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Meeting the Emerging Public Health Needs of Persons With Blood Disorders

Christopher S. Parker, PhD

Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia

James Tsai, MD, MPH

Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia

Azfar-e-Alam Siddiqi, MD, PhD

Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia

Hani K. Atrash, MD, MPH

Division of Healthy Start and Perinatal Services, Maternal and Child Health Bureau, Health Resources and Services Administration, Rockville, Maryland

Lisa C. Richardson, MD, MPH

Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia

Abstract

In its decades-long history, the Division of Blood Disorders (DBD) at CDC has evolved from a patient-focused, services-supporting entity at inception, to one of the world leaders in the practice of public health to improve the lives of people at risk for or affected by nonmalignant blood disorders. The DBD's earliest public health activities consisted of working with care providers in a network of hemophilia treatment centers to provide AIDS risk reduction services to people with hemophilia. Because this infectious disease threat has been reduced over time as a result of the development of safer treatment products, the DBD—under the auspices of congressional appropriations guidance—has expanded its core activities to encompass blood disorders other than hemophilia, including hemoglobinopathies such as thalassemia and sickle cell disease, and Diamond Blackfan anemia. Simultaneously, in transitioning to a greater public health role, the DBD has expanded its network of partners to new consumer and professional organizations, as well as state and other federal health agencies. The DBD has also developed and maintains many surveillance and registry activities beyond the Universal Data Collection system aimed at providing a better understanding of the health status, health needs, and health-related quality of

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Address correspondence to: Christopher S. Parker, PhD, Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, CDC, 1600 Clifton Road, Mail Stop E-64, Atlanta GA 30333. csp2@cdc.gov..

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life of people with nonmalignant blood disorders. The DBD has integrated applicable components of the Essential Services of Public Health successfully to promote and advance the agenda of blood disorders in public health.

Introduction

The mission of CDC is to collaborate to create the expertise, information, and tools that people and communities need to protect their health through health promotion; prevention of disease, injury, and disability; and preparedness for new health threats.¹ CDC seeks to accomplish its mission by working with partners throughout the nation and the world to monitor health, detect and investigate health problems, conduct research to enhance prevention, develop and disseminate evidence-based public health policies, implement prevention strategies, promote healthy behaviors, foster safe and healthful environments, and provide leadership and training.¹ By applying the Essential Services of Public Health that describe the public health activities that all communities should undertake and serve as the framework for the National Public Health Performance Standards,² the Division of Blood Disorders (DBD) within the National Center on Birth Defects and Developmental Disabilities at CDC monitors the epidemiology of non-malignant blood disorders (hereafter referred to simply as “blood disorders”) and supports efforts for the prevention and management of these disorders.

The DBD initially developed and targeted activities and interventions mainly for the community directly affected by hemophilia. The primary need of this population was intervening to prevent exposure to and transmission of HIV.^{3,4} Institutionalized procedures to ensure the safe donation and receipt of blood and blood products subsequently have eliminated the transmission of HIV and hepatitis B and C via these pathways.⁵⁻⁷ As people with hemophilia live longer and more productive lives, they experience many chronic conditions such as heart and renal disease, joint deterioration, hypertension, and obesity at rates similar to those among the general U.S. population.⁸⁻¹¹

Effective management of these comorbidities, better characterization of the risks for inhibitor development, and identification of prevention and treatment opportunities have emerged as the prevailing needs of this community. To meet these changing needs, the division has shifted its focus from clinical concerns related to HIV transmission to public health concerns of the larger population with hemophilia. Additionally, the DBD has expanded its portfolio of partners, programs, and projects to address the emerging needs of populations with other blood disorders, such as venous thromboembolism (VTE) and sickle cell disease (SCD), which stand to benefit from a public health practice approach.

