

APHL Opioids Biosurveillance Task Force

Laboratory Data in Neonatal Abstinence Syndrome Surveillance



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OBTF Members

- Co-Chair: Ewa King, PhD, formerly of the Rhode Island Department of Health, State Health Laboratories
- Co-Chair: Amy Miles, BS, Wisconsin State Laboratory of Hygiene
- Sanaa Akbarali, MPH, Association of State and Territorial Health Officials (ASTHO)
- Mei Baker, MD, FACMG, Wisconsin State Laboratory of Hygiene
- Grant Baldwin, PhD, MPH, CDC National Center for Injury Prevention and Control (NCIPC)
- Melissa Carter, PhD, MBA, formerly of the CDC National Center for Environmental Health (NCEH)
- Jennifer Colby, PhD, DABCC, LabCorp
- Hayley Friedman, MD, Washington University School of Medicine/American Academy of Pediatrics (AAP)
- Suzanne Gilboa, PhD, CDC National Center on Birth Defects and Developmental Disabilities (NCBDDD)
- Kate Goodin, MPH, Tennessee Department of Health
- Shin Kim, MPH, CDC NCBDDD
- Leland McClure, MSci, PhD, F-ABFT, Drug Testing Consultations LLC
- Charles McKay, MD, American College of Medical Toxicology (ACMT)
- Desiree Mustaquim, PhD, MPH, CDC NCIPC
- Jason Peterson, MS, Minnesota Department of Health
- Tricia Wright, MD, MS, FACOG, DFASAM, University of California, San Francisco/American College of Obstetricians and Gynecologists (ACOG)

Organizational Liaisons

- Valerie Goodson, MPA, Council of State and Territorial Epidemiologists (CSTE)
- Daniel Mandel, PhD, CDC NCEH
- Rachel Gandell Tetlow, ACOG
- Megan Toe, MSW, CSTE

APHL Staff

- Nicholas Ancona, MPH
- Kuki Hansen, BVMS, MPH, DACVPM
- Jennifer Liebreich, MPH
- Julianne Nassif, MS
- Jelili Ojodu, MPH
- Sikha Singh, MHS

EXECUTIVE SUMMARY

In January 2019, the APHL Opioids Biosurveillance Task Force (OBTF) was established by the APHL Board of Directors to consider how public health laboratories might contribute to the opioid epidemic response. Given the advanced analytical capabilities and expertise in public health laboratories to identify and measure chemical toxicants in clinical specimens, OBTF acknowledged that there was an opportunity to fill critical data gaps in existing state health department opioid overdose surveillance systems related to non-fatal opioids overdoses.

In July 2020, OBTF published [Model Opioids Biosurveillance Strategy for Public Health Practice](#), which outlines guidance and considerations for state public health laboratories and state health agencies in designing and implementing opioids biosurveillance in their jurisdictions. The guidance document addresses various aspects of opioids biosurveillance program design, including specimen collection and testing strategies, data reporting, and program evaluation. Several states have initiated opioids biosurveillance programs currently at various stages of implementation and data sharing and are assessing its use in informing public health intervention and policy.

As *Model Opioids Biosurveillance Strategy for Public Health Practice* was being written, OBTF recognized common elements between opioids biosurveillance and Neonatal Abstinence Syndrome (NAS) surveillance and recommended that the group explore the added value of laboratory data in NAS surveillance, and consider the potential roles of public health laboratories, toxicology and clinical laboratories in that work. In September 2020, OBTF was re-configured to provide multi-disciplinary expertise in analytical chemistry, toxicology, medicine and epidemiology to explore the scope and magnitude of NAS nationally, and to provide comment on various aspects of laboratory-informed NAS surveillance. This re-configuration (OBTF 2.0) included subject matter experts in neonatology, pregnant/birthing individual and child health, obstetrics and gynecology, epidemiology and surveillance, and diagnostic and public health laboratory science. Public health partners representing national professional organizations and federal partners (The Association of State and Territorial Health Officials, Council of State and Territorial Epidemiologists, US Centers for Disease Control and Prevention's National Center on Birth Defects and Developmental Disabilities, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists) provided valuable national perspective.

Scope and Purpose

OBTF explored the value and utility of laboratory data in NAS surveillance and the feasibility of assessing prenatal/*in utero* opioid exposure through neonatal testing.

To accomplish this, OBTF outlined:

1. Current NAS surveillance activities in the US.
2. Considerations for jurisdictions exploring laboratory testing to assess *in utero* exposure.
3. Opportunities and challenges associated for enhancing epidemiology, surveillance and pregnant/birthing individual and child health programs through the provision of *in utero* opioid exposure laboratory data.
4. Social, ethical and legal implications of conducting *in utero* opioid exposure testing.

Neonatal Abstinence Syndrome, or NAS, is a syndrome characterized by a collection of non-specific symptoms including tremors, twitching, convulsions, tight muscle tone, fussiness, excessive crying, poor feeding, slow weight gain, breathing problems, fever, sweating and blotchy skin.

The symptoms may be the result of in-utero exposure to opioids and/or other substances.

