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## Public Health Surveillance of Nonmalignant Blood Disorders

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### Abstract

Nonmalignant blood disorders currently affect millions of Americans, and their prevalence is expected to grow over the next several decades. This is owing to improvements in treatment leading to increased life expectancy of people with hereditary conditions, like sickle cell disease and hemophilia, but also the rising occurrence of risk factors for venous thromboembolism. The lack of adequate surveillance systems to monitor these conditions and their associated health indicators is a significant barrier to successfully assess, inform, and measure prevention efforts and progress toward national health goals. The CDC is strengthening surveillance activities for blood disorders by improving and developing new methods that are tailored to best capture and monitor the epidemiologic characteristics unique to each disorder. These activities will provide a robust evidence base for public health action to improve the health of patients affected by or at risk for these disorders.

### Introduction

Ranging from rare inherited conditions like hemophilia, to common acute events with strong nonhereditary triggers such as venous thromboembolism (VTE), nonmalignant blood disorders comprise a group of diverse conditions that are increasingly recognized as important illnesses to be addressed by the public health sector.<sup>1,2</sup> These conditions currently affect millions of Americans, and their prevalence is expected to grow over the next several decades owing to improvements in treatment leading to increased life expectancy of people with hereditary conditions, like sickle cell disease (SCD) and hemophilia, and the rising occurrence of risk factors for VTE.<sup>3–5</sup> Given the public health impact of these disorders, a new topic area, Blood Disorders and Blood Safety, was created for *Healthy People 2020* (HP2020), introducing 19 new objectives for reducing the burden of bleeding disorders, hemoglobinopathies (SCD and thalassemia), and VTE as well as improving and assuring blood safety.<sup>6</sup> However, the lack of adequate surveillance systems to monitor these conditions and their health indicators is a significant barrier to successfully informing and assessing prevention efforts as well as measuring progress toward these objectives. Currently, there are no established national population-based monitoring or surveillance systems for SCD, thalassemia, or VTE. Although there has been ongoing monitoring of

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bleeding disorders, this system historically has not collected information on patients who received health care outside of federally funded hemophilia treatment centers (HTCs) or comprehensive care centers for patients with bleeding disorders. Monitoring has also not tracked health indicators of emerging health challenges such as chronic diseases like cardiovascular disease or inhibitors (the development of antibodies to treatment products) experienced by people with bleeding disorders.

Given the diversity in the clinical presentation, healthcare needs, and affected populations, no single surveillance approach can effectively monitor all blood disorders. Instead, the selection of an appropriate method is strongly influenced by several factors, including: diagnosis and screening practices; the acute or chronic nature of the condition; and the healthcare utilization pattern, geographic distribution, and social and cultural norms of the affected population. These factors pose challenges, but also provide strategic opportunities when choosing and implementing surveillance methods. This paper discusses the principles, challenges, and successes experienced in developing and redesigning the CDC-sponsored surveillance of bleeding disorders, hemoglobinopathies, VTE, and blood safety.

## Bleeding Disorders

Bleeding disorders impair the effectiveness of blood clotting, leading to excessive bleeding, prolonged bleeding, or both. Congenital or hereditary bleeding disorders include hemophilia, von Willebrand disease (VWD), and various platelet and clotting factor disorders.

Hemophilia is an absolute or functional deficiency of clotting factor protein VIII (hemophilia A) or IX (hemophilia B), components in the series of reactions creating fibrin, a major constituent of blood clots. In its severe form, hemophilia can result in crippling joint bleeds and other serious or life-threatening bleeds such as intracranial hemorrhages. An X-linked condition, it is observed primarily in males (about 1 in 5,000 births), affecting an estimated 20,000 Americans.<sup>7,8</sup> VWD, a deficiency or dysfunction of von Willebrand protein, important for platelet aggregation and stabilization of blood clots, is a heterogeneous condition with bleeding phenotypes ranging from asymptomatic to relatively severe. It is thought to affect up to 1% of the U.S. population, occurring equally in male and female patients, though women are more likely to be symptomatic due to the hemostatic challenges of menstruation and childbirth.<sup>9</sup>