In April 2010, the DBD published the first of two journal supplements, titled “Blood Disorders in Public Health: Making the Connection” in the *American Journal of Preventive Medicine*, describing its move to streamline and better align its programs and activities with CDC’s agency mission and core functions.¹² Based on the information presented in the first supplement, the renewed vision of the DBD entailed becoming the global leader in the practice of public health to improve the lives of people at risk for or affected by blood disorders. The DBD is working to achieve this vision by using and promoting a

comprehensive set of public health approaches to reduce morbidity, mortality, and impaired health-related quality of life among people with blood disorders. The purpose of this article is to review the DBD's progress in advancing a public health agenda to improve the health of people with blood disorders, and to propose ways to integrate applicable components of the Essential Services of Public Health to meet the emerging needs of this population.

Inception of National Prevention Programs for Blood Disorders

In 1975, a Congressional appropriation was awarded to the Health Resources and Services Administration (HRSA) to establish a program to support the provision of comprehensive care to people with hemophilia and their families through an integrated regional network of centers—hemophilia treatment centers (HTCs)—for the diagnosis and treatment of hemophilia and other bleeding disorders (Pub L. 94-62).¹³ Subsequently, Congress awarded a separate appropriation to CDC in 1983 to provide AIDS risk reduction services for people with hemophilia and others who relied on the use of blood products for treatment.

In 1996, CDC broadened its focus to a more comprehensive health approach that brought people (particularly women) with bleeding and clotting disorders under its mission purview. This comprehensive health approach moved beyond health protection from infectious agents to instituting programs to promote and improve overall health.

More recently, CDC's approach to blood disorders was broadened to encompass work in addressing many secondary conditions including the health of people with disabling or rare blood disorders, and women's health issues, as well as in acquiring high-capacity molecular diagnostic technology and increasing the DBD's intellectual expertise in genetics. CDC received a funding appropriation for thalassemia in 2004 and another for Diamond Blackfan anemia in 2005, and a year later, the appropriation for hemochromatosis was moved from the National Center for Chronic Disease Prevention and Health Promotion at CDC to the DBD as part of an organizational realignment.

Early Work to Support Hemophilia Treatment Centers

Early on, the DBD collaborated with the HTCs to ensure replacement product safety and monitor for potential outbreaks of bloodborne infections. In support of these objectives, the DBD established the Universal Data Collection (UDC) system, a public health surveillance system employed throughout a network of 135 HTC clinics across the U.S. and its territories.¹⁴ CDC's hemophilia program collaborates with the HRSA in support of HTCs. The HTCs provide treatment and multidisciplinary preventive health care to people with bleeding and clotting disorders. Studies have shown that this system of care has reduced mortality and morbidity among patients with hemophilia.^{15,16}

Historically, the hemophilia program has been the largest blood disorder program continuously supported by CDC from congressional appropriations. Based on this program's successful work in hemophilia surveillance among people with bleeding disorders, congressional appropriators expressed interest in CDC's "efforts to develop a surveillance system for deep vein thrombosis"¹⁷ and encouraged CDC "to develop and implement a hemoglobinopathy surveillance and registry program with particular attention to SCD."¹⁸ As

a result, the DBD has expanded activities to address other blood disorders, including VTE and hemoglobinopathies.

Transition to a Public Health Approach

Within CDC, the DBD's work has aligned with the agency's mission, transitioning from an initial clinical treatment monitoring approach aimed primarily at improving the care of patients with hemophilia to a broader comprehensive set of public health approaches such as pilot population-based surveillance of SCD and VTE. During this transition, the DBD has prioritized its activities by using criteria that encompass the magnitude of the public health problem, the potential economic savings and benefits associated with decreasing mortality and morbidity and improving quality of life, the demonstrated effectiveness of interventions, and compliance with healthcare reform and other legislation.

Subsequently, the division has instituted a four-step process to achieve its goals, comprising (1) defining and monitoring the problem (public health surveillance); (2) identifying risk and protective factors (epidemiologic and health services research); (3) developing and testing prevention strategies; and (4) ensuring widespread adoption of effective prevention strategies. These changes were necessary to meet the emerging needs of people with blood disorders. In addition, the changes have allowed the division to direct its resources more effectively to support these surveillance, epidemiologic research, laboratory investigation, prevention research, and awareness activities among those in the blood disorders community.

