



Original Contribution

Maternal and Child Health Epidemic-Assistance Investigations, 1946–2005

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Initially submitted February 2, 2010; accepted for publication March 18, 2011.

In this article, the authors focus on epidemic-assistance investigations that dealt with maternal and child health problems, including unintended and adolescent pregnancy and family planning; international reproductive health surveys among refugees; pregnancy outcomes, including abortion, maternal mortality, infant mortality, and birth defects; leukemia; and Reye syndrome. During 1946–2005, a total of 1,969 investigations had sufficient data to classify them as possibly related to maternal and child health and were characterized by distinctive periods. Those related to family planning, pregnancy intention, and reproductive health among refugees began in the early 1970s and continued through 2005. Abortion-related investigations occurred during 1971–1982. Investigations of non-abortion-related maternal morbidity and mortality began in 1979 and included 2 international epidemic-assistance investigations. Investigations of clusters of disease among infants began in the 1960s, with a special focus on Reye syndrome during 1964–1984. Investigations of childhood cancer and birth defects began in the late 1950s. The Centers for Disease Control and Prevention has used the epidemic-assistance investigations mechanism to respond to a wide range of health concerns of women and children. The investigations of abortion-related health problems might have had the best-documented impact on public policy and public health.

abortion, induced; congenital abnormalities; family planning services; infant mortality; maternal health services; pregnancy in adolescence; reproductive medicine; Reye syndrome

Abbreviations: CDC, Centers for Disease Control and Prevention; EISOs, Epidemic Intelligence Service officers; Epi-Aids, epidemic-assistance investigations.

The majority of epidemic-assistance investigations (Epi-Aids) performed by the Centers for Disease Control and Prevention (CDC) staff and the Epidemic Intelligence Service officers (EISOs) include women and children, in part because they constitute the majority of the population and in part because of their unique vulnerabilities to health problems (1). For example, women are vulnerable because of their unique risk of unintentionally becoming pregnant, and infants and children are particularly vulnerable to developmental problems and infectious diseases. Maternal and infant mortality are common sentinel health indicators and often reflect health disparities.

In this paper, we describe patterns of Epi-Aids, illustrative investigations, and, when possible, the public health impact of the Epi-Aids. Our analysis is organized into 7 sections: 1) unintended pregnancy and pregnancy among adolescents;

2) reproductive health surveys; 3) elimination of maternal mortality from abortion in the United States; 4) pregnancy-associated morbidity and mortality; 5) unexpected increases or clusters of disease among infants; 6) Reye syndrome; and 7) child cancer and birth defects.

MATERIALS AND METHODS

To determine how many and what proportion of Epi-Aids were related to maternal and child health, we combined paper-based and electronic databases of Epi-Aids for all years and selected those covering reproductive health topics and maternal and child health problems not related to infectious disease (1). We used Excel (Microsoft, Inc., Redmond, Washington) pivot tables to summarize the data. Whenever

possible throughout this paper, we have cited published works, typically from peer-reviewed journals or CDC's *Morbidity and Mortality Weekly Report* (available at <http://www.cdc.gov/mmwr>), relating to the subject Epi-Aid. We then describe Epi-Aids for selected reproductive and maternal and child health topics, some of which are infection related. Where data are provided but a published source is unavailable, we have noted this in the text as "unpublished data, CDC."

RESULTS

Of the 4,484 Epi-Aids for which investigations were initiated during 1946–2005, a total of 1,969 (43.9%) had sufficient data regarding age, sex, and species (human) to classify them as possibly related to maternal and child health; 1,429 (72.6%) of those were in fact related to this topic: children, 70.7%; women, 12.3%; families, 9.3%; pregnancy, 2.8%; birth defects, 3.2%; and abortion, 1.8%. Of the 540 Epi-Aids not related to maternal and child health, the most common suspect diagnoses were typhoid, 11.9%; rabies, 9.3%; and encephalitis, 5.6%. Of the 2,527 investigations that cannot be classified by age or sex, the most common health problems were often infectious and might have involved children: hepatitis, 8.7%; gastroenteritis, 7.4%; salmonellosis, 4.9%, and polio, 2.4%.

