live-birth rates were observed among ART procedures using freshly fertilized embryos from donor eggs (47%). The greatest numbers of ART procedures were performed among residents of California (13,124), New York (12,379), Massachusetts (8,151), Illinois (7,933), and New Jersey (6,011). These five states also reported the highest number of live-birth deliveries and infants born as a result of ART. The ratio of number of ART procedures per million population ranged from 74 in Idaho to 1,273 in Massachusetts, with a national average of 371 ART procedures started per million persons. Among ART treatments in which freshly fertilized embryos from the patient's eggs were used, substantial variation in live birth rates by patient (e.g., women aged ≤40 years) and treatment characteristics (e.g., ovulatory dysfunction, endometriosis, or unexplained infertility) was observed. The risk for a multiple-birth delivery was highest for women who underwent ART transfer procedures using freshly fertilized embryos from either donor eggs (42%) or from their own eggs (36%). Among ART transfer procedures in which the patient's own eggs were used, an inverse relation existed between multiple-birth risk and patient age. Number of embryos transferred and embryo availability (an indicator of embryo quality) were also strong predictors of multiple-birth risk. Of the 40,687 infants born, 46% were twins, and 8% were triplet and higher order multiples. The total multiple-infant birth rate was 53%. Approximately 1% of U.S. infants born in 2001 were conceived through ART. Those infants accounted for 16% of multiple births nationally.

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.

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 (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) (*3,4*). 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. 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 2001. 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 multiple-birth risk for 2001.

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. 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, 2001, 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 usually 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 success 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 ≥1 live-born infant. Only ART procedures involving freshly fertilized eggs include an egg-retrieval stage; ART procedures using thawed eggs do not include egg retrieval because eggs were fertilized during a previous procedure and the resulting embryos were frozen until the current procedure. An ART procedure can be discontinued at any step for medical reasons or by the patient's choice.

Variations in a typical ART procedure are noteworthy. Although a typical ART procedure includes 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

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

† Data regarding population size are based on July 1, 2001, estimates from the U.S. Census Bureau (*9,10*).

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 past 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 >1 female cause; or
- multiple factors, male and female — diagnosis of ≥1 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 prior 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 because 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, success rates based on singleton live births according to treatment group and patient age are also presented. 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 ≥2 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 more) 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 (*3,5*). 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 2001, additional analyses including all ART infants born in 2001 are presented. Because the goal of the analysis was to assess the effect of ART on the 2001 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 2000 and born in 2001 (approximately 2/3 of live-birth deliveries reported to the ART Surveillance System for 2000); and 2) infants conceived from ART procedures performed in 2001 and born in 2001 (approximately 1/3 of live-birth deliveries reported to the ART Surveillance System for 2001). Data regarding the total number of live births and multiple births in the United States in 2001 were obtained from birth certificate data (U.S. natality files) from CDC's National Center for Heath Statistics (*6*). These data represent 100% of births registered in the United States in 2001. Data are presented in relation to the total number of infants born in the United States in 2001 by plurality of births. All analyses were performed by using the SAS® software system (*7*).

[§] 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 421 medical centers in the United States and surrounding territories that performed ART in 2001, a total of 384 (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 2001 were California (56), New York (29), Florida (28), Texas (25), and Illinois (23). Four states had no ART medical centers (Alaska, Maine, Montana, and Wyoming).

Success of ART

A total of 107,587 ART procedures performed in 2001 were reported to CDC (Table 1). The largest number of ART procedures occurred among patients who used their own freshly fertilized embryos (80,864; 75%). Of the 107,587 procedures started, 89,239 (83%) progressed to embryo transfer. Overall, 40% of ART procedures that progressed to the transfer stage resulted in a pregnancy; 33% resulted in a live-birth delivery; and 21% 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 (56% pregnancy rate, 47% live-birth rate, and 27% singleton live-birth rate). The lowest rates were observed among procedures using the patient's eggs and thawed embryos (29% pregnancy rate, 23% live-birth rate, and 17% singleton live-birth rate).

In all, the 29,344 live-birth deliveries from ART procedures resulted in 40,687 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 18,967 singleton infants were born as a result of ART. The largest proportion of infants born (75%; n = 30,383) were from ART procedures in which patients used freshly fertilized embryos from their own eggs.

Number and Type of ART Procedures

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 2001 were performed among residents of California (13,124), New York (12,379), Massachusetts (8,151), Illinois (7,933), and New Jersey (6,011). 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, 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 74 in Idaho to 1,273 in Massachusetts, with a national average of 371 ART procedures started per million persons.

Forty-seven percent of ART-transfer procedures using freshly fertilized embryos from the patient's eggs were performed on women aged <35 years; 22% on women aged 35–37 years; 19% on women aged 38–40 years; 8% on women aged 41–42 years; and 4% on women aged >42 years. Patient and treatment characteristics of these women varied by age (Table 3). The most common infertility diagnoses reported among couples in which the woman was aged <41 years were male factor and tubal factor; however, diagnoses varied overall. Tubal factor, 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 14% of women aged 41–42 years, and 20% 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 17%–21% were reported as having both male and female factors.

Approximately 60% 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 41% 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 2% of ART procedures used GIFT or ZIFT. Although use of ICSI among couples diagnosed with male factor infertility declined with the patient's age, ICSI use among those not diagnosed with male factor infertility increased with patient's age. Despite variation among all age groups, the total proportion of ICSI use (i.e., combined ICSI for male factor and ICSI for other diagnoses) was greater than the proportion of in vitro fertilization with transcervical embryo transfer (IVF-ET) without ICSI. Among all age groups, the majority of procedures included embryo culture for 3 days; the next most common procedure involved embryo culture to day 5. Culture to day 5 coincides with development of the embryo to the blastocyst stage, which was used more frequently among younger women.

Although limited variation existed by age, the majority of ART procedures involved transfer of >1 embryo. Among women aged <35 years, 96% of procedures involved transfer of ≥2 embryos, and 59% involved transfer of ≥3 embryos. For women aged >42 years, 87% involved transfer of ≥2 embryos, and 70% involved transfer of ≥3 embryos. The availability of extra embryos (an indicator of overall embryo quality) decreased with age. Extra embryos were available and cryopreserved for >40% 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, 0.8% of ART transfer procedures used a gestational carrier or surrogate. Limited variation existed by patient age.

Live Birth Rates

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 33%, live-birth rates ranged from 41% among women aged <35 years to 7% among women aged >42 years. Women aged ≤40 years who had an infertility diagnosis of ovulatory dysfunction, endometriosis, male factor, or had unexplained infertility tended to have higher live-birth rates. Women aged ≤40 years with an infertility diagnosis of diminished ovarian reserve or with multiple infertility diagnoses tended to have lower live-birth rates. Although women aged 41–42 years with a diagnosis of uterine factor appear to have had above average live-birth rates (21%), the variation in success rates across diagnostic categories was not statistically significant for this age group, nor for the oldest age group (women aged >42 years). 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. Women in all age groups who had had ≥1 previous birth had higher live-birth rates than those with no previous births.

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

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 (Table 4) (data not indicated).

Within all age groups, live-birth rates were higher among ART procedures that used IVF-ET without ICSI, in comparison to procedures that used ICSI, whether or not male factor was reported (Table 4). Live-birth rates were particularly low among couples who used ICSI in the absences of male factor infertility. Within all age groups, live-birth rates were increased among women who had extended embryo culture to day 5, transferred ≥2 embryos, and had extra embryos available and cryopreserved for future use. Variations in live-birth rates were statistically significant for all treatment factors within all age groups with the exception of number of days of embryo culture for women aged 41–42 years. 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 35–37 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 for 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 (<5). 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 indicated). 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 above average number of eggs retrieved (≥10), women with diagnoses other than diminished ovarian reserve, and women with extra embryos cryopreserved for future use. Again, the pattern of results for analyses within each of these subgroups remained consistent with the findings presented (Table 4) (data not indicated). 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 41% among women aged <35 years to 7% among women aged >42 years, and singleton live-birth rates ranged from 25% among women aged <35 years to 6% among women age >42 years.

Multiple Births

Of 10,377 multiple-birth deliveries, 7,805 were from pregnancies conceived with freshly fertilized embryos from the patient's eggs; 823 were from thawed embryos from the patient's eggs; 1,514 were from freshly fertilized embryos from a donor's eggs; and 235 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 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 36%. This rate varied from 40% among women aged <35 years to 14% among women aged >42 years.

Of 40,687 infants born through ART, 53% (21,720) 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 3–7). Among all age groups, transfer of ≥2 embryos resulted in increased live-birth delivery rates. However, the multiple-birth risk was also substantially increased. Among all age groups, with the exception of women aged >42 years (Figures 3–6), the percentage of multiple-birth

deliveries increased with increasing number of embryos transferred from 2 to ≥5. 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 ≥3 embryos were transferred than when 2 embryos were transferred (Figures 3 and 4). For women aged 38–40 years (Figure 5), transfer of ≥3 embryos offered a certain advantage in terms of live-birth delivery rates. However, as among younger age groups, the percentage of twin deliveries and triplet or higher order multiple-birth deliveries were increased with ≥3 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. The percentage of triplet or higher order multiple-birth deliveries did not demonstrate a trend. For women aged >42 years (Figure 7), the percentage of multiple-birth deliveries did not demonstrate a trend by number of embryos (≥2) having been transferred.**

A further assessment of multiple-birth risk among patients who used freshly fertilized embryos from their own eggs and set aside extra embryos for future use is also presented (Figures 8–11). 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, 35–37 years, and 38–40 years, live-birth rates were highest when only two embryos were transferred (Figures 8–10). In addition, live-birth rates among women in these three youngest age groups were ≥29% with elective transfer of only one embryo. Thus, singleton live-birth rates did not demonstrate any or much improvement when two embryos were transferred. Rather, the added live-birth rates observed with two embryos transferred incurred a substantial risk of multiple births. The number of cases of elective transfer of one embryo among women aged 41–42 years was too limited to allow adequate evaluation. Live-birth rates with elective transfer of 2–≥5 embryos demonstrated limited variation for this age group. Data are not provided for women aged >42 years because in this age group limited sample sizes existed for all numbers of elective embryo transfer.

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 (2,673), New York (2,353), Massachusetts (1,399), New Jersey (1,358), Texas (1,286), and Illinois (1,278). Nationally, the percentage of infants born in multiple-birth deliveries after ART was used was 53%; the percentage of twins and triplets or more were 46% 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 Alabama (61%), Colorado (61%), Montana (69%) Rhode Island (61%), and Tennessee (61%).

The contribution of ART infants to the total number of U.S. infants born in 2001 is presented (Table 7). Of 4,025,933 total infants born in the U.S. in 2001, a total of 37,087 (1%) were conceived by using ART. Infants conceived with ART accounted for 0.4% of singleton births and 16% of multiple births nationally. Fourteen percent of all twins and 42% of infants born in triplets and higher order multiples were conceived with ART.

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 reported a past infertility-associated health-care visit, and 2% reported a visit in the past year (*8*). 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 2001, the number of ART procedures performed increased 66%, from 64,724 to 107,587 (*1*). Additionally, from 1996 to 2001, 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 33% in 2001. The number of infants conceived through ART increased 94%, from 20,921 infants conceived through ART procedures performed in 1996 to 40,687 infants conceived through ART procedures performed in 2001.

This report documents that in 2001, ART use varied according to patient's state of residency. Residents of California,

** Results are based on total multiple-birth risk and thus do not provide an indication of pregnancies that began as twins, triplets, or more, but reduced (either spontaneously or through medical intervention) to singletons or twins (Figures 3–11).

New York, Massachusetts, Illinois, and New Jersey reported the highest number of ART procedures. These states also reported the highest number of infants conceived through ART. In 2001, ART use by state of residency was not completely in line with expectations based on the total population within states (*9,10*). Whereas Massachusetts had the third highest number of ART procedures performed, it ranked thirteenth in terms of total population size.[††] Likewise, residents of Rhode Island underwent more ART procedures than would have been expected based on their population size. 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 (1,273), Maryland (758), New Jersey (706), District of Columbia (695), and Rhode Island (682). This divergence is not unexpected because in 2001 both Massachusetts and Rhode Island had a statewide mandate 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 past infertility treatment, and past 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, type of ART procedures, 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 (*11,12*).[§§] However, success-rate data must 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 (*13–15*). 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. In 2001, the estimated costs per delivery resulting from ART procedures ranged from $38,345 to $84,819 (*12*). Hospital charges have been estimated to be four times higher for delivery of twins and 11 times higher for delivery of triplets than for singleton deliveries (*16*).