OBTF limited the scope of their discussions—and ultimately this document—to laboratory-informed NAS surveillance associated with opioids exposure. However, the recommendations and conclusions related to use of laboratory data to support NAS surveillance may be applicable to other substances. OBTF acknowledges that considerable sophisticated analytical testing capability is needed to adequately address *in utero* polysubstance exposure.

OBTF is aware of the term Neonatal Opioid Withdrawal Syndrome (NOWS) and acknowledges that NAS is a more general term that encompasses neonatal withdrawal. However, for consistency with the [CSTE NAS Standardized Surveillance Case Definition](#), OBTF uses NAS in this document when referring to this syndrome.

Conclusions & Recommendations

After review of the available literature, discussions with public health partners, clinicians and laboratory scientists, and careful consideration of multiple and sometimes conflicting perspectives, OBTF reached the following conclusions:

1. Laboratory data has the potential to enhance NAS surveillance.
2. Laboratory testing is recommended for symptomatic neonates, not for screening of all newborns.
3. Residual newborn dried blood spot specimens collected for the detection of diseases on the Recommended Uniform Screening Panel should not be used for NAS surveillance.
4. Population-based research studies are recommended to determine the prevalence of *in utero* opioids exposure.

This document is intended for use by public health professionals (i.e., laboratory scientists, epidemiologists and health officials). It is not envisioned as clinical guidance on the use of laboratory tests for NAS diagnosis and treatment.

BACKGROUND

In October 2017, the US Department of Health and Human Services (HHS) released a call for federal action to address Neonatal Abstinence Syndrome (NAS), a newborn syndrome comprised of a constellation of signs of *in utero* exposure to, and withdrawal from, one or more medications, drugs and other substances known to cause withdrawal in adults. In that same month, the Trump Administration declared the opioid epidemic a public health emergency, bringing an additional sense of urgency to the issue. In March 2021, the Biden Administration released their drug control policy statement which continued to identify the opioid epidemic as an urgent priority. These statements demonstrate commitment at the federal level and may encourage state and local health agencies to develop or enhance programs and policies aimed at addressing *in utero* opioid exposure and NAS.

Public health leaders at the Council of State and Territorial Epidemiologists (CSTE), the US Centers for Disease Control and Prevention (CDC) National Centers for Birth Defects and Developmental Disabilities (NCBDDD), the Association of State and Territorial Health Officials (ASTHO), and several state health departments are engaged in multiple activities related to enhancing NAS surveillance and supporting the overall goals outlined in CDC's [Five Key Strategies for Preventing Opioid Overdoses and Related Harms](#). It's important to note that many of these NAS surveillance activities were not being informed or supplemented by laboratory data at the time of publication.

Data from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP), indicate that nearly seven (6.8) newborns were diagnosed with NAS per 1,000 newborn hospitalizations in the United States in 2018 alone. Additionally, research published in the *Journal of the American Medical Association* estimated that approximately one newborn was diagnosed with NAS every 19 minutes in 2017, culminating in 80 newborn diagnoses daily. Diagnoses increased substantially over time and resulted in an 82% increase between 2010 and 2017. These data underscore the need for swift action to limit adverse impacts of the opioid epidemic on pregnant/birthing individual and child health.

There are alarming differences between the rates of NAS in rural and urban populations. According to the 2010 Census, approximately 20% of the US population resides in rural areas. AHRQ HCUP found that the rate of NAS in rural regions of the US from 2004–2013 was nearly double that of the NAS rate in metropolitan areas and has continuously increased over time. Research has shown that rural populations may experience several disparities ranging from availability and access to care, lower socioeconomic status, and cultural differences—adversely impacting health outcomes in these communities. In terms of access and availability to care, rural communities have fewer primary care physicians and subspecialists compared to urban communities. Socioeconomic barriers such as lower family income, higher rates of children living in poverty, and health insurance plans with limited benefits are contributing factors that impact the higher rates of NAS and opioid use seen in rural populations. The impact of the COVID-19 pandemic further exacerbated health disparities among populations impacted by prenatal opioid exposure.

There is considerable evidence of racial disparity amongst birthing individuals with an opioid use disorder (OUD) and neonates with NAS. One study found that Black birthing individuals had higher parity, higher THC and cocaine use, and higher positive urine drug screen when compared to White birthing individuals. The study also found that although all birthing individuals were referred to an opioid management treatment program by their obstetricians, only 45% attended one (63% of White and 22% of Black birthing individuals). Not attending the treatment program was likely due to the economic barriers, since many only accept cash payments and only 20% may accept patients with Medicaid insurance. The length of stay in hospitals for neonates with NAS continues to be a topic of interest when identifying mechanisms to reduce healthcare costs; however, racial disparities in length of stays continue to be a persistent issue. A study found

NAS RISK FACTORS

Geographic

Poor access to care in rural and/or tribal communities, misdistribution of primary care physicians and clinical subspecialists.

Socioeconomic

Low family income, elevated rates of childhood poverty, limited health insurance benefits.