Unintended pregnancy and pregnancy among adolescents

Eight Epi-Aids investigated unintended pregnancy, beginning in the early 1970s, by providing technical assistance to the family planning programs of health departments and other organizations. These investigations provided consultation on program performance (e.g., numbers of women enrolled and proportions of women initiating and continuing contraceptive methods), expenditures (e.g., dollars spent on different aspects of the program and alternatives to reduce costs), and evaluation (e.g., ways to improve surveillance, including computerized patient record systems to monitor clinic activity and achievement of program goals).

Three Epi-Aids focused on pregnancy among adolescents. In 1997, stimulated by recent legislation mandating efforts to reduce pregnancy among adolescents, an Epi-Aid in Maine investigated a substantial decline in pregnancy rates during 1980–1996, from 67.9 to 45.6 pregnancies/1,000 females aged 15–19 years (2). By using data from multiple sources (e.g., the Family Planning Association of Maine, the Maine Youth Risk Behavior Survey, and the Maine Department of Education), the investigators concluded that changes in behavioral factors, including increased intent to pursue post-secondary education, decreased high school dropout rates, and increased condom use, might have had the greatest impact on this decline. The collaborating agencies recommended a prospective system to monitor trends and possible determinants of adolescent pregnancy to guide research and prevention efforts.

In 1989, an Epi-Aid in the state of Washington estimated adolescent pregnancy rates and identified methodological challenges (e.g., lack of data on spontaneous abortions). In 2000, an Epi-Aid in Kansas examined an increase in adolescent pregnancies among Hispanics; here, geographic information

system analyses identified clustering of increased adolescent birth rates in certain counties. These counties had meatpacking industries that recruited employees from Mexico during the 1990s, a sociodemographic change that might have affected Hispanic adolescent birth rates. This Epi-Aid recommended promoting awareness of cultural norms and evaluating the cultural sensitivity of existing adolescent pregnancy prevention programs.

Reproductive health surveys

The reproductive health of women is especially vulnerable in refugee settings. Two Epi-Aids involved international reproductive health surveys among refugees. In 1998, an assessment of poor pregnancy outcomes was conducted among Burundian refugees in Tanzania (3), where poor pregnancy outcomes were common and maternal and neonatal deaths contributed substantially to overall mortality. Such pregnancy outcomes were associated with low parity, 3 or more episodes of malaria during pregnancy, and prior high socioeconomic status. Women of prior high socioeconomic status were likely to suffer the greatest loss of social status and were likely to lack beneficial survival skills (e.g., gardening and collecting firewood). This Epi-Aid increased attention on this global public health problem and built a strong foundation for future reproductive health refugee activities (4).

A 1999 Epi-Aid involved reproductive health rapid assessment of refugees and internally displaced persons in Azerbaijan and contributed to understanding differences in economic indicators and access to care among internally displaced versus local women (5). Additionally, it laid groundwork for future work on forced sex among internally displaced women in Azerbaijan (6) and diagnosis of bacterial vaginosis in a resource-limited setting (7). Both Epi-Aids demonstrated CDC's capacity to conduct rapid epidemiologic assessment of health problems in refugee settings that are uniquely related to women.

Elimination of maternal mortality from abortion in the United States

CDC's early and continued vigilance in conducting abortion surveillance, investigating abortion-related deaths, and studying the safety of abortion techniques has helped to virtually eliminate maternal mortality from abortion in the United States (8–10). CDC first established a formal Family Planning Evaluation Activity in 1966. As US states began to legalize abortion during the late 1960s, CDC epidemiologists worked with health departments and hospitals to develop surveillance for legal abortions (11, 12). CDC investigated the first documented cluster of abortion complications in early 1971 (13). The complications, associated with a single physician using the suction curette, indicated 2 chief risk factors: gestation of 11 or more weeks at the time of abortion and delayed medical care for postabortion complications because a woman was an out-of-state resident. This investigation demonstrated the value of a national abortion surveillance system.

In 1972, CDC epidemiologists evaluated New York City's abortion surveillance system, 2 years after New York State revised its abortion law to allow physicians to perform abortions

in their offices as well as hospitals. Because the laws were more restrictive in other states, approximately half the women obtaining abortions in New York City had come from other states. In response to the lack of regulatory guidelines for physicians performing abortions in offices, the New York City Health Department established a health code for the office practice of abortion in October 1970. A 1972 Epi-Aid documented a rapid decline in maternal mortality from abortions associated with the revised law, and data from this investigation and other reports (14–17) supported the successful appeal of Georgia's restrictive law before the US Supreme Court (*Doe v. Bolton*, 410 US. 179 (1973)). CDC epidemiologists again made a case for a national surveillance system, stating that review of abortion mortality, already tested at the state level, should be established at the national level (18).

