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Perspectives from the Founding CDC Leadership of the National Birth Defects Prevention Study

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The Centers for Disease Control and Prevention (CDC) conducted its first formal case-control study to better understand the causes of major birth defects in the early 1980s (Erickson et al., 1984). The primary purpose of the study was to evaluate the possible causal contribution of paternal experiences during military service in Vietnam, with particular emphasis on exposures to the herbicide known as “Agent Orange.” The cases and controls were drawn from births that occurred in the Atlanta, Georgia area, where CDC has operated a birth defects surveillance program since 1967. The case-control design permitted evaluation of a wide array of potential maternal exposures that might cause birth defects, as well as additional paternal influences (Erickson, 1991). For example, the study identified a neural tube defect preventive benefit of periconceptional multivitamin use which paved the way for folic acid intervention to prevent neural tube defects (Mulinare et al., 1988).

Building on this experience, the CDC launched the multicenter National Birth Defects Prevention Study (NBDPS) in 1997 to advance understanding of the causes of birth defects. Because the causes of most birth defects are unknown and might be preventable if risk factors are identified, the NBDPS focused on birth defects of unknown etiology (Holmes, 1989). These included neural tube defects, congenital heart defects, orofacial clefts, limb deficiencies, abdominal wall defects, intestinal atresias, and other major birth defects that can be reliably ascertained in early infancy. One unique aspect of the NBDPS addressed the variability of birth defects classification across previous epidemiologic studies. In an effort to increase homogeneity within analytic groups of defects, clinical geneticists collaborated to develop classification guidelines that were applied across the study sites (Rasmussen et al., 2003). This and other efforts to coordinate work and maintain consistent methodology across participating Centers in multiple states, improved the power of NBDPS to identify potential causes of specific birth defects despite the relatively low prevalence of each individual defect type. This is particularly important for studying the epidemiology of birth defects because to date, exposures identified as causing birth defects have a relatively

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specific impact on one or a few types of birth defects rather than increasing the risk of all birth defects (Tinker, Gilboa, et al., 2015). The NBDPS methods and final counts of data collected are summarized by Reefhuis et al. in this issue (Reefhuis et al., 2015), and the strengths and weaknesses of the NBDPS have been assessed (Dolk, 2015).

In addition to the statistical power gained by taking a multicenter approach, the NBDPS provided a diverse sample in terms of geographic residence, race/ethnicity, and socioeconomic status. The NBDPS has also benefited from the tremendous epidemiological, clinical, and biological expertise contributed by each Center. Across the period of the study, the CDC Center in Georgia and the funded Centers in Arkansas, California, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah have each contributed birth defects expertise and have also developed a new cadre of birth defects researchers including many masters and doctoral students trained in NBDPS data analysis. NBDPS data have provided training to a wide range of students in MPH, doctoral, postdoctoral, and other fellowship training programs. As of December 2014, over 50 trainees had published one or more papers using NBDPS data, including at least 27 doctoral students who used this data for their dissertation. In addition, the careful data collection and extensive quality control efforts at each site have greatly contributed to the value of the NBDPS and the resulting data.