In the United States, multiple births have increased dramatically during the last 2 decades (*6,17*). The rise in multiple births has been attributed to an increased use of ART and delayed childbearing (*4,18,19*). Although infants conceived with ART accounted for 1% of the total births in the U.S. in 2001, the proportion of twins and triplets or more attributed to ART were 14% and 42%, 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. Indeed, in the United States, high-order embryo transfer is still common practice. In 2001, approximately 66% of ART cycles that used fresh, nondonor eggs or embryos and progressed to the embryo-transfer stage involved the transfer of ≥3 embryos; approximately 32% of cycles involved the transfer of ≥4; and 11% of cycles involved the transfer of ≥5 embryos. Recent reports published in the scientific literature have advocated for the presentation of singleton live-birth rates as a distinct indicator of ART success (*20–24*). This report includes this measure and presents it with total live-birth rates. Success rates

[††] Data regarding population size are based on July 1, 2001, estimates from the U.S. Census Bureau (*9,10*).

[§§] Estimated costs for one cycle of IVF range from $7,854 to $11,000 (*12*).

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.

Data regarding multiple-birth deliveries and proportion of multiple-birth infants as distinct outcomes are provided also. Data in this report indicate that 54% of infants born through ART in 2001 were multiple births; this compares with 3% in the general U.S. population during the same period (*6,25*). The twin rate was 45%, 15 times higher than in the general U.S. population (3%); the triplet and higher order multiples rate was 8%, a total of 42 times higher than the general U.S. population (0.2%). Regarding the specific type of ART treatment, the rates are even higher for women who underwent ART procedures using freshly fertilized embryos from their own eggs (54% total multiple births) or from donor eggs (60% total multiple births).

In the majority of states, >50% of infants conceived through ART were born in multiple-birth deliveries. Alabama, Colorado, Montana, Rhode Island, and Tennessee reported ART-associated multiple-birth rates >60%. Multiple births resulting from ART are an increasing public health problem, nationally and for the majority of states. The findings in this report confirm the need to reduce the occurrence of multiple births resulting from ART.

For women who underwent ART procedures using freshly fertilized embryos from their own eggs, the multiple-birth risk increased when multiple embryos were transferred (≥2). 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, for certain subgroups, high live-birth rates and singleton live-birth rates were achieved with the transfer of one or two embryos. Thus, among certain groups, multiple-birth risk can be minimized by limiting the number of embryos transferred without compromising success rates.

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 >1 ART procedure in a given year is not possible. Because patients undergoing >1 procedure in a given year are most likely to be those who failed ≥1 treatment, the success rates reported here 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 2001; therefore, success rates do not represent all couples with infertility who were potential ART users in 2001. Third, 9% of medical centers that performed ART in 2001 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 (*18*), ART data were not presented by state of residence because of incomplete residency data. In 2001, 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 45 states had <5% missing residency data; medical centers located in five states had 5%–9% 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 indicated).

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. This rate is even higher for persons aged 20–35 years (*26*).

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 2001, a total of 771 (0.7%) 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 for which ≥1% of ART procedures among state residents were performed in a military medical center were Alabama, Colorado, Kansas, Louisiana, Maine, Maryland, New Mexico, North Carolina, Oklahoma, South Carolina, and Texas. States for which >5% of ART procedures among

state residents were performed in a military medical center were Alaska, the District of Columbia, Hawaii, and Virginia.

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 of multiple 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 has led to a substantial increase in multiple-birth rates in the United States (*4,17*). Although balancing the chance of success with ART against the risk of multiple births is difficult in certain cases, efforts should be made to limit the number of embryos transferred for patients undergoing 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, 2001

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	80,864	69,515	65,363	26,550	40.6	21,813	33.4	14,008	21.4	30,383
Thawed embryos	14,705	N/A*	13,126	3,850	29.3	3,075	23.4	2,252	17.2	3,971
Donor's eggs used										
Freshly fertilized embryos	8,592	7,977	7,722	4,302	55.7	3,629	47.0	2,115	27.4	5,257
Thawed embryos	3,426	N/A	3,028	1,024	33.9	827	27.3	592	19.6	1,076
Total	**107,587**	**N/A**	**89,239**	**35,726**	**40.0**	**29,344**	**32.9**	**18,967**	**21.3**	**40,687**

* Not applicable.

TABLE 2. Number of reported assisted reproductive technology (ART) transfer procedures performed, number of pregnancies, and number of live-birth deliveries, by patient's state/territory of residence* at time of treatment — United States, 2001

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§	558	482	194	162	242	124.9
Alaska§	82	72	29	22	29	129.4
Arizona	1,484	1,233	498	422	578	279.6
Arkansas	419	353	159	137	191	155.5
California§	13,124	11,239	4,336	3,559	4,943	379.3
Colorado§	1,666	1,445	715	598	883	376.0
Connecticut	2,115	1,719	703	584	791	615.8
Delaware	440	316	143	112	155	552.3
District of Columbia§	399	335	115	90	120	695.3
Florida	4,539	3,758	1,568	1,310	1,832	277.2
Georgia	2,453	1,942	792	666	918	291.8
Guam	¶	¶	¶	¶	¶	¶
Hawaii§	402	314	123	95	133	327.6
Idaho	97	84	36	34	47	73.5
Illinois	7,933	6,452	2,336	1,886	2,551	633.6
Indiana	1,792	1,500	523	433	614	292.5
Iowa	842	705	355	304	433	287.2
Kansas§	795	621	275	234	318	294.2
Kentucky	770	640	248	199	282	189.2
Louisiana§	700	521	183	145	214	156.6
Maine§	126	105	49	43	52	98.1
Maryland§	4,082	3,269	1,278	1,040	1,449	757.9
Massachusetts	8,151	6,874	2,718	2,194	2,915	1273.4
Michigan	3,286	2,664	1,033	877	1,198	328.4
Minnesota	2,092	1,850	825	688	929	419.7
Mississippi	313	257	91	78	102	109.5
Missouri	1,454	1,182	518	417	596	257.9
Montana	116	101	47	39	62	128.1
Nebraska	786	650	229	186	263	457.0
Nevada	465	380	162	132	192	221.7
New Hampshire	554	501	206	173	230	439.9
New Jersey	6,011	4,828	2,169	1,761	2,470	706.3
New Mexico§	190	167	81	65	91	103.8
New York	12,379	10,180	4,079	3,280	4,498	648.6
North Carolina§	1,775	1,497	600	516	752	216.3
North Dakota	154	136	51	46	63	241.9
Ohio	2,996	2,503	1,021	859	1,216	263.0
Oklahoma§	548	474	222	196	275	157.9
Oregon	760	621	285	244	341	218.8
Pennsylvania	3,941	3,150	1,128	936	1,287	320.3
Puerto Rico	391	338	112	78	101	101.9
Rhode Island	723	646	217	181	269	682.3
South Carolina§	774	640	298	254	350	190.5
South Dakota	130	100	33	27	36	171.4
Tennessee	839	709	322	265	392	145.9
Texas§	5,568	4,627	1,902	1,593	2,265	260.5
Utah	436	380	138	115	155	191.3
Vermont	167	141	61	48	66	272.4
Virgin Islands	¶	¶	¶	¶	¶	¶
Virginia§	3,080	2,568	1,041	828	1,141	428.0
Washington	1,994	1,615	637	529	723	332.7
West Virginia	223	190	73	59	76	123.8
Wisconsin	709	610	203	154	217	131.2
Wyoming	47	39	18	14	18	95.2
Non U.S. resident	1,698	1,499	543	434	613	N/A
Total	**107,587**	**89,239**	**35,726**	**29,344**	**40,687**	**371.1****

* In cases of missing residency data, the patient's state of residency was assigned as the state in which the ART procedure was performed. Medical centers in all but 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, 2001 state population estimates. Population Division, U.S. Census Bureau.

§ Approximately 1% of ART procedures were reported from military medical centers located in California, the District of Columbia, Hawaii, and Texas. States for which ≥1% of ART procedures among state residents were performed in a military medical center were Alabama, Colorado, Kansas, Louisiana, Maine, Maryland, New Mexico, North Carolina, Oklahoma, South Carolina, and Texas. States for which >5% of ART procedures among state residents were performed in a military medical center were Alaska, District of Columbia, Hawaii, 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, 2001

	Patient age (yrs)				
	<35 (n = 30,849) (%)	35–37 (n = 14,422) (%)	38–40 (n = 12,553) (%)	41–42 (n = 5,053) (%)	>42 (n = 2,486) (%)
Patient factors					
Diagnosis					
Tubal factor	15.3	17.1	14.8	12.0	9.3
Ovulatory dysfunction	7.8	5.0	3.8	3.4	3.1
Diminished ovarian reserve	1.3	2.4	6.4	14.0	20.0
Endometriosis	8.5	7.8	6.0	3.1	2.1
Uterine factor	0.9	1.5	1.7	1.7	1.9
Male factor	23.8	20.1	16.6	11.0	7.6
Other causes	4.2	4.9	5.6	7.2	8.5
Unexplained cause	10.3	12.9	12.4	11.5	11.2
Multiple factors, female only	10.2	11.2	14.0	16.9	15.9
Multiple factors, female and male	17.6	17.3	18.7	19.3	20.6
Number of previous ART procedures					
0	60.1	51.0	46.4	43.0	41.4
≥1	39.9	49.0	53.6	57.0	58.6
Number of previous births					
0	80.4	70.8	67.2	64.5	63.7
≥1	19.6	29.2	32.8	35.5	36.3
Treatment factors					
Method of embryo fertilization and transfer*					
IVF-ET without ICSI	38.9	40.8	41.8	45.5	47.1
IVF-ET with ICSI	59.8	58.1	56.5	52.8	51.5
IVF-ET with ICSI among couples diagnosed with male factor infertility	37.2	33.3	30.6	25.4	23.1
IVF-ET with ICSI among couples not diagnosed with male factor infertility	22.6	24.8	25.9	27.4	28.4
GIFT	0.4	0.4	0.5	0.7	0.9
ZIFT	0.8	0.6	1.1	0.8	0.5
Combination	0.1	0.1	0.1	0.2	0.0
No. of days of embryo culture†					
1	0.6	0.5	0.7	0.5	0.7
2	5.1	4.5	5.0	4.5	4.6
3	72.4	77.1	79.7	83.8	84.4
4	3.0	3.3	3.8	3.7	4.0
5	15.6	12.1	8.3	5.1	3.7
6	2.2	1.5	1.2	0.8	0.6
Number of embryos transferred					
1	4.2	6.2	8.1	10.4	12.9
2	36.4	22.2	17.5	15.8	17.6
3	39.7	36.5	28.1	20.6	19.3
4	14.5	25.8	28.8	24.4	18.9
≥5	5.2	9.3	17.4	28.8	31.3
Extra embryo(s) available and cryopreserved					
Yes	40.5	28.2	18.9	9.5	5.1
No	59.5	71.8	81.1	90.5	94.9
Use of gestational carrier					
Yes	0.7	0.8	0.8	0.7	1.2
No	99.3	99.2	99.2	99.3	98.8