The CDC's public health activities to address bleeding disorders began during the 1980s after hemophilia patients were disproportionately infected with HIV through contaminated treatment products.<sup>10</sup> In 1983 CDC began supporting HIV risk reduction activities in the national network of HTCs (funded by the Health Resources and Services Administration), and in 1989 supported the development and analysis of the Hemophilia Minimal Data Set to monitor HIV risk reduction service delivery at HTCs.<sup>11–13</sup> From 1995 to 1999, the CDC conducted the six-state population-based Hemophilia Surveillance System (HSS), which established the incidence and prevalence of hemophilia in the U.S.<sup>14,15</sup> Sixty-six percent of patients identified in the HSS received at least some care at an HTC and were found to have reduced mortality and hospitalizations compared to those who did not.<sup>8,13,15</sup> This was followed by The Universal Data Collection (UDC) project (1998–2011), a national, HTC-

based surveillance system for longitudinal monitoring of the complications of bleeding disorders, especially joint disease and bloodborne infections.

In 2010, CDC evaluated the scope and utility of the UDC and convened a stakeholder meeting to identify ongoing and emerging health indicators of importance for those with bleeding disorders. Stakeholders identified numerous areas of concern and interest, including conditions of aging, inhibitors, and the healthcare utilization and experiences of patients receiving care outside of HTC. Based on recommendations from these activities, in September 2011, CDC initiated three new projects for monitoring the complications of bleeding disorders. Longitudinal monitoring of health conditions in patients receiving care in HTCs continues, including the collection of blood specimens for centralized monitoring for inhibitors, bloodborne pathogens, and other conditions. As sites of clinical care seeing large numbers of bleeding disorder patients, the HTCs are ideal for collection of detailed and specific clinical data and specimens.

Additionally, collection of data from people with bleeding disorders who do not attend HTCs is being piloted at non-HTC care centers and through a patient survey to assess strategies for identifying and conducting bleeding disorder surveillance among these patients as well as to initiate a description of their health status. Data are not expected to be representative of the entire non-HTC population and thus are not expected to allow direct comparison of health outcomes between patients receiving care in and outside of federally funded HTCs or to explain previously observed differences. However, they are a step forward in understanding the care and health status of non-HTC patients, which will contribute to our knowledge of the public health burden of bleeding disorders and the ultimate goal of improving health outcomes for all bleeding disorder patients.

## Hemoglobinopathies

The hemoglobinopathies are a group of inherited blood disorders caused by mutations in the globin genes and includes SCD and the thalassemias. There are an estimated 72,000–98,000 people living with SCD in the U.S.<sup>16</sup>; an estimate of the number of people living with thalassemia is unavailable. In 2010, CDC partnered with the NIH and seven U.S. state health departments to pilot the Registry and Surveillance System for Hemoglobinopathies (RuSH), the first statewide, population-based surveillance system for hemoglobinopathies in the U.S. The intent of this first phase of RuSH was to utilize pre-existing data sets to identify unique individuals living with a hemoglobinopathy in each of the participating states. The NIH's plan for the next phase of the project is to use the RuSH information to create a national hemoglobinopathy registry.<sup>17</sup>

RuSH was conducted within state health departments to leverage their public health authority or legislative mandate to access the wide variety of data sets that were required to implement the activities of RuSH.<sup>18</sup> The states received 2 years of funding, although most continued their work beyond this time period. A novel, three-tiered case definition was developed for the project, based on laboratory results and ICD-9 and ICD-10 codes. Data sets for the project included, but were not limited to: newborn screening (NBS) records, vital statistics records (birth and death), state Medicaid databases, state hospital and emergency

department databases, and specialty care clinics. The project included data for a 5-year period (2004–2008) that was extracted, de-duplicated, and linked across all data sets.