CDC continued to investigate maternal deaths from abortion among women who traveled from states with restrictive abortion services to cities with legal abortion services. During 1971–1982, CDC responded to 12 health department requests for investigation of abortion-related deaths (12). Two of the earliest investigations identified key factors associated with abortion-related deaths. In 1971, a college sophomore aged 17 years, seeking to avoid asking for parental consent, traveled from Arkansas to New York City to obtain a saline abortion. She returned home the next day and sought medical care for fever without disclosing her history of an abortion. Without that history, she did not obtain correct treatment and died (19). In 1972, after police closed an abortion clinic in Chicago, Illinois, a group of 20 women seeking late-term abortions traveled by bus from Illinois and Indiana to Philadelphia, Pennsylvania. Fifteen women had their pregnancies terminated by a physician and a psychologist using a relatively unknown method called super coils. Three of the 15 women suffered major complications. CDC investigators concluded that new abortion methods should be tested according to a detailed research protocol, under careful scientific and medical supervision, and in a hospital environment with adequate personnel and facilities to diagnose and treat any possible complications (20–22).

CDC's success using Epi-Aids to improve surveillance and conduct credible investigations led the Population Council to transfer its Joint Program for the Study of Abortion to CDC. During 1971–1978, CDC conducted this program, which included 2 multicenter prospective studies of the early medical complications of legally induced abortions in the United States (23). These studies definitively demonstrated, first, that regardless of procedure, maternal morbidity was associated with increasing gestational age at time of procedure, and second, that after 12 weeks' gestation, dilatation and evacuation was a safer method than either saline or prostaglandin installation (24).

In July 1977, obtaining legal abortions became more difficult for women of low socioeconomic status because the federal government and the majority of states substantially restricted public funding for legal abortions (25). In Texas, an Epi-Aid determined that after restrictions were imposed, a cluster of septic complications was associated with illegally induced abortions. CDC epidemiologists reported that the incidence of hospitalizations of Medicaid-eligible women

with febrile abortion-related complications was greater after August 5 than in the earlier period (26). In its last published investigation of abortion-related mortality in 1982, CDC and Florida health officials reported that 2 women had died after obtaining abortions from a provider who was not a licensed physician (27).

CDC's continuing surveillance for abortions and investigation of abortion deaths have documented that the maternal risk of dying from abortion early in pregnancy is approximately 1/1 million procedures, but the risk increases exponentially with increasing gestational age (9). CDC's abortion surveillance, death investigations, and research provided scientific evidence that influenced major court decisions and medical practice that has substantially improved the reproductive health of women.

Pregnancy-associated morbidity and mortality

After successful efforts to virtually eliminate maternal mortality resulting from abortion, CDC applied its reproductive epidemiologic expertise to other causes of maternal morbidity and mortality. During 1979–2002, CDC conducted 12 investigations on maternal health problems.

In 1979, CDC investigated 2 autopsy-diagnosed maternal deaths in New Jersey associated with acute hemorrhagic pancreatitis in the same month in the same hospital. The investigators concluded that this unusual occurrence was attributable to chance but recommended improved statewide surveillance. Five months later, New Jersey requested an Epi-Aid to investigate increased maternal mortality at a hospital serving an indigent population. These CDC investigators first applied the term *behavioral risk factors* rather than *preventable factors* to maternal deaths, because the factors were related to human behavior, which, in their judgment, increased patients' risk of death. The most common behavioral risk factor was patient delay in seeking care, including 2 women who died before getting medical care and another who had obtained no prenatal care. The most common health care provider behavioral risk factors were associated with administration of anesthesia. This method then was applied to national review of abortion deaths (28).

In 1983, CDC investigated perinatal and maternal mortality in Indiana among a religious group that avoided medical care for any health problem. The maternal mortality ratio was 872/100,000 livebirths, or 92 times higher than the state maternal mortality ratio. This higher rate was not explained by demographic characteristics of the religious group's members (29–31). Legal prosecution was associated with a decline in maternal and infant mortality (32).