The transition to a public health approach has afforded the DBD the opportunity to immediately activate programs and projects aimed at promoting and improving the health not only of people for whom a blood disorder is an inheritable condition but also of the hundreds of thousands for whom it might be a preventable event. This approach, supported by the guidance derived from the congressional appropriations process, has allowed the DBD to expand its portfolio of surveillance activities to address the lack of existing quality data for conditions such as SCD and adverse events like VTE. Equally important, this approach has allowed the division to initiate prevention research activities needed to identify vulnerabilities that conspire to produce disparately poor outcomes among certain populations.

More specifically, a broad public health approach has extended the DBD's reach from initially an approximate 20,000 people seen at HTC's to other patients with bleeding disorders who are being treated outside the HTC's and to the roughly 4 million people with one of the targeted blood disorders. Additionally, it has afforded the DBD the opportunity for pilot population-based (as opposed to facility-based), individually targeted, registrylike surveillance. Through this public health approach, the DBD has sought to reposition itself from being an agent for "better care" to an agent for "better health."

Efforts to Integrate Applicable Components of the Essential Services of Public Health in the Division of Blood Disorders

As enumerated in the following, the DBD has made concerted efforts to integrate the five components of the Essential Services of Public Health that are most applicable to the work it performs.

1. Monitor health status to identify community health problems

Responding to the needs of individuals with bleeding disorders and their families is an important function of the DBD. However, attention has been given to other conditions in addition to bleeding disorders and providers beyond the HTC. As a first step in aligning the functions of the DBD with the Essential Services of Public Health, the DBD assessed the epidemiology of blood disorders—occurrence rates, characteristics of the conditions, associated morbidities, and risk profiles of people affected by them. In the area of hemoglobinopathies, the DBD, in collaboration with the National Heart, Lung, and Blood Institute (NHLBI), initiated the Registry and Surveillance System in Hemoglobinopathies (RuSH), the first population-based public health surveillance system for SCD and thalassemia.^{19,20} RuSH included seven states whose combined populations, based on census tract data, accounted for 42% of blacks or African Americans and 53% of Asian Americans residing in the U.S. This innovative surveillance program was designed to produce needed data for participating states²¹ and federal health agencies on the number of people affected by, mortality statistics for, and healthcare costs associated with these blood disorders. Data from this program also will be used to strengthen health services and provide education and outreach to patients and their families. In addition, the DBD has initiated pilot projects to conduct population-based surveillance of VTE and surveillance of hemophilia among individuals who receive care outside the HTCs.

2. Diagnose and investigate health problems and hazards in communities

To ensure that programs and activities are evidence based and information driven, the DBD has conducted and supported studies to define the characteristics of affected populations and identify the risk factors for and consequences of various blood disorders. For example, the DBD conducted the national, cutting-edge “Hemophilia Inhibitor Research Study,” which defined the patterns of antibody formation to factor VIII (FVIII) and factor IX (FIX) and correlated this information with the FVIII and FIX DNA sequences of individuals with hemophilia.^{22,23} The study’s accomplishments resulted in the identification of 151 mutations that had not been previously reported and led to the CDC Hemophilia A Mutation Project (CHAMPS, an international database) in which data on these mutations are recorded.²⁴ In addition, the DBD conducted analyses of nationally representative complex sample surveys using administrative healthcare data sets.^{25,26} As an example, the DBD acquired access to the MarketScan[®] Medicaid Multi-State, Commercial and Medicare Supplemental data to compare healthcare utilization and expenditures among people in the U.S. with hemophilia who were publicly insured to those with employer-sponsored insurance.²⁵