* 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, 2001

	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	**41.1**	**35.1**	**25.4**	**14.5**	**6.7**
Patient factors					
Diagnosis					
Tubal factor	39.8*	34.2*	24.9*	13.7	6.1
Ovulatory dysfunction	42.3	35.7	29.5	14.0	5.2
Diminished ovarian reserve	34.5	30.2	22.6	14.9	7.1
Endometriosis	42.7	36.4	26.3	15.4	2.0
Uterine factor	39.4	34.0	23.7	21.4	2.1
Male factor	42.7	38.1	27.3	14.8	8.5
Other causes	42.7	35.1	26.9	16.9	9.0
Unexplained cause	42.1	37.1	28.3	14.6	7.2
Multiple factors, female only	38.4	32.9	24.4	14.6	7.1
Multiple factors, female and male	39.7	32.4	22.5	12.7	5.7
Number of previous ART procedures					
0	43.3*	36.7*	27.0*	14.8	7.5
≥1	37.7	33.4	24.0	14.3	6.2
Number of previous births					
0	39.8*	33.6*	24.5*	13.9	6.4
≥1	46.4	38.6	27.2	15.5	7.3
Treatment factors					
Method of embryo fertilization and transfer†					
IVF-ET without ICSI	43.1*	38.0*	27.3*	16.3*	8.4*
IVF-ET with ICSI among couples diagnosed with male factor infertility	41.3	34.6	24.5	12.8	5.9
IVF-ET with ICSI among couples not diagnosed with male factor infertility	37.4	31.1	23.5	13.1	4.7
Number of days of embryo culture§					
3	40.2*	34.4*	24.9*	14.8	6.2*
5	47.7	43.2	33.2	17.1	18.3
Number of embryos transferred					
1	17.0*	14.8*	8.1*	4.2*	0.3*
2	44.4	34.4	21.5	8.1	3.4
3	42.3	37.9	26.6	12.8	7.3
4	37.7	37.4	29.6	17.2	6.8
≥5	37.6	33.1	28.7	20.6	10.8
Extra embryos available and cryopreserved					
Yes	48.6*	44.1*	37.7*	22.2*	17.5*
No	36.0	31.6	22.6	13.7	6.2
Use of gestational carrier					
Yes	45.7	48.2*	31.7	20.6	10.0
No	41.0	35.0	25.3	14.4	6.7

* $P < 0.05$; χ^2 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.
§ 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, 2001

	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	21,813	7,805	35.8	30,383	16,375	53.9
	<35	12,668	5,028	39.7	18,219	10,579	58.1
	35–37	5,059	1,756	34.7	6,978	3,675	52.7
	38–40	3,188	866	27.2	4,124	1,802	43.7
	41–42	731	131	17.9	871	271	31.1
	>42	167	24	14.4	191	48	25.1
Thawed embryos	All ages	3,075	823	26.8	3,971	1,719	43.3
	<35	1,833	512	27.9	2,397	1,076	44.9
	35–37	692	188	27.2	895	391	43.7
	38–40	394	87	22.1	486	179	36.8
	41–42	102	24	23.5	126	48	38.1
	>42	54	12	22.2	67	25	37.3
Donor's eggs used†							
Freshly fertilized embryos	All ages	3,629	1,514	41.7	5,257	3,142	59.8
Thawed embryos	All ages	827	235	28.4	1,076	484	45.0
Total	**All ages**	**29,344**	**10,377**	**35.4**	**40,687**	**21,720**	**53.4**

* 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, 2001

Patient's state of residency	No. of infants born	No. of infants born in multiple-birth deliveries	Infants born in multiple-birth deliveries† (%)	Infants born in twin deliveries (%)	Infants born in triplet or more deliveries (%)
Alabama§	242	147	60.7	44.6	16.1
Alaska§	29	14	48.3	48.3	0.0
Arizona	578	293	50.7	40.3	10.4
Arkansas	191	104	54.5	49.2	5.2
California	4,943	2,673	54.1	48.1	5.9
Colorado§	883	542	61.4	51.1	10.3
Connecticut	791	403	50.9	44.9	6.1
Delaware	155	82	52.9	44.5	8.4
District of Columbia§	120	58	48.3	43.3	5.0
Florida	1,832	995	54.3	45.5	8.8
Georgia	918	478	52.1	43.2	8.8
Guam	¶	¶	¶	¶	¶
Hawaii§	133	73	54.9	45.9	9.0
Idaho	47	26	55.3	55.3	0.0
Illinois	2,551	1,278	50.1	42.6	7.5
Indiana	614	336	54.7	42.0	12.7
Iowa	433	247	57.0	49.2	7.9
Kansas§	318	157	49.4	39.0	10.4
Kentucky	282	153	54.3	40.4	13.8
Louisiana§	214	125	58.4	41.1	17.3
Maine§	52	17	32.7	26.9	5.8
Maryland§	1,449	786	54.2	47.3	7.0
Massachusetts	2,915	1,399	48.0	43.5	4.5
Michigan	1,198	611	51.0	41.7	9.3
Minnesota	929	467	50.3	44.5	5.8
Mississippi	102	48	47.1	42.2	4.9
Missouri	596	338	56.7	47.3	9.4
Montana	62	43	69.4	54.8	14.5
Nebraska	263	139	52.9	35.4	17.5
Nevada	192	114	59.4	50.0	9.4
New Hampshire	230	109	47.4	40.9	6.5
New Jersey	2,470	1,358	55.0	47.1	7.9
New Mexico§	91	51	56.0	52.7	3.3
New York	4,498	2,353	52.3	45.8	6.6
North Carolina§	752	442	58.8	45.3	13.4
North Dakota	63	33	52.4	47.6	4.8
Ohio	1,216	687	56.5	48.6	7.9
Oklahoma§	275	151	54.9	46.2	8.7
Oregon	341	191	56.0	50.7	5.3
Pennsylvania	1,287	668	51.9	43.7	8.2
Puerto Rico	101	43	42.6	33.7	8.9
Rhode Island	269	165	61.3	48.3	13.0
South Carolina§	350	179	51.1	38.9	12.3
South Dakota	36	18	50.0	50.0	0.0
Tennessee	392	240	61.2	49.0	12.2
Texas§	2,265	1,286	56.8	48.3	8.5
Utah	155	75	48.4	40.0	8.4
Vermont	66	36	54.5	54.5	0.0
Virgin Islands	¶	¶	¶	¶	¶
Virginia§	1,141	606	53.1	48.0	5.1
Washington	723	370	51.2	42.3	8.9
West Virginia	76	34	44.7	44.7	0.0
Wisconsin	217	116	53.5	39.6	13.8
Wyoming	18	¶	¶	¶	¶
Non U.S. resident	613	345	56.3	48.8	7.5
Total	**40,687**	**21,720**	**53.4**	**45.6**	**7.8**

* 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.

§ Approximately 1% of ART procedures were reported from military medical centers located in California, District of Columbia, Hawaii, and Texas. States for which ≥1% of ART procedures among state residents were performed in a military medical center were Alabama, Colorado, Kansas, Louisiana, Maine, Maryland, New Mexico, North Carolina, Oklahoma, South Carolina, and Texas. States for which >5% of ART procedures among state residents were performed in a military medical center were Alaska, District of Columbia, Hawaii, and Virginia.

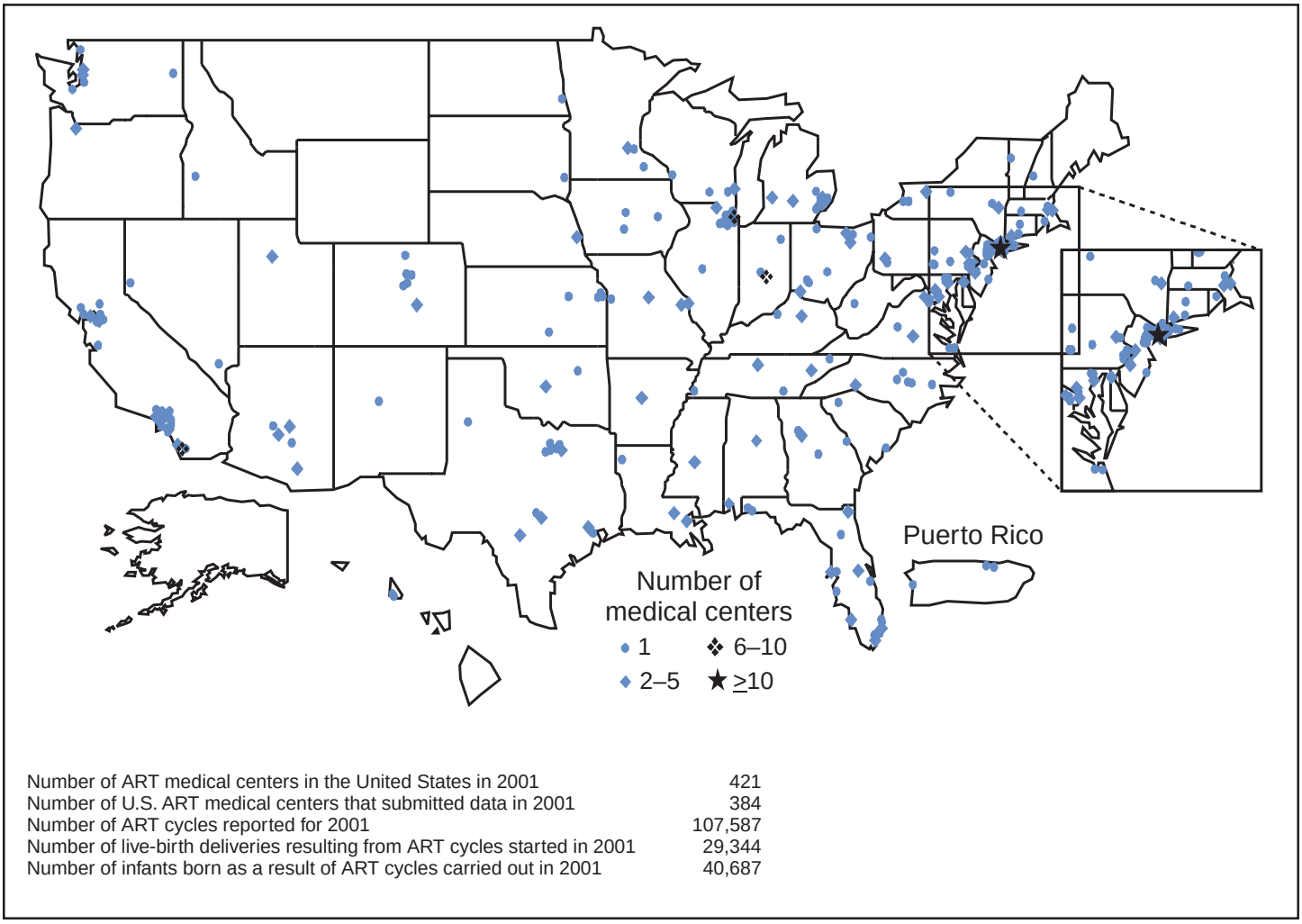
¶ Data not indicated to preserve confidentiality, but included in total.

TABLE 7. Effect of assisted reproductive technology (ART) on total births by plurality — United States, 2001

	Number of ART infants*† (% of total)	Number of total U.S. infants§ (% of total)	Contribution of ART to total births in the United States (%)
Live births in single deliveries	17,123 (46.2%)	3,897,216 (96.8%)	0.4
Live births in multiple deliveries	19,964 (53.8%)	128,717 (3.2%)	15.5
Twin deliveries	16,838 (45.4%)	121,246 (3.0%)	13.9
Triplets or higher order deliveries	3,126 (8.4%)	7,471 (0.2%)	41.8
Total number of live births	**37,087**	**4,025,933**	**0.9**

* **Source:** Assisted Reproductive Technology Surveillance System.
† Includes infants conceived from ART procedures performed in 2000 and born in 2001 and infants conceived from ART procedures performed in 2001 and born in 2001.
§ **Source:** U.S. natality file, CDC, National Center for Health Statistics.