By using multiple data sets, the RuSH project allowed for a more comprehensive understanding of the hemoglobinopathy populations in the seven states than was already available. Previously, NBS results were used to determine the incidence of SCD, but few states mandate comprehensive NBS for the thalassemias. Also, there were no systems that collected information on people born prior to the implementation of NBS or those born in other countries, which affected the validity of current prevalence estimates. Moreover, most of the studies that were published on healthcare utilization (e.g., hospitalizations, emergency department visits, therapeutic blood transfusions, transcranial Doppler screening) or mortality used only one or two sources of data, which meant that the results were limited in scope and not generalizable to the overall hemoglobinopathy population.<sup>19–21</sup>

RuSH data will provide a clearer understanding of the public health burden of hemoglobinopathies in the participating states. The information will equip patients, community members, healthcare providers, policy makers, and public health with a more accurate idea of where individuals with a hemoglobinopathy live, what kind of health care they receive, and the areas where improvement is needed. Currently, work is being conducted with two of the RuSH states to evaluate and validate the RuSH activities and refine the case definition and data collection methods. CDC's ultimate goal is to implement a refined, RuSH-like program to collect hemoglobinopathy data from all states in the U.S., subject to availability of funding. These data will allow for a comparison among states of the prevalence of the conditions, access to high-quality health care throughout the lifespan, and hemoglobinopathy-related health outcomes. Preliminary analysis of the RuSH data (data not shown) indicates that these measures vary greatly from state to state. However, without a national surveillance system, it will not be possible to fully understand and improve upon these disparities.

## Venous Thromboembolism

VTE includes both deep vein thrombosis (DVT), a condition in which a blood clot forms in the deep veins of the body, and pulmonary embolism (PE), a potentially fatal condition that occurs when a clot breaks free and enters the arteries of the lungs. Numerous risk factors have been identified and include advanced age, surgery, hospitalization, cancer, immobilization, pregnancy, and hormones.<sup>3,22–24</sup> The actual number of people affected by VTE in the U.S. is uncertain but VTE incidence has been estimated at 300,000–900,000 cases annually and annual deaths from PE are estimated at 100,000 or more.<sup>22–27</sup> However, many VTE experts have suggested that the current estimates are not nationally representative and likely understated given the complexity of documenting VTE occurrence.<sup>27,28</sup>

Fortunately, many VTEs are preventable, and in 2008, the Surgeon General released a “Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism,” urging a coordinated effort to reverse projected trends and reduce the national burden of VTE.<sup>28</sup> An important part of prevention is conducting surveillance that can accurately quantify the

burden of VTE, identify those in need of prevention efforts, and measure the effectiveness of those efforts. However, surveillance of this condition is challenging. DVT and PE can be diagnosed and managed by healthcare providers in various specialties in both inpatient and outpatient settings. Furthermore, PE may be misdiagnosed and often presents as sudden death, requiring an autopsy for confirmation of diagnosis. Therefore, to comprehensively capture VTE events, it is essential to have a population-based surveillance system with the capacity to collect and link data from multiple sources.

In April 2012, CDC initiated funding of two 2-year pilot VTE surveillance projects. Each awardee is developing and implementing population-based surveillance to capture inpatient, outpatient, and death-related VTE events in a specific geographic area (county). Both projects will be evaluated to assess their ability to: (1) describe and establish population-based estimates of VTE burden; (2) monitor and describe associated morbidity and mortality; (3) monitor trends over time and evaluate outcomes, recurrence, and the effect of prevention measures; and (4) identify areas for further public health research. Although they are each implementing unique approaches to case ascertainment and data collection, similar case definitions and indicators are being used and collected to ensure consistency and comparability between the two projects.

Capturing the entire burden of VTE in a county is challenging because of cases in which PE presents as sudden death and an autopsy is not performed or instances in which county residents develop VTE and obtain care outside of the county. Both awardees are implementing methods to limit these challenges. Nevertheless, these pilot programs will help inform future scaled-up surveillance of VTE that will aid CDC in establishing a baseline to monitor and assess effectiveness of prevention efforts, focus research and prevention messages, and guide a comprehensive approach to reducing death and illness due to VTE.