3. Inform, educate, and empower people about health issues

To raise awareness and help develop an agenda for action related to blood disorders, the DBD participated in the Healthy People 2020 process. This led to the addition of a new topic area—blood disorders and blood safety—and 18 new, related objectives.²⁷ Most of the published literature related to blood disorders has been focused clinically, with limited general applicability to a public health context. To help address this issue, the DBD published two *American Journal of Preventive Medicine* journal supplements on blood disorders in public health. The first supplement, “Making the Connection” (April 2010), comprised peer-reviewed articles in the areas of surveillance and burden of disease.¹⁰ The second supplement, “Bridging the Gap” (December 2011), included peer-reviewed articles on public health practice, policy, and finance issues.²⁸ The supplements supported the development of a nationally recognized public health framework for promoting the health of and improving outcomes among people experiencing a blood disorder by highlighting the potential of public health strategies to address the complications they experience. In addition to the special journal supplements, the DBD has published its findings in many other peer-reviewed journals and government reports. Through the RuSH project, the DBD has published data collection field reports and made state-specific data on SCD accessible to the public.^{21,29,30}

4. Mobilize community partnerships and action to identify and solve health problems

In March 2010, in partnership with the HRSA, NHLBI, American Society of Hematology, and Hemophilia of Georgia, the DBD hosted the first National Conference on Blood Disorders in Public Health. The conference served as a platform for developing a nationally recognized public health framework for promoting the health of and improving outcomes among people with a blood disorder. Additionally, the hosts highlighted the potential of public health strategies to address complications experienced by people with blood disorders. The results of a post-conference evaluation suggested using Healthy People 2020 objectives (rather than the Essential Services of Public Health) as the framework for future National Conferences on Blood Disorders in Public Health. Additional recommendations included highlighting specific themes, such as surveillance, workforce development, advocacy, outreach, awareness, and education techniques (e.g., webinars, social media). Lastly, there was a strong call to establish a blood disorders coalition with less segregated sessions to speak for all blood disorders, preferably under the umbrella of the American Society of Hematology.

In 2010, the DBD established a moderated blood disorders listserv that provided global access for its partners to share and receive important blood disorders information. The listserv, with its global reach, provides a repository for the immediate dissemination of information on funding opportunity announcements, meetings, group discussions, and other important happenings in the field.

Also in 2010, the DBD enhanced collaboration with the WHO and other global partners to provide technical assistance to countries with large populations affected by hemoglobinopathies to develop national guidelines for prevention and management and to promote regional cooperation. In June 2011, the DBD supported a Regional Meeting on

Haemoglobinopathies and Genetic Diseases with the WHO's Regional Office for the Eastern Mediterranean. The meeting resulted in an agreement to develop a regional strategy on the care of people with and prevention of hemoglobinopathies and genetic disorders.

In addition, the DBD established the first global health initiative for hemoglobinopathies, successfully developing collaborations with Ghana, Kenya, and Nigeria to improve population screening to identify people with these blood disorders so that evidence-based, life-saving prevention practices could be implemented. In Ghana, the DBD partnered in the Genetic Education and Counselling in Sickle Project to provide the follow-up infrastructure for universal newborn screening. Information derived from formative research conducted during the period of 2010–2013 with mothers, healthcare workers, and community leaders regarding knowledge and attitudes about SCD, sickle cell trait, and newborn screening for SCD will be used to develop the first genetic counselor training curriculum in Ghana.

In June 2011, the DBD, in conjunction with the Sickle Cell Disease Association of America, hosted World SCD Day in Atlanta, Georgia.³¹ The event galvanized global support for promoting and improving the health of people with SCD to aid in achieving UN Millennium Development Goal 4 to reduce overall mortality among children younger than age 5 years.

In March 2012, along with the partners from the 2010 conference, the DBD hosted a second National Conference on Blood Disorders in Public Health, incorporating recommendations from the first conference. The second conference further advanced the public health context described during the first conference and proposed the adoption and full integration of evidence based and informed public health functions. Underlining its global reach, the conference was held in conjunction with the Conference of the Global SCD Network and the Second Meeting of the Worldwide Initiative on Social Studies on Hemoglobinopathies. Together, these conferences provided an impetus to move from examining process to reporting effects in improving the health of populations with blood disorders.