FIGURE 1. Location of assisted reproductive technology (ART) Medical Centers — United States and Puerto Rico, 2001



Number of ART medical centers in the United States in 2001	421
Number of U.S. ART medical centers that submitted data in 2001	384
Number of ART cycles reported for 2001	107,587
Number of live-birth deliveries resulting from ART cycles started in 2001	29,344
Number of infants born as a result of ART cycles carried out in 2001	40,687

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, 2001

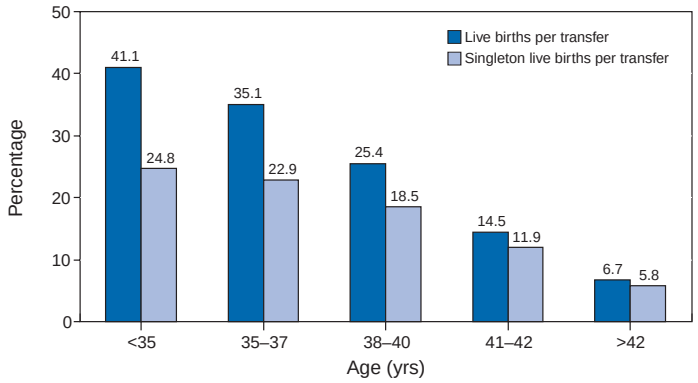
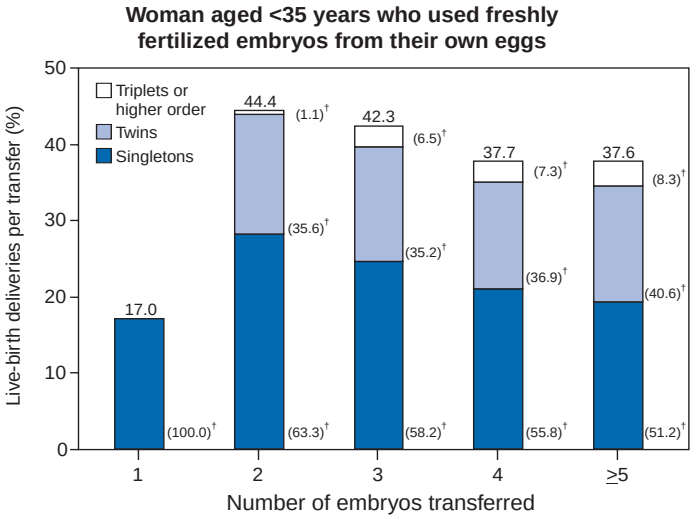
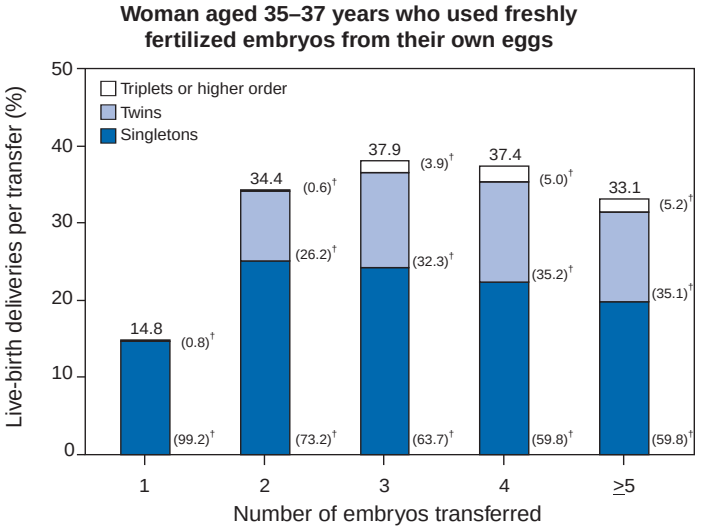


FIGURE 3. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001*



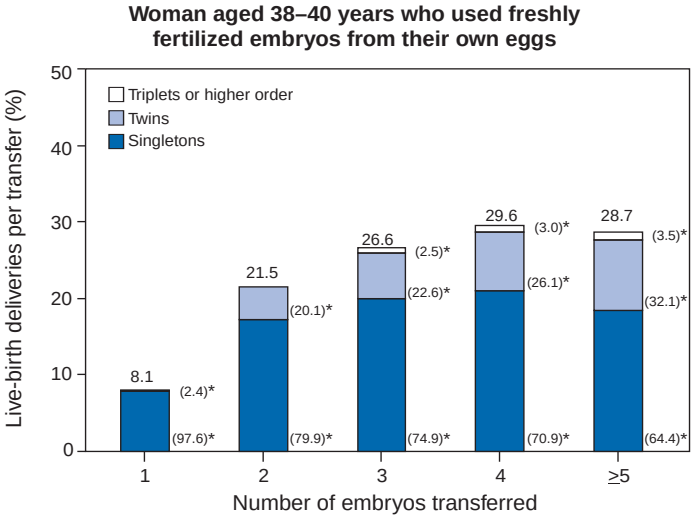
* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

FIGURE 4. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001*



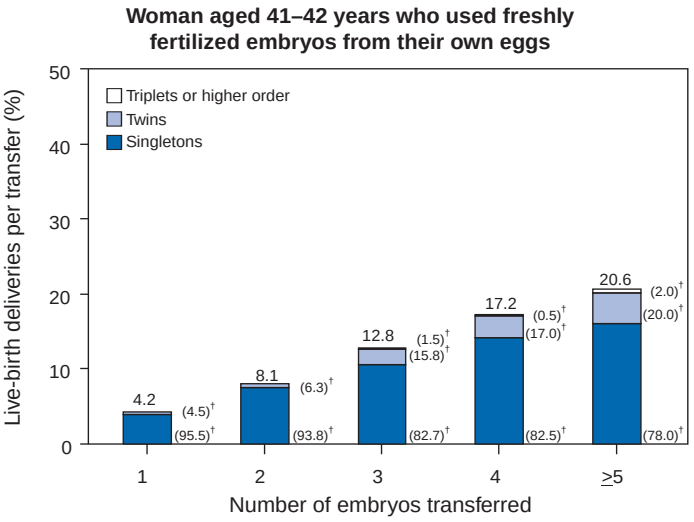
* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

FIGURE 5. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001



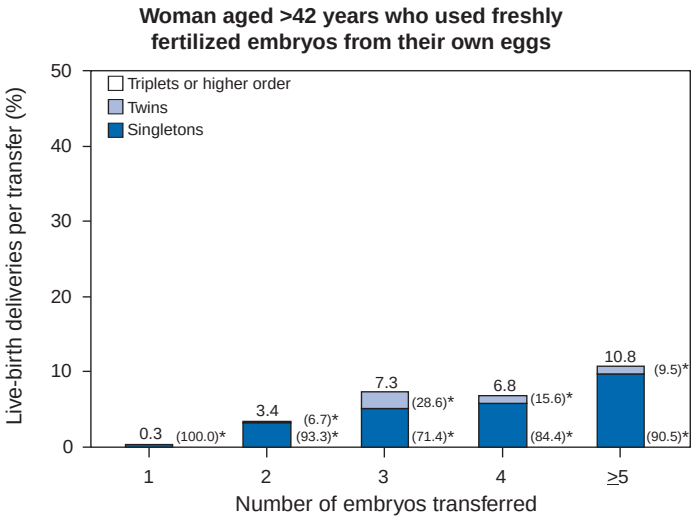
* Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

FIGURE 6. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001*



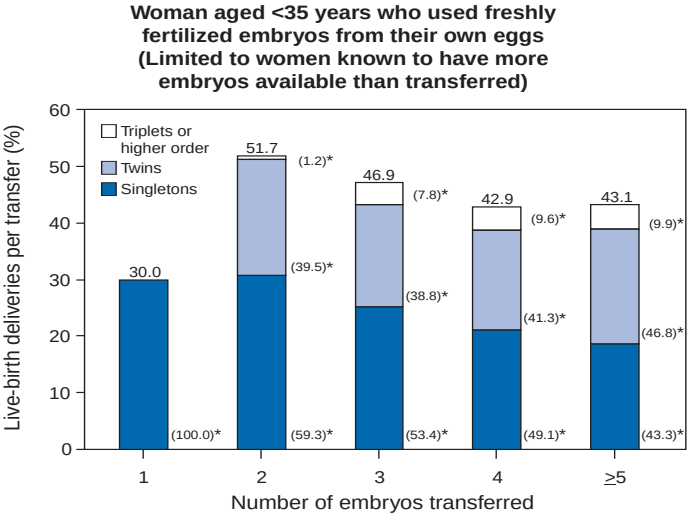
* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

FIGURE 7. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001



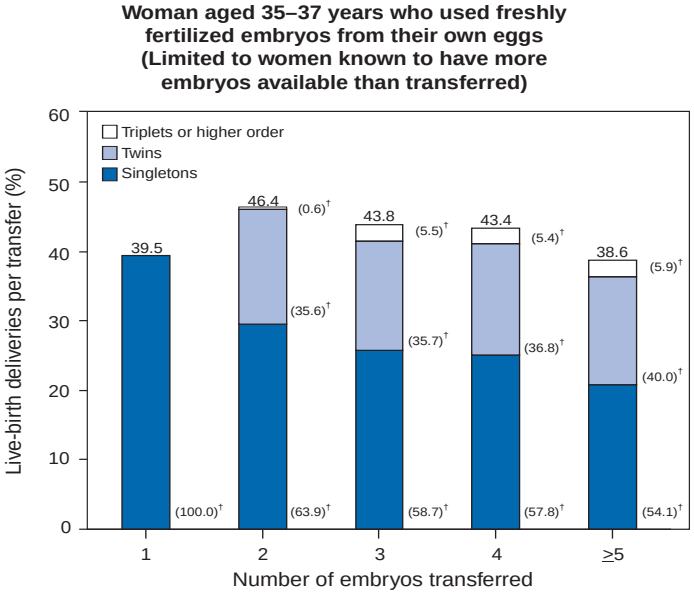
* Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

Figure 8. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001



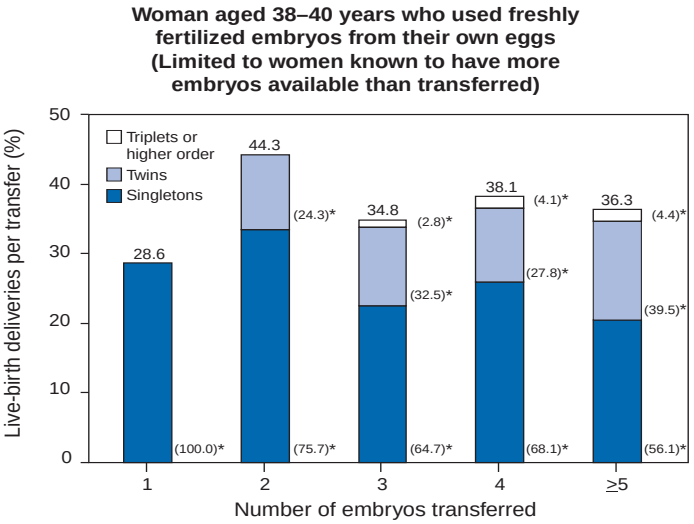
* Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

Figure 9. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001*



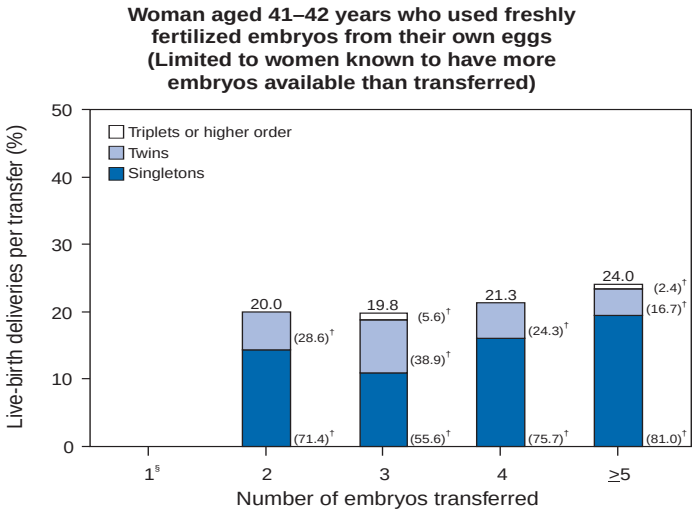
* Numbers might not add to 100% because of rounding.
† Percentages of live births that were singletons, twins, and triplets or higher order are in parentheses.

Figure 10. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001



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

Figure 11. Live birth rates and multiple-birth risk, by number of embryos transferred — United States, 2001*



* 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, 2002

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Abstract

Problem/Condition: Malaria 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* species 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 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 2002.