In 1997, CDC epidemiologists investigated the first reported pregnancy-related death associated with heparin and aspirin treatment for infertility. Although the US Food and Drug Administration had not approved this treatment, a July 1997 national survey of providers of assisted reproductive technology services reported that 74% of providers had used that combination treatment at least once. CDC urged vigorous scientific investigation before the treatment is practiced routinely and requested that deaths or severe morbidity associated with heparin and aspirin to prevent pregnancy loss be reported to CDC or the Food and Drug Administration (33).

In 1998, CDC investigated a possible increase in uterine rupture associated with the trial of labor for vaginal birth after a cesarean delivery (34). This is the first known field investigation that linked hospital discharge records with birth and fetal death certificates. It documented the inadequacy of the codes in the *International Classification of Diseases*, Ninth Revision, and the *International Classification of Diseases and Related Health Problems*, Tenth Revision, for accurately detecting uterine rupture cases (35, 36).

In 2000, CDC cluster investigation guidelines (37) were used to evaluate molar pregnancies and adverse pregnancy outcomes among members of an American Indian tribe. One critical challenge was finding adequate reference rates for molar pregnancies and spontaneous miscarriages. The molar pregnancy rate did not differ substantially from the rate in surrounding counties, but the overall miscarriage rate was higher. The investigators recommended improved personal health care during pregnancy, delivery, and postpartum periods (unpublished data, CDC, 2000).

In 2001, CDC investigated barriers to successful pregnancies among women with phenylketonuria. Among 24 women with phenylketonuria who were interviewed, 51 pregnancies had occurred: 28 (55%) had resulted in livebirths, 18 (35%) of which were planned; 15 (29%) ended in miscarriage; and 8 (16%) were terminated. Two liveborn infants had microcephaly. All but one woman had discontinued the special diet of avoiding high-protein foods early in life. The investigation identified 2 possible causes: a relatively high rate of unintended pregnancies and inadequate dietary control. Barriers to dietary control included financial difficulties, proof of pregnancy to obtain public assistance, time and distance to the metabolic clinic, lack of confidence in obstetricians' knowledge about phenylketonuria, having a high school education or less, variations by state of residence, and unpleasant taste of maternal diet formula. Because maternal phenylketonuria might be one of multiple diseases with second-generation effects, the investigators recommended developing programs that provide services from infancy to adulthood for children with special health care needs who are identified through newborn screening programs (38).

Two Epi-Aids of maternal mortality were conducted outside the United States. The first investigated an apparent increase in maternal mortality in Mexico in 1989. The most common causes included pregnancy-induced hypertension, hemorrhage, sepsis, and abortion complications. Factors associated with these problems included lack of physician training and experience, noncompliance with existing management protocols for pregnancy-associated complications, lack of patient compliance with learned public health and family planning information, and inconsistencies in availability of recommended ancillary services and pharmaceuticals. The possibility of physician work overload was attributed to Mexico's economic deficiencies, high inflation, and a 6-year freeze on hiring.

A second international investigation occurred in 2002 in collaboration with the Afghan Ministry of Public Health and UNICEF. CDC staff conducted a retrospective cohort study of women of reproductive ages who had died in 4 districts of 4 provinces of Afghanistan. The team collected data regarding 2,560 deaths in approximately 14,000 households. Of the

154 maternal deaths identified through verbal autopsy, 109 were determined to be direct maternal deaths. Hemorrhage (38%) and obstructed labor (26%) were the most common causes of death. Certain regions of Afghanistan have the highest maternal mortality ever measured, with approximately half of all deaths to women of reproductive age caused by pregnancy and its complications. Overall, three-fourths of infants born alive to mothers who died also died. The more remote areas had the highest mortality (39).

Unexpected increases or clusters of disease among infants

Unexpected increases or clusters of disease among infants led to multiple investigations in the 1960s and 1970s, primarily in nursery or hospital settings. Three separate Epi-Aids during 1974–1976 addressed increased rates of necrotizing enterocolitis among infants in hospital or intensive care nurseries in West Virginia, Colorado, and Texas (40, 41). Associations identified included *Escherichia coli*-positive cultures, care by certain personnel, and lack of antibiotic treatment, but findings were not definitive and no recommendations were made. In the early 1980s, a series of Epi-Aids examined infant deaths in the United States. Two investigations responded to increases in the rate of sudden infant death syndrome among Alaska Natives and among American Indians living on a reservation in South Dakota. Among the latter population, maternal anemia and short pregnancy intervals were associated with a greater risk of sudden infant death syndrome, but, notably, the more useful finding was the absence of an association with diphtheria, tetanus, and pertussis vaccination, a problem of substantial community concern as a risk factor for sudden infant death syndrome.