5. Evaluate effectiveness, accessibility, and quality of personal and population-based health services and promote and strengthen research for new insights into and innovative solutions for health problems

In 2011, the DBD evaluated and repurposed the UDC surveillance system to monitor people with bleeding disorders, including hemophilia A and B and von Willebrand disease. The surveillance component was strengthened to collect information on inhibitor development, chronic conditions, and comorbidities in persons with bleeding disorders. The anticipated impact of these efforts has been enhanced data quality and availability that will enable consumers, clinicians, public health professionals, and policymakers to improve health outcomes among people with blood disorders.

Additionally, the DBD has increased its laboratory capacity by incorporating technology that has allowed researchers to rapidly generate and analyze large amounts of genetic information from many people, thus facilitating large-scale genetic analysis that can be applied to an entire target population. Molecular genetic studies play an important role in public health by contributing to the understanding of both the causes and effects of diseases among different populations.³² An example of the DBD's use of this technology is

resequencing of the β -globin locus to redefine its haplotypes more accurately, in part to see if they can play a larger role in more precisely defining clinical phenotypes among children with SCD.³³

Conclusions

As people with blood disorders are living longer and more productive lives, many chronic conditions are emerging as major challenges to further improvements in their health outcomes. Public health practice provides an effective means of addressing the emerging health needs of people with blood disorders. The Essential Services of Public Health provide a useful framework for effective public health practice needed to promote and improve the health of people with blood disorders. Over the last several years, the DBD has successfully integrated applicable components of this framework to develop a comprehensive set of public health approaches with its expanded network of partners to reduce morbidity and mortality, and to improve the health-related quality of life among populations at risk for or affected by blood disorders.

References

1. CDC. CDC-Info; Atlanta GA: 2013. www.cdc.gov/about/organization/mission.htm
2. CDC. National public health performance standards. Office for State, Tribal, Local and Territorial Support; Atlanta GA: www.cdc.gov/nphpsp/essentialServices.html
3. CDC. Update: Acquired immunodeficiency syndrome (AIDS) in persons with hemophilia. MMWR Morb Mortal Wkly Rep. 1984; 33(42):589–91. 10/26/. [PubMed: 6434934]
4. CDC. Blood safety monitoring among persons with bleeding disorders— U.S., May 1998–June 2002. MMWR Morb Mortal Wkly Rep. 2003; 51(51):1152–4. [PubMed: 12553567]
5. Evatt B. Infectious disease in the blood supply and the public health response. Semin Hematol. 2006; 43(2S3):S4–S9. [PubMed: 16631825]
6. Watson S. Safe journey: plasma-derived factor is safer than ever. Hemaware. 2009; 14(1):60–5.
7. Soucie JM, Richardson LC, Evatt BL, et al. Risk factors for infection with HBV and HCV in a large cohort of hemophiliac males. Transfusion. 2001; 41(3):338–43. [PubMed: 11274587]
8. Soucie JM, Cianfrini C, Janco RL, et al. Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. Blood. 2004; 103(7):2467–73. [PubMed: 14615381]
9. Kulkarni R, Soucie JM, Evatt BL, Hemophilia Surveillance System Project Investigators. Prevalence and risk factors for heart disease among males with hemophilia. Am J Hematol. 2005; 79(1):36–42. [PubMed: 15849761]
10. Kulkarni R, Soucie JM, Evatt; Hemophilia Surveillance System Project Investigators. Prevalence and risk factors for heart disease among males with hemophilia. Am J Hematol. 2005; 79(1):36–42. [PubMed: 15849761]
11. Kulkarni R, Soucie JM, Evatt BL, Hemophilia Surveillance System Project Investigators. Renal disease among males with hemophilia. Haemophilia. 2003; 9(6):703–10. [PubMed: 14750936]
12. Lottenberg R, Soucie JM, Grant AM, Atrash HK. Blood disorders in public health. Making the connection. Am J Prev Med. 2010; 38(S4):S449–S579. [PubMed: 20331941]
13. Public Health Service Act, Pub. L. No. 96-63, Sect. 606 (month day 1975). Amended Title XI of the Public Health Service Act
14. CDC. About the universal data collection system. Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities; Atlanta GA: [updated Nov 2, 2011]www.cdc.gov/ncbddd/blooddisorders/udc/aboutus.html
15. Evatt BL. The tragic history of AIDS in the hemophilia population, 1982–1984. J Thromb Haemost. 2006; 4(11):2295–301. [PubMed: 16972935]