Description of System: Malaria cases confirmed by blood film are 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 1,337 cases of malaria with an onset of symptoms in 2002 among persons in the United States or one of its territories. This number represents a decrease of 3.3% from the 1,383 cases reported for 2001. *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 52.3%, 25.4%, 2.8%, and 2.8% of cases, respectively. Eleven patients (0.8% of total) were infected by ≥2 species. The infecting species was unreported or undetermined in 213 (15.9%) cases. Compared with 2001, the number of reported malaria cases acquired in Asia (n = 171) and Africa (n = 903) increased by 4.3% and 1.9%, respectively, whereas the number of cases acquired in the Americas (n = 141) decreased by 41.2%. Of 849 U.S. civilians who acquired malaria abroad, 317 (37.3%) reported that they had followed a chemoprophylactic drug regimen recommended by CDC for the area to which they had traveled. Five patients became infected in the United States, one through congenital transmission, one probable transfusion-related, and three whose infection cannot be linked epidemiologically to secondary cases. Eight deaths were attributed to malaria. All deaths were caused by *P. falciparum*.

Interpretation: The 3.3% decrease in malaria cases in 2002, compared with 2001, resulted primarily from a marked decrease in cases acquired in the Americas, but this decrease was offset somewhat by an increase in the number of cases acquired in Africa and Asia. This limited 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, fluctuation in reporting to state and local health departments, or an increased use of effective antimalarial chemoprophylaxis. 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 eight fatal cases and the five 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.

Introduction

Malaria in humans is caused by infection with one or more of four species of *Plasmodium* (i.e., *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*). The infection is transmitted by the bite of an infective female *Anopheles* species 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 except Hawaii.

The majority of 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*).

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, increased 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 malarious areas. This report summarizes malaria cases reported to CDC with onset of symptoms in 2002.

Methods

Data Sources

Malaria case data are reported to the National Malaria Surveillance System (NMSS) and the National Notifiable Diseases Surveillance System (NNDSS) (*6*). Both systems rely on passive reporting, and the numbers of reported cases might differ because of differences in collection and transmission of data. A substantial difference in the data collected in these two systems is that NMSS receives more detailed clinical and epidemiologic data regarding each case (e.g., information concerning the area to which the infected person has traveled). This report presents only data regarding cases reported to NMSS.

Cases of blood-film–confirmed malaria among civilians and military personnel are identified by health-care providers or laboratories. Each 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.

Definitions

The following definitions are used in this report:

- **Laboratory criteria for diagnosis:** Demonstration of malaria parasites in blood films.
- **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* species 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* species 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:** An isolated malaria case that cannot be linked epidemiologically to secondary cases.

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 a malarious area. If malaria is suspected, a Giemsa-stained film of the patient's peripheral blood should be examined for parasites. Thick and thin blood films must be prepared correctly because diagnostic accuracy depends on blood-film quality and examination by experienced laboratory personnel* (Appendix).

* 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 Epidemiology Branch at 770-488-7788.

Results

General Surveillance

For 2002, CDC received 1,337 malaria case reports occurring among persons in the United States and its territories, representing a 3.3% decrease from the 1,383 cases reported with a date of onset in 2001 (*8*). This incidence is the sixth highest number of reported cases since 1980 and represents the second highest number of U.S. civilian cases reported in the previous 30 years (Table 1). In 2002, a total of 849 cases occurred among U.S. civilians, compared with 891 cases reported for 2001; the number of cases among foreign civil-

TABLE 1. Number of malaria cases* among U.S. and foreign civilians and U.S. military personnel — United States, 1973–2002

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**

* 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.

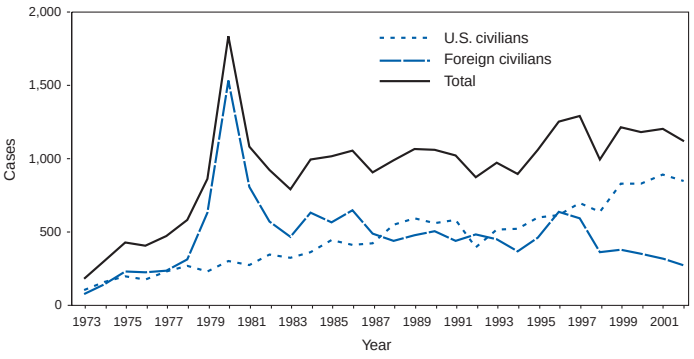
† The increase in persons with unknown civil status that occurred in the 1990s might be attributed to a change in the surveillance form.

ians decreased from 316 cases to 272 (Table 1). During 1997–2001, an increase in cases among U.S. civilians has occurred, but cases among foreign civilians have decreased (Figure 1). Cases among U.S. military personnel increased from 18 to 33 in 2002. For 183 cases, information was insufficient to determine civilian or military status.

Plasmodium Species

The infecting species of *Plasmodium* was identified in 1,124 (84.1%) of the cases reported in 2002. *P. falciparum* and *P. vivax* were identified in blood films from 52.3% and 25.4% of infected persons, respectively (Table 2). The 699 *P. falciparum* cases reported for 2002 represented a 0.8% increase from the 693 cases in 2001, and the number of *P. vivax* infections decreased by 11.9% (from 385 in 2001 to 339 in 2002). Among 1,044 cases in which both the region of acquisition and the infecting species were known, 81.7 % of infections acquired in Africa were attributed to *P. falciparum*; 9.5% were attributed to *P. vivax*. The converse was true of infections acquired in the Americas and Asia: 70.0% and 82.8% were attributed to *P. vivax*, and only 26.2% and 11.5% were attributed to *P. falciparum*, respectively.

FIGURE 1. Number of malaria cases among U.S. and foreign civilains — United States,* 1973–2002†



* 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.

Region of Acquisition and Diagnosis

All but five reported cases (n = 1,332) were imported. Of 1,252 imported cases in which the region of acquisition was known, the majority (72.1%; n = 903) were acquired in Africa; 13.7% (n = 171) and 11.3% (n = 141) were acquired in Asia and the Americas, respectively (Table 3). A limited number of imported cases were acquired in Oceania (3.0%; n = 37). The highest concentration of cases acquired in Africa came from countries in West Africa (69.7%; n = 629); a substantial percentage of cases acquired in Asia came from the Indian subcontinent (52.6%; n = 90). From within the Americas, the majority of cases were acquired in Central America and the Caribbean (68.1%; n = 96), followed by South America (24.8%; n = 35) and Mexico (7.1%; n = 10). Information regarding region of acquisition was missing for 80 (6.4%) of the imported cases. Compared with 2001, the number of reported malaria cases acquired in Asia and Africa increased by 4.3% and 1.9%, respectively, and the number of cases acquired in the Americas decreased by 41.2%.

In the United States, the five health departments reporting the highest number of malaria cases were New York City (n = 202), California (n = 197), Maryland (n = 101), Florida (n = 87), and Texas (n = 67) (Figure 2). Whereas the majority of these health departments reported an increase in cases compared with 2001, an overall decrease in cases occurred 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, decreased travel to malaria-endemic regions, fluctuation in reporting to state and local health departments, or an increased use of effective antimalarial chemoprophylaxis.

Interval Between Arrival and Illness

The interval between date of arrival in the United States and onset of illness and the infecting *Plasmodium* species were known for 681 (51.1%) of the imported cases of malaria (Table 4). Symptoms began before arrival in the United States

TABLE 2. Number of malaria cases, by *Plasmodium* species — United States, 2000, 2001, and 2002

Plasmodium species	2000		2001		2002	
	No.	(%)	No.	(%)	No.	(%)
P. falciparum	611	(43.6)	693	(50.1)	699	(52.3)
P. vivax	522	(37.2)	385	(27.8)	339	(25.4)
P. malariae	67	(4.8)	62	(4.5)	38	(2.8)
P. ovale	32	(2.3)	50	(3.6)	37	(2.8)
Mixed	9	(0.6)	14	(1.0)	11	(0.8)
Undetermined	161	(11.5)	179	(12.9)	213	(15.9)
Total	**1,402**	**(100.0)**	**1,383**	**(100.0)**	**1,337**	**(100.0)**

TABLE 3. Imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2002

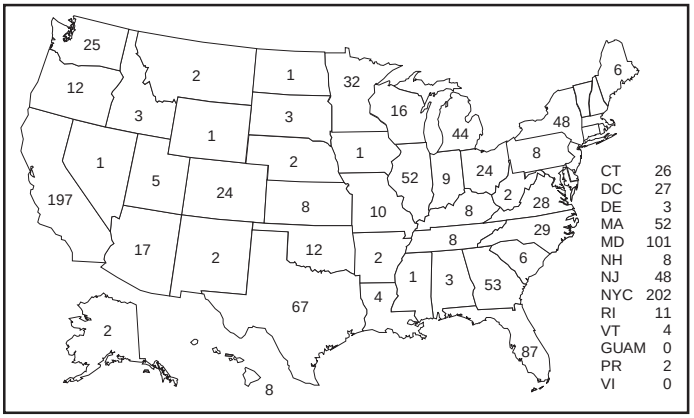
Country of acquisition	*Plasmodium* species						
	P. falciparum	*P. vivax*	*P. malariae*	*P. ovale*	Unknown	Mixed	Total
Africa	**613**	**71**	**30**	**30**	**153**	**6**	**903**
Benin	2	0	0	0	1	0	3
Burkina Faso	7	0	0	0	2	0	9
Burundi	0	0	1	0	0	0	1
Cameroon	27	5	1	5	9	0	47
Central African Republic	6	0	0	0	0	0	6
Chad	0	0	1	0	3	0	4
Congo	4	1	0	1	4	0	10
Cote d'Ivoire	28	4	1	1	4	1	39
Equatorial Guinea	1	0	0	0	0	0	1
Eritrea	0	1	0	0	0	0	1
Ethiopia	3	10	0	1	2	0	16
Gabon	1	0	0	0	2	0	3
Gambia	5	2	0	0	1	0	8
Ghana	104	6	4	3	19	2	138
Guinea	8	1	0	0	1	0	10
Kenya	33	6	2	2	9	0	52
Liberia	28	3	2	0	6	0	39
Madagascar	2	1	0	0	1	0	4
Malawi	5	0	1	1	1	0	8
Mali	12	0	0	0	0	0	12
Mauritania	0	1	0	0	0	1	2
Mozambique	1	1	0	0	0	0	2
Niger	1	2	0	0	0	0	3
Nigeria	225	9	10	6	57	2	309
Rwanda	1	0	0	0	0	0	1
Senegal	17	2	1	0	0	0	20
Sierra Leone	15	1	0	0	1	0	17
Somalia	2	0	0	0	0	0	2
South Africa	4	1	1	0	0	0	6
Sudan	2	2	0	2	0	0	6
Tanzania	4	3	0	0	3	0	10
Togo	5	0	0	0	2	0	7
Tunisia	0	0	0	0	1	0	1
Uganda	15	3	1	3	8	0	30
Zaire	0	0	1	0	1	0	2
Zambia	8	0	0	2	3	0	13
Zimbabwe	2	0	1	0	0	0	3
West Africa, unspecified	12	0	0	1	2	0	15
Central Africa, unspecified	1	0	0	0	0	0	1
East Africa, unspecified	0	3	0	0	0	0	3
Africa, unspecified	22	3	2	2	10	0	39
Asia	**18**	**130**	**3**	**3**	**14**	**3**	**171**
Afghanistan	0	2	0	0	0	0	2
Burma (Myanmar)	0	3	0	0	0	0	3
China	0	2	0	0	0	0	2
India	5	72	2	1	10	0	90
Indonesia	1	13	0	1	1	0	16
Iraq	1	0	0	0	0	0	1
Korea (South)	0	21	0	0	2	0	23
Lao PDR	2	1	0	0	0	0	3
Pakistan	0	10	0	1	0	2	13
Philippines	3	2	1	0	1	0	7
Thailand	3	1	0	0	0	0	4
United Arab Emirates	0	0	0	0	0	1	1
Vietnam	0	1	0	0	0	0	1
Yemen	2	0	0	0	0	0	2
Asia, unspecified	0	1	0	0	0	0	1
Southeast Asia, unspecified	1	1	0	0	0	0	2