Folic acid fortification is a major public health success story that resulted from both observational data and randomized controlled trials, and has led to the prevention of approximately 1,300 neural tube defects per year since 1998 (Williams et al., 2015). An aspirational goal of the NBDPS was to identify the next folic acid-type risk factor that could be rapidly translated into birth defects prevention efforts of a similar magnitude. The NBDPS has yielded an extensive number of publications identifying potentially risky exposures before and during pregnancy as well as publications that offer some reassurance about an apparent lack of risk. While no single exposure with the prevention potential of folic acid has been identified to date, the NBDPS has made important contributions to our understanding of the potential effect of prepregnancy obesity, opioid analgesics, antibacterial medications, assisted reproductive technology, antidepressant medications and other pregnancy exposures (Alwan and Chambers, 2015). Findings from the NBDPS have served a confirmatory role in some cases, such as adding evidence to a prior link between smoking and orofacial clefts that resulted in the conclusion from the 2014 Surgeon General’s Report that smoking was a cause of some orofacial clefts (US DHHS, 2014). In other instances, NBDPS has generated hypotheses about relatively new exposures with unknown teratogenicity such as the antidepressant venlafaxine (Polen et al., 2013). NBDPS has encouraged the development of collaborations between Centers as well as with outside investigators. There is not a public use version of the data available because de-identifying the data would remove critical information that is needed in most analyses; how- ever, there is a process in place for outside investigators to propose research plans and use the data either as part of a special agreement or under controlled conditions as specified in the protocol (http://www.cdc.gov/ncbddd/documents/nbdpsprotocolrev4-10.pdf). The successor to the NBDPS is the Birth Defects Study To Explore Pregnancy exposureS, or BD-STEPS, and this study builds on the findings and the lessons learned from NBDPS (Carmichael et al., 2015).

This special issue highlights some of the contributions of NBDPS and provides various perspectives on these contributions, describes some methods used for data exploration, assesses the changing landscape of birth defects epidemiology during the time period of the study, and points to future opportunities. As the initial architects of the NBDPS, we take great pride in reflecting on the many accomplishments to date and are confident that the NBDPS will continue to be a valuable data source for identifying potential environmental and genetic risk factors for birth defects in the years to come. Many of the early publications from the NBDPS can now be replicated using independent data from the latter years of the study and the accumulation of data on more rare birth defects offers a first opportunity to study their epidemiology. Researchers around the world can further explore the many hypotheses generated by analyses of the rich NBDPS data and further elucidate birth defects etiology with the ultimate goal of prevention.

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References

Alwan S, Chambers CD. Findings from the National Birth Defects Prevention Study: interpretation and translation for the clinician. Birth Defects Res A Clin Mol Teratol. 2015; (Special Issue)

Dolk H. Preventing birth defects: the value of the NBDPS case-control approach. Birth Defects Res A Clin Mol Teratol. 2015; (Special Issue)

Erickson JD, Mulinare J, McClain PW, et al. Vietnam veter- ans' risks for fathering babies with birth defects. JAMA. 1984; 252:903–912. [PubMed: 6748190]

Erickson JD. Risk factors for birth defects: data from the Atlanta Birth Defects Case-Control Study. Teratology. 1991; 43:41–51. [PubMed: 2006471]

Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. JAMA. 1998; 260:3141–3145.

Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. N Engl J Med. 1989; 320:19–23. [PubMed: 2909875]

Polen KN, Rasmussen SA, Riehle-Colarusso T, et al. Association between reported venlafaxine use in early pregnancy and birth defects, National Birth Defects Prevention Study, 1997–2007. Birth Defects Res A Clin Mol Teratol. 2013; 97:28–35. [PubMed: 23281074]

Rasmussen SA, Olney RS, Holmes LB, et al. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol. 2003; 67:193–201. [PubMed: 12797461]

Reefhuis J, Gilboa SM, Anderka M, et al. The National Birth Defects Prevention Study: a review of the methods. Birth Defects Res A Clin Mol Teratol. 2015; (Special Issue)

Tinker SC, Carmichael SL, Anderka M, et al. Next steps for birth defects research and prevention: the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS). Birth Defects Res A Clin Mol Teratol. 2015; (Special Issue)

Tinker SC, Gilboa S, Reefhuis J, et al. Challenges in studying modifiable risk factors for birth defects. Curr Epidemiol Rep. 2015; 2:23–30. [PubMed: 26236577]

U.S. Department of Health and Human Services. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. The health consequences of smoking: 50 years of progress. 2014. Printed with corrections, January 2014

Williams J, Mai CT, Mulinare J, et al. Updated estimates of neural tube defects prevented by mandatory folic Acid fortification - United States, 1995–2011. MMWR Morb Mortal Wkly Rep. 2015; 64:1–5. [PubMed: 25590678]