During the mid-1980s, Epi-Aids evaluated increases in infant mortality rates by using linked birth and death certificate files. In one study, EISOs used these linked files to examine an increase in infant mortality in Jersey City, New Jersey, in 1984 (42). EISOs were able to demonstrate that increased mortality was concentrated in one specific hospital, where infants often were born at very low birth weights and a substantial proportion of the mothers had had 3 or fewer prenatal care visits.

Low birth weights were also identified as a factor associated with sudden infant death syndrome among Alaska Natives in an analysis of linked birth-death records of all infant deaths in Alaska during 1976–1980 (43). However, this association did not explain the 3 times higher risk of sudden infant death syndrome for Alaska Natives compared with white Alaska residents, and review of medical charts or personal interviews was recommended to elucidate etiologic differences between these groups.

A linked birth-death record analysis conducted in Puerto Rico examined birth weight-specific neonatal mortality rates on the island (44). Although at that time Puerto Rico had a shortage of neonatal intensive care unit beds, the study revealed that access to hospitals with neonatal intensive care units did not improve neonatal survival substantially. This finding might have been explained by a perinatal regionalization plan that allowed lower-risk deliveries to compete for scarce resources available at the tertiary level. A more

comprehensive response to public health concerns raised in the Epi-Aid, published later (6), emphasized prevention of low birth weight, which was highest among mothers less than 18 years of age.

Adolescent mothers contributed to the infant mortality rate according to an Epi-Aid conducted in Kentucky in 1987. This investigation was prompted by a Kentucky Department of Health division director who noted that in contrast with the 12% decline in the national infant mortality rate during 1979–1983, the relatively high rate for Kentucky (13th among all US states) remained stable for 5 years. An evaluation of linked infant birth-death records determined that the rate of births to mothers aged 10–20 years is higher in Kentucky, particularly in the southeastern Appalachian region, than in the rest of the country. A high proportion of these adolescent mothers were married at the time of delivery, and EISOs recommended that efforts to reduce unintended pregnancy recognize cultural differences that can affect childbearing in this area of Kentucky.

A similar Epi-Aid examined a disproportionately high infant mortality rate among black infants in 2 districts comprising the Mississippi Delta region, a rate approximately twice that for black infants in other areas in Mississippi. An examination of linked infant birth-death records revealed that the difference was explained partly by a larger number of postneonatal deaths that had occurred outside a hospital or clinic. In 1 of the 2 delta districts, only 24% of black postneonatal deaths occurred in a hospital or clinic compared with 44% of black postneonatal deaths in other districts and 56% of white postneonatal deaths statewide (45). The higher proportion of deaths occurring outside a medical setting indicated less access to or usage of hospitals or clinics, and differences in the prevalence of risk factors (e.g., adolescent pregnancy and low-birth-weight infants) explained only part of the mortality pattern. These investigations demonstrate the usefulness of linked birth-death records in identifying factors associated with infant mortality.

Reye syndrome

After an earlier health department investigation of an encephalitis-like illness (46), during 1964–1984, CDC investigated 20 possible cases or clusters of cases of brain and liver disease known as Reye syndrome (47). One notable investigation was conducted during 1973–1977 (48) and was followed by a prospective case-control study of 159 cases during 1978–1980. This study identified aspirin taken during influenza or varicella illnesses as a risk factor for Reye syndrome (49), thus confirming the findings of 2 other studies (50, 51). In 1980, an investigation of 3 siblings in Tennessee determined that multiple factors previously hypothesized to be risk factors were not associated with Reye syndrome (52). Another investigation in New Mexico demonstrated an association with varicella (53). Soon afterward, the US Surgeon General and the American Academy of Pediatrics issued advisories against using salicylates among children with chickenpox and influenza-like illnesses (54), and, in 1982, CDC evaluated the impact on parental knowledge in Minnesota. Overall, 41% of parents knew of the association between salicylates and Reye syndrome, and those who knew of the

association were less likely to provide salicylates to their ill children (33% vs. 66%) (unpublished data, CDC, 1984).