TABLE 3. (*Continued*) Imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2002

Country of acquisition	*Plasmodium* species						
	P. falciparum	*P. vivax*	*P. malariae*	*P. ovale*	Unknown	Mixed	Total
Central America and the Caribbean	**23**	**62**	**1**	**1**	**9**	**0**	**96**
Costa Rica	0	3	0	0	0	0	3
Dominican Republic	0	1	0	0	0	0	1
El Salvador	1	6	0	0	0	0	7
Guatemala	1	19	0	0	2	0	22
Haiti	19	1	0	0	2	0	22
Honduras	2	22	1	1	3	0	29
Nicaragua	0	1	0	0	2	0	3
Panama	0	7	0	0	0	0	7
Central America, unspecified	0	2	0	0	0	0	2
North America	**2**	**7**	**0**	**0**	**1**	**0**	**10**
Mexico	2	7	0	0	1	0	10
South America	**8**	**19**	**2**	**1**	**5**	**0**	**35**
Brazil	0	4	0	0	1	0	5
Ecuador	4	8	1	1	2	0	16
Guyana	4	1	1	0	1	0	7
Peru	0	2	0	0	0	0	2
Venezuela	0	3	0	0	1	0	4
South America, unspecified	0	1	0	0	0	0	1
Oceania	**5**	**23**	**1**	**1**	**7**	**0**	**37**
Papua New Guinea	5	21	1	0	6	0	33
Solomon Islands	0	0	0	1	1	0	2
Vanuatu	0	2	0	0	0	0	2
Europe/Newly Independent States	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Unknown	**29**	**24**	**0**	**1**	**24**	**2**	**80**
Total	**698**	**336**	**37**	**37**	**213**	**11**	**1,332**

for 92 (13.5%) persons, whereas symptoms began after arrival in the United States for 589 (86.5%) of these patients. Clinical malaria developed within 1 month after arrival in 385 (79.9%) of the 482 *P. falciparum* cases and in 57 (36.8%) of the 155 *P. vivax* cases (Table 4). Only seven (1.0%) of the 681 persons became ill >1 year after returning to the United States.

FIGURE 2. Number of malaria cases, by state in which the disease was diagnosed — United States, 2002



Imported Malaria Cases

Imported Malaria Among U.S. Military Personnel

In 2002, a total of 33 cases of imported malaria were reported among U.S. military personnel. These cases were reported by state health departments. Of the 28 cases for whom information regarding chemoprophylaxis use was available, 19 (67.9%) patients were not using any chemoprophylaxis.

Imported Malaria Among Civilians

A total of 1,121 imported malaria cases were reported among civilians. Of these, 849 (75.7%) cases occurred among U.S. residents, and 272 (24.3%) cases occurred among residents of other countries (Table 5). Of the 849 imported malaria cases among U.S. civilians, 641 (75.5%) had been acquired in Africa, an increase of 1.1% from cases reported in 2001. Asia accounted for 89 (10.5%) cases of imported malaria among U.S. civilians, and travel to the Central American and Caribbean regions accounted for an additional 57 (6.7%) cases. Of the 272 imported cases among foreign civilians, the majority of cases were acquired in Africa (66.2%; n = 180).

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, 2002

	P. falciparum		*P. vivax*		*P. malariae*		*P. ovale*		Mixed		Total	
Interval (days)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<0†	73	(15.1)	13	(8.4)	3	(15.0)	2	(11.1)	1	(16.7)	**92**	**(13.5)**
0–29	385	(80.0)	57	(36.8)	12	(60.0)	4	(22.2)	3	(50.0)	**461**	**(67.7)**
30–89	19	(3.9)	35	(22.6)	3	(15.0)	3	(16.7)	0	0	**60**	**(8.8)**
90–179	1	(0.2)	23	(14.8)	1	(5.0)	6	(33.3)	1	(16.7)	**32**	**(4.7)**
180–364	1	(0.2)	24	(15.5)	0	0	3	(16.7)	1	(16.7)	**29**	**(4.3)**
≥365	3	(0.6)	3	(1.9)	1	(5.0)	0	0	0	0	**7**	**(1.0)**
Total	**482**	**(100.0)**	**155**	**(100.0)**	**20**	**(100.0)**	**18**	**(100.0)**	**6**	**(100.0)**	**681**	**(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.

Antimalarial Chemoprophylaxis Use

Chemoprophylaxis Use Among U.S. Civilians

Information concerning chemoprophylaxis use and travel area was known for 799 (94.1%) of the 849 U.S. civilians who had imported malaria. Of these 799 persons, 482 (60.3%) had not taken any chemoprophylaxis, and 136 (17.0%) had not taken a CDC-recommended drug for the area visited (*9*). Only 167 (20.9%) U.S. civilians had taken a CDC-recommended medication (*9*). Data for the specific drug taken were missing for the remaining 14 (1.8%) travelers. A total of 110 (65.9%) patients on CDC-recommended prophylaxis had reported taking mefloquine weekly; 30 (18.0%) had taken doxycycline daily; nine (5.4%) had taken atovaquone-proguanil daily; and six (3.6%) who had traveled only in areas where chloroquine-resistant malaria has not been documented had taken chloroquine weekly. Information on adherence to the drug regimen for these persons is presented in the following section. Twelve patients (7.2%) had taken combinations of drugs that included ≥1 CDC-recommended drug for the travel region. Of the 136 patients taking a nonrecommended drug, 67 (49.3%) 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 185 patients (i.e., 167 U.S. civilians, eight persons in the U.S. military, three foreign civilians, and seven persons whose information regarding their status was missing) experienced malaria after taking a recommended antimalarial drug for chemoprophylaxis. Information regarding infecting species was available for 158 (85.4%) patients taking a recommended antimalarial drug; the infecting species was undetermined for the remaining 27.

Cases of *P. vivax* or *P. ovale* After Recommended Prophylaxis Use. Of the 185 patients who experienced malaria after recommended chemoprophylaxis use, 69 cases (37.3%) were caused by *P. vivax* and 13 (7.0%) by *P. ovale*. Twenty-two (26.8%) of these 82 patients were noncompliant with antimalarial chemoprophylaxis.

A total of 41 (50.0%) cases of *P. vivax* or *P. ovale* occurred >45 days after arrival in the United States. These cases were consistent with relapsing infections and, thus, do not indicate primary prophylaxis failures. Information was insufficient, because of missing data regarding symptom onset or return date, to assess whether 28 cases were relapsing infections. Thirteen cases, 10 by *P. vivax* and three by *P. ovale*, occurred

TABLE 5. Number of imported malaria cases among U.S. and foreign civilians, by region of acquisition — United States, 2002*

	United States		Foreign		Total	
Area or region	No.	(%)	No.	(%)	No.	(%)
Africa	641	(75.5)	180	(66.9)	**821**	**(73.2)**
Asia	89	(10.5)	45	(16.9)	**134**	**(12.0)**
Central America and the Caribbean	57	(6.7)	29	(10.2)	**86**	**(7.7)**
South America	23	(2.7)	8	(3.0)	**31**	**(2.8)**
North America	3	(0.4)	6	(1.9)	**9**	**(0.8)**
Oceania	32	(3.8)	3	(1.1)	**35**	**(3.1)**
Europe/Newly Independent States	0	(0)	0	(0)	**0**	**(0)**
Unknown†	4	(0.4)	1	(0.3)	**5**	**(0.4)**
Total	**849**	**(100.0)**	**272**	**(100.0)**	**1,121**	**(100.0)**

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

≤45 days after the patient returned (n = 9) or before return (n = 4) to the United States. Six of the 13 patients were known to be noncompliant with their antimalarial chemoprophylaxis regimen, and four patients were not known to be noncompliant. The region of acquisition varied for the four patients who were not known to be noncompliant (one from East Africa, one from West Africa, one from Central Africa, and one from Asia). The remaining three patients reported compliance with an antimalarial chemoprophylaxis regimen. Of these three, two had traveled to Papua New Guinea and one to sub-Saharan Africa. Two of these patients reported taking mefloquine, and one reported using doxycycline. Blood samples for serum drug levels were not available for these three patients. The possible explanations for these cases include inappropriate dosing, noncompliance that was not reported, malabsorption of the drug or emerging parasite resistance.

Cases of *P. falciparum* and *P. malariae* after Recommended Prophylaxis Use. The remaining 103 cases of malaria reported among persons who had taken a recommended antimalarial drug for chemoprophylaxis include 69 cases of *P. falciparum*, six cases of *P. malariae*, one case of mixed infection, and 27 cases in which the infecting species was unidentified.

A total of 61 of the 69 *P. falciparum* cases among those who reported taking a recommended antimalarial drug were acquired in Africa, five in Asia, and three in Oceania. In 42 (60.9%) of these 69 cases, noncompliance with antimalarials was reported. In five (7.2%) of these 69 cases, patients reported compliance with antimalarial chemoprophylaxis. All five of these patients had traveled to Africa. Of the four who had traveled to West Africa, three had traveled to Ghana and one to Sierra Leone. Three had reported taking mefloquine, and two had reported taking atovaquone-proguanil for malaria chemoprophylaxis. A mefloquine blood level was available for one of the patients who had traveled to Ghana; this patient's mefloquine level was undetectable, thus indicating either noncompliance with the recommended regimen or complete malabsorption of the drug. Blood samples were not available for the remaining four patients who reported compliance with a recommended regimen. Twenty-two cases occurred of *P. falciparum* for which patient compliance was unknown. The majority of these cases were acquired in Africa (n = 19): 11 in West Africa, three in East Africa, two in Central Africa, and three in an unspecified African region. Three cases were acquired outside Africa: one in Indonesia and two in Papua New Guinea. Blood samples were not available for the 22 patients whose compliance status was unknown.

Five of the six *P. malariae* cases among those who reported taking a recommended antimalarial drug were acquired in Africa. In three (50.0%) of these six cases, noncompliance with antimalarials was reported. One (16.7%) case reported compliance with a recommended chemoprophylaxis regimen using doxycycline. This patient traveled to southern Africa and became ill before returning to the United States. In the two remaining cases, patient compliance with prophylaxis was unknown and blood samples were not available; both had traveled in Africa.

Purpose of Travel

Purpose of travel to malaria-endemic areas was reported for 745 (87.8%) of the 849 U.S. civilians with imported malaria (Table 6). Of the U.S. civilians with malaria, the largest proportion (45.0%) were persons who had visited friends or relatives in malarious areas; the second and third highest proportion, 10.6% and 10.2%, had traveled to do missionary work and for tourism, respectively.

Malaria During Pregnancy

A total of 32 cases of malaria were reported among pregnant women in 2002, representing 7.4% of cases among women. Twelve of the 32 (37.5%) were among U.S. civilians. Six of these twelve women had traveled to visit friends and relatives; seven had traveled in Africa, and five in Asia. A total of 28.1% of pregnant women and 28.7% of nonpregnant women reported taking malaria chemoprophylaxis.

Malaria Acquired in the United States

Congenital Malaria

One case of congenital malaria was reported in 2002 and is described in the following case report:

- **Case 1.** On August 22, 2002, a full-term female, age 3 weeks, was admitted to a local hospital with a 2-day history of inadequate feeding and somnolence. She had

TABLE 6. Number of imported malaria cases among U.S. civilians, by purpose of travel at the time of acquisition — United States, 2002

	Imported cases	
Category	No.	(%)
Visiting friends/relatives	382	(45.0)
Tourism	87	(10.2)
Missionary or dependent	90	(10.6)
Business representative	65	(7.7)
Student/teacher	52	(6.1)
Peace Corps volunteer	9	(1.0)
Refugee/immigrant	2	(0.3)
Air crew/sailor	2	(0.3)
Other/mixed purpose	56	(6.6)
Unknown	104	(12.2)
Total	**849**	**(100.0)**

had suspected meconium aspiration and sepsis at birth. At that time, she was admitted to the neonatal intensive care unit. All cultures were negative, and she was discharged from the hospital at age 3 days. At the time of the subsequent admission, her physical examination was normal. Laboratory examination revealed thrombocytopenia (85,000/mm^3). Blood, urine, and cerebrospinal fluid cultures were obtained, and the patient was treated with ampicillin and cefotaxime. A blood film indicated intraerythrocytic parasites consistent with *P. vivax*. She recovered completely after treatment with quinine for 7 days. The infant had been born via normal spontaneous vaginal delivery to a mother who had worked in Guyana and who had a history of malaria. The mother's first episode of malaria was in April 1999, with three subsequent episodes in April, June, and August 2001. During the episodes, she was treated with either chloroquine or sulfadoxine-pyrimethamine, with complete resolution of symptoms. Three days before giving birth, the mother experienced fever, chills, and severe headache. A blood film sent on the day she gave birth revealed *P. vivax* parasites. The mother recovered completely after treatment with chloroquine and primaquine.