16. Soucie JM, Nuss R, Evatt BL, et al. Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. *Blood*. 2000; 96(2): 437–42. [PubMed: 10887103]
17. 2008. Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill 2009, 110th Cong., 2nd sess
18. 2009. Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill 2010, 111th Cong., 1st sess
19. National Center on Birth Defects and Developmental Disabilities. Registry and surveillance system for hemoglobinopathies. CDC; Atlanta GA: 2013. www.cdc.gov/ncbddd/hemoglobinopathies/documents/rushfactsheet2010.pdf
20. NIH. NIH News. NHLBI, CDC launch surveillance and research program for inherited blood diseases. 2010. www.nih.gov/news/health/feb2010/nhlbi-18.htm
21. Wang Y, Kennedy J, Caggana M, et al. Sickle cell disease incidence among newborns in New York State by maternal race/ethnicity and nativity. *Genet Med*. 2013; 15(3):222–8. [PubMed: 23018751]
22. Miller CH, Benson J, Ellingsen D, et al. F8 and F9 mutations in U.S. haemophilia patients: correlation with history of inhibitor and race/ethnicity. *Haemophilia*. 2012; 18(3):375–82. [PubMed: 22103590]
23. Soucie JM, Miller CH, Kelly FM, et al. A study of prospective surveillance for inhibitors among persons with haemophilia in the U.S. *Haemophilia*. 2014; 20(2):230–7. [PubMed: 24261612]
24. Payne AB, Miller CH, Kelly FM, Soucie MJ, Hooper WC. The CDC Hemophilia A Mutation Project (CHAMP) mutation list: a new online resource. *Hum Mutat*. 2013; 34(2):E2382–E2391. [PubMed: 23280990]
25. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Health care expenditures for Medicaid-covered males with haemophilia in the U.S., 2008. *Haemophilia*. 2012; 18(2):276–83. [PubMed: 22188641]
26. Grosse SD, Boulet SL, Grant AM, Hulihan MM, Faughnan ME. The use of US health insurance data for surveillance of rare disorders: Hereditary hemorrhagic telangiectasia. *Genet Med*. 2014; 16(1):33–9. [PubMed: 23703685]
27. USDHHS. Blood Disorders and Blood Safety. Office of Disease Prevention and Health Promotion; Washington DC: Healthy People 2020. www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=4
28. Gross SD, Lloyd-Puryear MA, James AH. Blood disorders in public health. Bridging the gap. *Am J Prev Med*. 2011; 41(6S4)
29. Division of Blood Disorders. Strategies from the field: health promotion. CDC; Atlanta GA: 2012. Registry and surveillance system for hemoglobinopathies. www.cdc.gov/ncbddd/hemoglobinopathies/documents/rush-strategies_508.pdf
30. Division of Blood Disorders. Strategies from the field: data collection. CDC; Atlanta GA: 2012. Registry and surveillance system for hemoglobinopathies. www.cdc.gov/ncbddd/hemoglobinopathies/documents/12_232856A_RuSH-StrategiesDATA_CVR&TXT_508.pdf
31. United Nations General Assembly. Sixty-third session. Recognition of sickle-cell anaemia as a public health priority. 2008. Agenda item 155. Document A/63/L.63 www.un.org/ga/search/view_doc.asp?symbol=A%2F63%2FL.63p&Submit=Search&Lang=E
32. Halliday JL, Collins VR, Aitken MA, Richards MP, Olsson. Genetics and public health—evolution, or revolution? *J Epidemiol Community Health*. 2004; 58(11):894–9. [PubMed: 15483303]
33. Bean CJ, Boulet SL, Yang G, et al. Acute chest syndrome is associated with single nucleotide polymorphism–defined beta globin cluster haplotype in children with sickle cell anaemia. *Br J Haematol*. 2013; 163(2):268–76. [PubMed: 23952145]