Child cancer and birth defects

CDC's involvement in epidemiologic studies of childhood cancer and birth defects began in the late 1950s with investigations of time-place clustering of leukemia cases in residential communities. In the mid-1960s, CDC developed a similar program regarding birth defects, partly because of findings in 2 towns indicating clustering of both leukemia and congenital heart disease (55, 56).

Well into the 1970s, investigations of community case clusters, especially cancers, paid particular attention to possible infectious causes, although other etiologies received attention, especially potential environmental exposures to chemicals or radiation, as well as inherited or acquired genetic influences. Into the 1980s, a total of 57 childhood cancer studies and 48 birth defect studies were recorded on Epi-Aid memos, reflecting investigations conducted in 34 states and 5 non-US locations.

Soon after the start of CDC's case-cluster investigations, 2 programs of population-based case surveillance were established (cancer and birth defects). Surveillance under both programs began by developing mechanisms for case reporting throughout the 5-county area of metropolitan Atlanta, Georgia.

Cancers. Initial investigations of cancer case clusters focused primarily on childhood leukemia. From the start, CDC collaborated with the National Cancer Institute, where laboratory research had demonstrated the viral etiology of leukemia among multiple animal species. Although ensuing cancer studies at CDC did not find clear evidence of infectious etiology (57), Epi-Aid investigations (1 in 1961, 3 in 1970, 1 in 1971, and 3 in 1972) indicated patterns of community case occurrence compatible with infection (58). Two Epi-Aid investigations in the 1970s addressed particular forms of childhood cancer believed to be caused by the Epstein-Barr virus: Burkitt lymphoma in a northern Virginia neighborhood (59) and nasopharyngeal cancer in Bermuda (60).

Other settings in which Epi-Aids explored questions of cancer causation included contacts between humans and animals (61), persons sharing the same house (62), and case occurrence within families (63–65). As time passed, however, studies increasingly focused on potential exposures to environmental toxins and radiation. Observing convincing cause-and-effect associations was possible only in adult workplace settings, where sizable doses often were involved. In lower-dose settings, as in communities located near hazardous waste dumps, cause-and-effect associations were much more difficult for EISOs to assess (66).

By the late 1960s, CDC began work with Emory University (Atlanta, Georgia), local health departments, and physicians and hospitals throughout metropolitan Atlanta to establish ongoing surveillance for newly diagnosed cases of cancer in the 5-county area. Eventually, the program became an integral part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Initially, attention was focused on leukemia so that the frequency of leukemia case clusters might be assessed and epidemiologic investigations

could be undertaken for unusual case groupings. Although 2 statistical assessments in the Atlanta area identified modest evidence of statistically significant time-space clustering among childhood cases (67, 68), the majority of clusters being reported to CDC for possible epidemiologic investigation were probably the result of statistical time-space case distributions.

Birth defects. The first 3 Epi-Aid birth defects investigations all concerned occurrence of central nervous system malformations. The first was in 1968 regarding 10 cases (8 meningomyelocele and 2 anencephaly) associated with paternal employment at a naval air station near Jacksonville, Florida (expected incidence: 3 cases). No potential exposures to environmental toxins or irradiation were identified, and the incidence of such defects in Jacksonville as a whole had not increased. The second investigation concerned 17 infants with spina bifida cystica born near Columbia, South Carolina, during 1970–1972, and the third investigation was related to 6 infants with anencephaly born in 1972 in Vernon Township, Connecticut.

In all, 12 such community studies of neural tube defects were conducted during the 1966–2005 Epi-Aid period, more than for any other form of birth defect. One study in 1976 explored, with negative results, neural tube defect occurrence in West Virginia in relation to possible vinyl chloride exposure (69). Another Epi-Aid in 1987 examined gastric bypass surgery as a potential maternal risk factor for neural tube defect occurrence (70). During 1990–1991, an Epi-Aid of a cluster of anencephaly cases in Cameron County, Texas, led to prospective surveillance of neural tube defect occurrence from 1993 through 1998 in the 14 counties along the Texas-Mexico border (71). Increased incidence, especially among Hispanic births, clearly was reduced by maternal folic acid therapy. In 1992, the US Public Health Service recommended that all women of reproductive age consume folic acid to reduce neural tube defect occurrence, and, in 1998, the Food and Drug Administration issued regulations requiring that all enriched cereal grains be fortified with folic acid.