Cryptic Malaria

Three cases of cryptic malaria were reported in 2002 and are described in the following case reports:

- **Case 1.** On January 21, 2002, a male aged 56 years from New Jersey was admitted to a local hospital with a 3-week history of fever. He was started on levofloxacin and ceftriaxone for possible pneumonia. On hospital day 2, the laboratory identified *P. falciparum* on a blood film; this result was subsequently confirmed by blood film and polymerase chain reaction (PCR) at CDC. The patient reported no recent history of travel. His last reported trip to a malarious region was to Afghanistan 15 years earlier. He denied any history of blood transfusions or intravenous drug use. He was an obstetrician-gynecologist, and his patient population consisted of immigrants from Africa. He denied any knowledge of needle sticks or cuts on his hands while examining, delivering, or performing surgery on patients with risk factors for malaria. He was successfully treated with quinine, doxycycline, and clindamycin. He made a complete recovery and was discharged.
- **Case 2.** On August 23, 2002, a person aged 19 years from Virginia was examined at a family health clinic; the patient had a 4-day history of fatigue, fever, chills, muscle aches, and sinus pain. Her illness was diagnosed as a sinus infection, and she was treated with azithromycin and desloratadine. Four days later, the patient returned to the clinic with persistent symptoms and also had dizziness and nausea. On physical examination, the patient had fever (temperature: 103.5°F) and tachycardia. Laboratory findings included pancytopenia (platelet count: 61,000 mm^3; hemoglobin: 10g/dL; and white blood cell count: 3,300/µL). The patient's therapy was changed to levofloxacin. Malaria parasites were identified on a routine complete blood count; a review of the blood film by a local university hospital confirmed the diagnosis of *P. vivax* malaria. The patient had no risk factors for malaria, including international travel, blood transfusion, organ transplantation or needle sharing. The patient recovered after treatment with chloroquine and primaquine (*10*).
- **Case 3.** On August 25, 2002, a person aged 15 years from Virginia was examined at a local emergency department; the patient had a 2-week history of headaches and 4 days of fever, nausea, vomiting, malaise, and nose bleeds. The patient did not have a history of travel, blood transfusion, organ transplantation, or needle sharing. On physical examination, the patient had a temperature of 105°F, tachycardia, splenomegaly, and jaundice. Laboratory studies revealed pancytopenia (platelet count: 48,000 mm^3; hemoglobin: 11.6 mg/dL; and white blood cell count: 3,200/µL). A malaria film revealed *Plasmodium* species, initially diagnosed as nonfalciparum. The patient was admitted to the hospital and treated with quinine and clindamycin. The blood film results were subsequently confirmed as *P. vivax* by the Virginia Department of Health. The patient experienced tinnitus, requiring discontinuation of the quinine, and subsequently completed treatment with chloroquine and primaquine (*10*).

These two cases from Northern Virginia were investigated by local public health officials and CDC, who concluded that the cases represented an outbreak of locally acquired mosquito-transmitted malaria. The investigation revealed that the patient aged 19 years often visited friends who lived directly across the street from the home of the patient aged 15 years. PCR was performed on blood from both patients, and it revealed that the infecting parasites were genotypically identical to each other, indicating a common source. Medical charts from two local hospitals were reviewed, and local physicians were contacted; however, no other cases of malaria were identified (*10*).

Induced Malaria

One case of induced malaria was reported in 2002 and is described in the following case report:

- **Case 1.** On June 30, 2002, *P. malariae* was diagnosed in a female aged 84 years, who was being regularly trans-

fused with red blood cells for anemia and angiodysplasia. The laboratory result was subsequently confirmed by blood film and PCR at CDC. Ten donors from whom the patient had received packed red blood cells in the previous 4 months were tested, and one was positive for *P. malariae* by serology. The implicated infective donor, a male aged 17 years, had emigrated from West Africa in 1994 and had donated blood in 2002. The patient was transfused with this unit on May 1, 2002. Blood samples from the donor sent to CDC revealed immunoflourescent antibody titers of >1:16384 for *P. malariae*. Parasites were not detected in the donor's blood film nor by PCR testing. Upon subsequent notification and interview, the donor denied ever having had malaria and reported no history indicative of prior malarial infection (personal communication, Monica Parise, M.D., CDC, National Center for Infectious Diseases, January 2004).

Deaths Attributed to Malaria

Eight deaths attributable to malaria were reported in 2002 and are described in the following case reports:

- **Case 1.** On February 12, 2002, a female aged 33 years, with a history of seizure disorder, was brought by paramedics to a hospital emergency department with respiratory distress. She had a 5-day history of fever, and a 1-day history of lethargy and difficulty breathing. During the course of her illness, she sought care at a clinic on two separate occasions and was discharged with a diagnosis of viral syndrome. Three weeks before the onset of symptoms, the patient had returned from a 2-week missionary trip to Sudan. The patient had been prescribed weekly mefloquine for malaria chemoprophylaxis, but was reported to be noncompliant with the regimen. On triage examination, the patient had tachypnea (respiratory rate: 28 breaths/minute), tachycardia (pulse: 112 beats/minute), cool extremities, and scleral icterus. Before being seen by the physician in the emergency department, the patient suffered a prolonged generalized seizure, which was refractory to anticonvulsant therapy. She experienced respiratory failure and required endotracheal intubation and mechanical ventilation. Soon after intubation, she suffered a cardiac arrest and died. Postmortem examination revealed severe *P. falciparum* infection with diffuse pulmonary edema and hepatosplenomegaly.
- **Case 2.** On April 5, 2002, a male aged 54 years was examined at his primary-care physician's office. The patient had a 1-week history of fever, fatigue, and loose stools. He had been working in Cameroon and Chad for 2 months and had returned 10 days before the visit to his physician. He had not taken malaria chemoprophylaxis. He was treated as an outpatient with metronidazole. During the next 4 days, he experienced weakness with difficulty standing up, anorexia, and dark urine, which lead him to return to his physician. Laboratory examination demonstrated renal insufficiency (blood urea nitrogen: 86 mg/dL; creatinine: 3.1 mg/dL) and thrombocytopenia (14,000/mm^3). A blood film was taken at the physician's office, and the patient was administered a dose of hydroxychloroquine presumptively, before results of the blood film were available. He was sent to the emergency department and subsequently admitted to the intensive care unit. On physical exam, he appeared ill, with pale conjunctiva, dry mucous membranes, and cool extremities. He was hypotensive (blood pressure: 82/52 mmHg) and tachycardic (heart rate: 125 beats/minute). Repeat laboratory examination in the emergency department demonstrated acidosis (bicarbonate: 15.5 mmol/L), renal insufficiency (creatinine: 3.7 mg/dL), and thrombocytopenia. He was initially continued on hydroxychloroquine. Approximately 10 hours after admission, the blood film revealed ring trophozoites consistent with *P. falciparum* infection. The parasite density was not reported. The patient was started on oral quinine and doxycycline. Approximately 20 hours after admission, the patient experienced a decreased level of consciousness, followed by sudden onset of severe respiratory distress. He was determined to be severely anemic (7.4 g/dL). The patient suffered a cardiac arrest, could not be resuscitated, and died 28 hours after admission.
- **Case 3.** On May 17, 2002, a male aged 43 years was admitted to a local hospital with a 5-day history of fever, chills, joint pain, and anorexia. Six days before admission, he had returned from Uganda, where he had worked as a missionary for 1 month. The patient had not taken malaria chemoprophylaxis. Physical examination revealed fever (temperature: 104.5°F), tachycardia (heart rate: 112 beats/minute), and hypotension (blood pressure: 86/63 mmHg). Initial laboratory findings included thrombocytopenia (platelets: 50,000 mm^3), prolonged prothrombin time (18.1 seconds), prolonged partial thromboplastin time (52 seconds), elevated total bilirubin (5.7 mg/dL), and elevated hepatic transaminases. A blood film demonstrated intraerythrocytic ring forms consistent with *P. falciparum*. The parasite density was not reported. The patient was started on oral quinine and doxycycline and admitted to the intensive care unit. On hospital day 2, he became afebrile, and his blood pressure stabilized. With his improved condition, he was transferred to the regular in-patient ward. On hospital day 3, he experienced respi-

ratory distress, and a chest radiograph revealed pulmonary edema and bilateral pleural effusions. His illness was diagnosed as adult respiratory distress syndrome, and his antimalarial treatment was changed to intravenous quinidine and doxycyline. He experienced respiratory failure and refractory hypotension on hospital day 4. He was treated with mechanical ventilation and vasopressors. A repeat blood film was negative for *P. falciparum*. On hospital day 5, the patient experienced wide-complex tachycardia during the placement of an internal jugular catheter, requiring treatment with an intravenous lidocaine infusion. The intravenous quinidine was discontinued after a repeat electrocardiogram revealed a prolonged Q-T interval (i.e., the time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole). He experienced bilateral pneumothoraces and acute renal failure. The patient never regained consciousness and died on hospital day 7.

- **Case 4.** On June 1, 2002, a previously healthy male aged 46 years was asked to return to the emergency department and admitted to the hospital after a blood film, taken 2 days earlier, revealed malaria parasites. He had returned from a 2-week trip to Nigeria 10 days earlier, and he had not taken malaria chemoprophylaxis. During his first visit to the emergency department, the patient complained of fever, fatigue, and chills and was sent home with a diagnosis of probable viral syndrome, before obtaining the results of the blood film. When he returned to the emergency department on June 1, he reported persistent fever and chills, as well as myalgias, night sweats, and anorexia. Physical examination revealed scleral icterus. Laboratory investigations on admission revealed thrombocytopenia (50,000/mm^3), elevated creatinine (2.7 mg/dL), elevated bilirubin (4.9 mg/dL), and elevated liver transaminases. The laboratory was unable to identify the malaria species and did not report a parasite density. A chest radiograph revealed bilateral patchy infiltrates. The patient was started on oral quinine and doxycycline. On hospital day 2, the patient had persistent high fever and experienced vomiting, worsening renal insufficiency (creatinine: 4.7 mg/dL), worsening anemia with a 3.2-g/dL drop in hemoglobin from admission (from 13.7 g/dL to 10.5 g/dL), and further elevation in bilirubin and liver transaminases. His blood film was reviewed by a pathologist who reported the species *P. falciparum* with >50% parasitemia. The patient underwent exchange transfusion and was treated with intravenous quinidine and doxycycline. During the following 48 hours, he suffered renal failure, pulmonary edema, and congestive heart failure. He required hemodialysis as well as mechanical ventilation for respiratory failure associated with adult respiratory distress syndrome. Repeat blood films on the fourth and fifth day after admission revealed 3% and 1% parasitemia, respectively. After receiving 2 days of oral doxycycline and quinine and 7 days of intravenous doxycycline and quinidine, all antimalarial medication was discontinued. A blood film collected 12 days after admission was negative. His clinical course continued to deteriorate. He experienced disseminated intravascular coagulopathy, and on hospital day 19, he suffered cardiac arrest and died.
- **Case 5.** On June 9, 2002, a female aged 51 years was admitted to a local hospital with a 1-week history of fever, chills, and back pain. Friends, who noted an altered level of consciousness, brought her to the emergency department. She had traveled to Nigeria and Ghana for 3 weeks and returned to the United States approximately 10 days before admission. The patient reportedly had not taken malaria chemoprophylaxis. Examination revealed mild hypotension (blood pressure: 94/50 mmHg), tachycardia (136 beats/minute), and altered mental status. Initial laboratory findings included anemia (hemoglobin: 9.7 g/dL); thrombocytopenia (platelets: 27,000 mm^3); decreased bicarbonate (15 mmol/L); renal failure (blood urea nitrogen: 138 mg/dL; creatinine: 8.5 mg/dL); elevated total bilirubin (8.1 mg/dL); and elevated hepatic transaminases. A malaria blood film demonstrated *P. falciparum* (parasitemia >10%). She was started on intravenous quinidine and doxycycline and placed on mechanical ventilation in the emergency department. She was admitted to the intensive care unit and received an exchange transfusion shortly after admission. She was treated with vasopressors and started on hemodialysis. On hospital day 3, she experienced pulmonary edema. Despite a repeat blood film on hospital day 3 that revealed <1% parasitemia, her clinical condition continued to deteriorate. She required increasing ventilatory support, remained hypotensive, and experienced disseminated intravascular coagulation. On hospital day 4, she was treated with one cycle of plasmapheresis, which was completed without complication. The patient demonstrated no improvement and died on hospital day 5.
- **Case 6.** On October 4, 2002, a male aged 67 years was admitted to the hospital with a 7-day history of progressive fatigue with episodes of mental confusion and a 3-day history of fevers, shaking chills, headache, gross hematuria, and nausea. He had returned from a 3-week trip to Zambia 3 days earlier. He had not taken malaria chemoprophylaxis. Initial physical exam was notable for hypotension (blood pressure: 86/58 mmHg), scleral icterus, and hepatosplenomegaly. Laboratory examination