## Blood Safety

For many patients with severe thalassemia, therapeutic blood transfusions are the foundation of care. Therapeutic transfusion also plays a major role in the care of patients with SCD and Diamond Blackfan anemia. Consequently, transfusion-related complications may become a major source of morbidity for these patients. Fortunately, improved vaccination strategies and advances in donor testing and deferral have helped reduce the risk of transfusion-transmitted infection. The risk of contracting HIV through transfusion has been reduced to 1 in 2.3 million and the risks for hepatitis B and C have been reduced to 1 in 277,000 and 1 in 1.9 million, respectively.<sup>29,30</sup> However, noninfectious transfusion complications continue to be a concern. Iron overload from repeated transfusions is a severe complication which can result in early death from organ failure. Alloimmunization, having an antibody to a transfused red blood cell antigen, can lead to increased incidence of adverse transfusion reactions and limit or delay the availability of compatible blood that a patient can receive.

From 2004 to 2012, CDC conducted the Thalassemia Data and Blood Specimen Collection Project for the early detection of infections that might be transmitted through blood transfusion. This system focused on patients receiving care at seven Thalassemia Treatment

Centers in the U.S. Participants enrolled in the project provided blood specimens annually that were tested for the presence of hepatitis A, B, C, and HIV. No transfusion-transmitted infections were detected during the project, suggesting that, to be timely and useful, surveillance may need to be broadened to include other blood disorder patients who receive transfusions as part of their standard care and to monitor new and emerging pathogens and noninfectious complications.

In 2012, CDC established the Blood Safety Surveillance for People with Blood Disorders project to address current infectious and noninfectious threats for patients who receive therapeutic red cell transfusions as part of their care regimen. Two-year cooperative agreements were awarded to four sites with access to at least 250 patients with nonmalignant blood disorders who receive at least one therapeutic red cell transfusion per year. Although CDC has previously partnered with clinical sites for blood safety surveillance, this is the first time that it has partnered with a state health department as an awardee for these activities. Each awardee has a unique approach to obtaining surveillance data, identifying patients, and obtaining blood specimens. Some look to utilize existing hospital data systems and others are developing novel systems of abstracting patient information. Blood specimens are collected upon enrollment to perform routine laboratory surveillance testing; remaining serum and cells are stored for deep sequencing for future studies or outbreaks involving blood safety.

This pilot project will help CDC obtain a better understanding of how best to monitor the rates of and risks related to transfusion complications and infectious transmissions as well as increase knowledge of rare blood types and blood banking practices to better address alloimmunization. Results will be used to develop and refine future blood safety surveillance activities with an ultimate goal of providing information to prevent or limit complications of chronic transfusion.

## Conclusions

Nonmalignant blood disorders are diverse in terms of the affected populations, incidence, prevalence, complications, and treatment. Different public health surveillance approaches are called for to effectively assess the burden and impact of these disorders, as well as to inform and monitor the effectiveness of prevention strategies. Public health surveillance is defined as “the ongoing, systematic collection, analysis, and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated with the dissemination of these data to those who need to know and linked to prevention and control.”<sup>31</sup> Although public health surveillance was once limited to monitoring infectious diseases, the focus, methods, and uses of surveillance continue to expand as the need for monitoring the evolving public health challenges facing people affected by chronic and inherited conditions grows.<sup>32,33</sup>

The CDC is strengthening surveillance activities for blood disorders by improving and developing new methods that are tailored to best capture and monitor the epidemiologic characteristics unique to each disorder. To be more timely and relevant to the needs of stakeholders and patients, bleeding disorders and blood safety surveillance is evolving to

address emerging complications and threats and is broadening its scope to include previously unmonitored patient groups. In the case of hemoglobinopathies, multiple data sources (including clinical, administrative, and laboratory) were used to develop more comprehensive surveillance that has resulted in more accurate estimates of hemoglobinopathy prevalence and burden in the U.S. For VTE, novel population-based surveillance models are being piloted to inform large-scale surveillance that can more accurately describe and monitor VTE burden in both inpatient and outpatient settings and provide a baseline for prevention efforts.

The described CDC blood disorder surveillance activities will provide much-needed public health data to assess the magnitude of these conditions and their related complications, monitor trends and effectiveness of interventions, and describe patient and provider practices. These data will inform and provide an evidence base for public health action to improve the health of patients affected by and at risk for these disorders.

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