Other birth defects-associated Epi-Aids included multiple problems: 5 neonatal jaundice, 5 fetal deaths, 4 cardiac malformations (72), 3 Down syndrome, 3 limb abnormalities, 2 facial clefts, and 13 other defects (73). In 1979, a total of 3 cases of infant metabolic alkalosis in Memphis, Tennessee, proved to be associated with use of a chloride-deficient soy-based infant formula. This association, confirmed in a survey of similar cases throughout the country, led to the creation of a health follow-up registry of such children and to the Infant Formula Act of 1980 (additional information is available at http://www.fda.gov/ohrms/dockets/ac/02/briefing/3852b1_01.htm). A later study by the National Institutes of Health determined that by age 9–10 years, children apparently had recovered fully from such early growth failure (74).

In 1984, an Epi-Aid conducted with the Food and Drug Administration concerned 29 cases of adverse reproductive outcomes among women using isotretinoin during the first trimester of pregnancy. Isotretinoin is an oral retinoic acid medication useful for treating severe nodular acne. Embryopathy included craniofacial, cardiac, thymic, and central nervous system malformations as well as an increased frequency of spontaneous abortion (75). Although programs were undertaken to educate reproductive-aged women against

using isotretinoin during pregnancy, a follow-up study by CDC in California in 1999 demonstrated the continued need to reinforce that education effort.

During 1988–1992, CDC conducted an Epi-Aid-initiated, population-based, multistate case-control study of infants with nonsyndromic limb deficiencies born to women who had undergone first-trimester chorionic villus sampling. The investigation revealed a 6-fold increase in risk of transverse digital deficiencies after such sampling but no overall increased risk of limb deficiencies (76).

Seven cases of infantile hypertrophic pyloric stenosis occurred among neonates born in February 1999 at a community hospital in Knoxville, Tennessee. An Epi-Aid investigation with the Tennessee Department of Health determined this case incidence to be 7 times greater than the level usually observed and to be the likely result of erythromycin given at birth during that month as prophylaxis against an outbreak of pertussis then occurring among neonates at that hospital (77).

In 2002, a birth defects-related Epi-Aid was conducted by CDC concerning reports of bacterial meningitis among patients who had received cochlear implants to treat hearing loss (78). The study included more than 4,000 children who had received implants before age 6 years in the United States during 1997–2002. Incidence of meningitis was more than 30 times higher than expected and appeared to occur especially among children whose implants had involved insertion of an electronic positioner.

The Metropolitan Atlanta Congenital Defects Program was established by CDC in 1967 to enhance identification of unusual patterns of birth defects occurrence for epidemiologic investigation. The program was based on regular review of medical information in community hospitals and vital records in public health departments. Laboratories at Emory University and CDC provided cytogenetic testing for newborns and prenatally by amniocentesis. In 1974, CDC helped establish a national surveillance program (the Birth Defects Monitoring Program) in which clinical data from approximately 25% of all livebirths were obtained from hospitals throughout the country (79).

CONCLUSION

Although the majority of CDC investigations involve women, infants, or children, the reports discussed in this article specifically focused on selected maternal, infant, or child health Epi-Aids. The investigations we selected for discussion highlight the importance of using surveillance and performing studies that use existing data sources (e.g., vital records), develop new data sources (e.g., linking birth and death records or hospital discharge records), and use epidemiologic tools (e.g., case-control studies) to identify risk factors. Moreover, evaluations are important for determining program effectiveness, and epidemiologic surveillance studies have been used to support judicial decisions (e.g., the *Doe v. Bolton* legal case cited previously). The cluster investigations led to CDC's establishing guidelines for investigating clusters of health events (37, 80) and development of the DOS-based software Statistical Analysis Battery for Epidemiologic

Research (SABER) (81). These Epi-Aids related to maternal and child health provided part of the scientific and federal-state collaborative framework on which maternal and child health epidemiology has been established (82).

ACKNOWLEDGMENTS

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The authors thank Flavia Klarner Traven (Association of Schools of Public Health/CDC Fellow, assigned to the Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, CDC) and Megan Ivankovich (Sexual Health Scholar, Morehouse School of Medicine, Morehouse College, Atlanta, Georgia) for their research assistance.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of interest: none declared.

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