revealed hyponatremia (125 mmol/L), elevated total bilirubin (4.2 mg/dL), and thrombocytopenia (17,000/mm^3). A blood film revealed *P. falciparum* (9.2% parasitemia). Treatment with oral quinine and doxycycline was initiated. On hospital day 2, he became obtunded, experienced a right gaze preference, and suffered a focal seizure. A computed axial tomography scan of the head was normal. Repeat laboratory studies revealed persistent hyponatremia, thrombocytopenia, renal insufficiency (blood urea nitrogen: 66 mg/dL; creatinine: 2.2 mg/dL), and acidosis (bicarbonate: 15 mmol/L). His antimalarial therapy was changed to intravenous quinidine and doxycycline. He was treated with mechanical ventilation and vasopressors. On hospital day 3, he experienced acute renal failure, adult respiratory distress syndrome, and severe anemia (hemoglobin: 6.3 g/dL). The parasitemia decreased with treatment, but the patient never regained consciousness and died on hospital day 5.

- **Case 7.** On November 2, 2002, a previously healthy male aged 55 years was transported to a local hospital emergency department after becoming acutely unresponsive at home. He suffered cardiac arrest and died shortly after arrival. He had been working as a missionary in Africa for 6 months and had recently returned to the United States. Whether the patient had taken malaria chemoprophylaxis was unknown. No further details regarding his symptoms were available. Autopsy findings included histopathologic changes in multiple organs consistent with malaria and focal marked atherosclerosis of the coronary arteries. PCR performed on whole blood revealed *P. falciparum* infection. The medical examiner identified the cause of death as atherosclerotic cardiovascular disease with malaria as a contributing factor.
- **Case 8.** On November 19, 2002, a male aged 50 years was found dead at his home. No further details regarding symptoms before his death were available. He had traveled to Sudan and Uganda and had returned two weeks before his death. He had not taken malaria chemoprophylaxis. He was reportedly philosophically opposed to allopathic medicine. He became ill soon after his return to the United States but did not seek care. Postmortem blood films demonstrated a substantial number of trophozoites consistent with *P. falciparum*.

Discussion

A total of 1,337 cases of malaria were reported to CDC for 2002, representing a 3.3% decrease from the 1,383 cases reported for 2001. This change primarily resulted from a decrease in cases acquired in the Americas. Since 2000, CDC has routinely contacted state health departments to ask for outstanding malaria case reports from the previous reporting year or for a statement that reporting is complete. The decrease in cases in 2002, compared with 2001, probably is a result of expected variation in the number of cases, although other possibilities include decreased international travel, changing patterns of travel (e.g., decreased immigration from malarious areas), or an increased use of effective antimalarial chemoprophylaxis.

One reason for conducting malaria surveillance is to monitor for prophylaxis failures that might indicate emergence of drug resistance; however, approximately 75% 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. Of the cases where appropriate prophylaxis was reported and for whom adequate information was available regarding 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 only available for one patient. Therefore, differentiating among inaccurate reporting of compliance, malabsorption of the antimalarial drug, and emerging drug resistance is impossible. No conclusive evidence exists to indicate a single national or regional source of infection among this group of patients or the failure of a particular chemoprophylactic regimen. Health-care providers are encouraged to contact CDC rapidly whenever they suspect chemoprophylaxis failure, thus enabling measurement of serum drug levels of the antimalarial drugs in question.

In 2001, to better evaluate chemoprophylaxis failures, CDC revised the NMSS case report form to facilitate collection of more thorough data regarding chemoprophylaxis. The revised form solicits more detailed information regarding the prescribed regimen, the degree of compliance with the regimen, and the reasons for noncompliance, if any. Data gathered from the responses will be useful in generating public health messages to improve use of antimalarial chemoprophylaxis and therefore decrease malaria-associated morbidity and mortality among U.S. civilians.

The importance of taking correct precautions and chemoprophylaxis is underscored by the eight fatal cases of malaria that occurred in the United States in 2002. An earlier review of deaths attributed to malaria in the United States identified specific risk factors for fatal malaria, including failure to take

recommended antimalarial chemoprophylaxis, refusal of or delay in seeking medical care, and misdiagnosis (*11*).

The occurrence of 12 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*); the fetus might be adversely affected as well (*13*). Pregnant travelers should be counseled to avoid travel to malarious areas, if possible. 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 from CDC's Internet site at http://www.cdc.gov/travel/mal_preg_pub.htm.

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 when evaluating febrile illnesses among international visitors, immigrants, refugees, migrant laborers, and international travelers.

Prompt treatment of suspected malaria is essential, because persons with *P. falciparum* infection are at risk for experiencing life-threatening complications soon after the onset of illness. Ideally, therapy for malaria should be initiated immediately after the diagnosis has been confirmed by a positive blood film. Treatment should be determined on the basis of the infecting *Plasmodium* species, the probable geographic origin of the parasite, the parasite density, and the patient's clinical status (*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 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, at 770-488-7788 during regular business hours or CDC's Emergency Operations Center, at 770-488-7100 during evenings, weekends, and holidays (ask to page person on call for Malaria Branch). These resources are intended for use by health-care professionals only.

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).

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

Detailed recommendations for preventing malaria are available to the general public 24 hours/day from CDC by telephone at 877-394-8747 (toll-free voice information system) or 888-232-3299 (toll-free facsimile request line), or on the Internet at http://www.cdc.gov/travel/diseases.htm#malaria. In addition, CDC biannually publishes recommendations in *Health Information for International Travel* (commonly referred to as *The Yellow Book*) (*10*), which is available for purchase from the Public Health Foundation (telephone: 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 diagnosing 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 regarding laboratory diagnosis, geographic distribution, clinical features, treatment, and life cycles of >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 can be submitted for diagnostic consultation through electronic 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

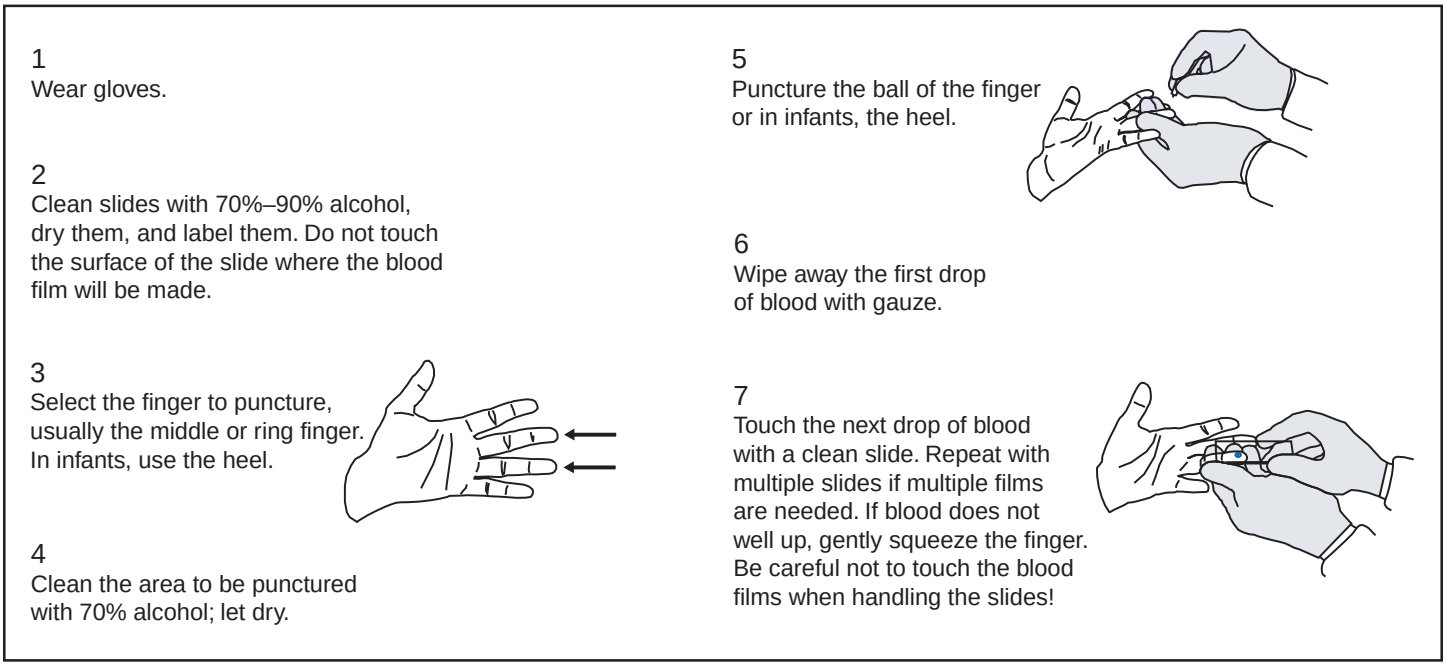
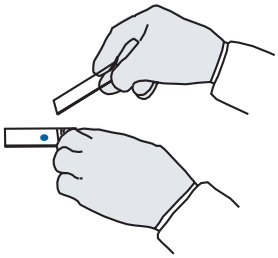


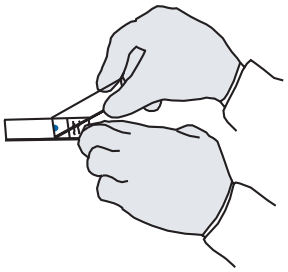
FIGURE A-2. Preparation of thin and thick blood films

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

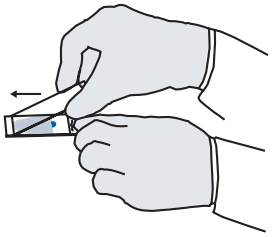
2
Thin film (a): Bring a clean spreader slide, held at a 45-deg angle, toward the drop of blood on the specimen slide.



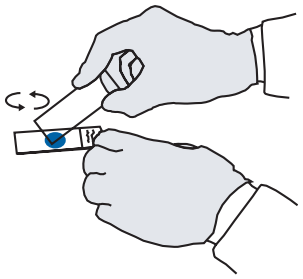
3
Thin film (b): Wait until the blood spreads along the entire width of the spreader slide.



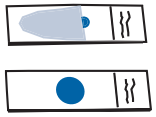
4
Thin film (c): While holding the spreader slide at the same angle, push it forward rapidly and smoothly.



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.

rec•om•men•da•tion: *n*

("rek-ə-mən-'dā-shən) 1 : something, such as a course of action, that is recommended; see also *MMWR*.

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