Racial

American Indian/Alaska Native (AI/AN) neonates are 1.6 times more likely to experience NAS than Non-Hispanic White neonates.

that Black neonates with NAS or neonatal opioid withdrawal syndrome (NOWS) had an increased length of stay from 2009 to 2016 (from 16.29 to 22.18 days); in comparison, there was a near-steady length of stay for the overall cohort and among White neonates (from 16.29 to 16.2 days).

Tribal communities also experience an elevated burden of NAS. A recent study conducted by the Northwest Portland Area Indian Health Board found that between 2010 and 2017, the rate of NAS diagnosis was 1.6 times higher for American Indian and Alaska Native (AI/AN) neonates than Non-Hispanic White neonates. In 2010, the rate of AI/AN neonates diagnosed with NAS was 6.7 per 1,000 live births. By 2017, that rate had increased by 153%, with 17.0 per 1,000 live births of AI/AN newborns diagnosed with NAS.

Diagnosics

Opioid Use Disorder

Positive neonatal urine screening results should not be used to diagnose OUD in pregnant individuals as these results may only reflect current or recent drug exposures, does not rule out sporadic drug use, and may detect medically prescribed drugs. Urine drug screening using immunoassay is also prone to false positive and false negative results, and generally detect a class of drugs, rather than the specific drug substance. Due to this, immunoassays will likely be unable to detect many emerging synthetic opioids and fentanyl analogues. It is recommended that healthcare providers seek definitive (confirmatory) testing when appropriate. Specimens may need to be referred to a laboratory with advanced analytical capabilities.

Neonatal Abstinence Syndrome

Knowledge of opioid use during pregnancy may help guide a clinician's ability to provide care for the exposed neonate, as *in utero* opioid exposure may be associated with NAS. Presentation of NAS symptoms may be delayed for several days after birth and are dependent on factors such as timing of a pregnant/birthing individual's drug use, drug type, infant metabolism and non-specific clinical symptoms of NAS (e.g., irritability, poor feeding). These complexities in NAS presentation lead to variability in diagnosis, as it may be difficult associate these symptoms with drug use and/or specific drugs without laboratory evidence.

Treatment

Opioid Use Disorder

The accepted medical treatment for opioid use disorder during pregnancy is replacement therapy, with either methadone or buprenorphine. These medications, which can also lead to neonatal withdrawal, have been shown to improve pregnancy outcomes. In accordance with ACOG recommendations, medically-assisted treatment (MAT) should not be denied in attempts to prevent neonatal withdrawal. Goals include providing pregnant individuals with the best access to recovery treatment during their pregnancies while continuing to support the family unit.

Neonatal Abstinence Syndrome

Neonates undergoing withdrawal may experience a range of symptoms associated with irritability, poor feeding coordination and difficulty soothing. Clinical evaluation tools such as Finnegan Scoring or Eat, Sleep, Console Methodology are utilized by clinical teams to assess the infant's wellness and withdrawal symptoms. Multidisciplinary teams including physicians, nurses, physical and occupational therapists, and social workers are all a part of the effort to support patients and families.

According to AAP, the primary modality of medical management for infants with clinical symptoms of withdrawal is non-pharmacologic care. Such management involves engaging family members in actively caring for their infant at bedside in a low stimulation environment, supporting breastfeeding (per institutional protocol), and providing soothing and consoling with measures such as swaddling and holding. Family members and medical team members work together to impart all non-pharmacologic measures.

In the setting of maximized non-pharmacologic care, if the infant continues to have difficulty eating well, consoling and soothing or sleeping; standardized clinical guidelines are utilized to initiate pharmacologic management while continuing non-pharmacologic interventions. The primary medication used nationwide is neonatal morphine solution, formulated for use in neonates and prescribed by weight. Additional second line medications that may be used pending the infant's needs include clonidine and phenobarbital. Additional medications including methadone and buprenorphine have recently been trialed as first line agents as well. Once the infant's clinical status has improved, protocols are followed to wean the infant off medication prior to discharge home.

Prior to discharge, all families are provided with newborn education including support with feeding practices, safe sleep interventions, and recovery and support services as needed. Clinical teams and social workers collaborate with family members to provide a comprehensive discharge plan for the family. Follow-up appointments are scheduled including primary care pediatrician as well as neurodevelopmental follow up clinic if applicable/available. Additional resources to support neurodevelopment include state funded and/or hospital based early intervention resources, follow-up physical and occupational/speech therapy, primary care, and coordination of follow-up with neonatologists. It is important to note that these clinical management decisions are not typically dependent on laboratory testing.

Implications of Potentially False Positive Results

False positive laboratory results may cause an unnecessary reluctance to breastfeed, a practice which should be supported in birthing individuals with a history of opioid use who would like to do so. It is recommended that interpretive guidance be provided for all test results. Immunoassays have the potential to produce false positive results, such as false detection of opioids after administration of quinolone antibiotics or other medications, so it is recommended to follow up with confirmatory/definitive testing with established cut-off levels.

Immunoassays may also produce false negative results and may be unable to detect novel fentanyl analogues. If such novel fentanyl analogues are outside the scope of testing for the immunoassay, they will not be detected.

Labor & Delivery Considerations

Drugs administered during delivery are detectable soon after delivery in both birthing individual and neonatal urine, as well as in umbilical cord tissue and meconium. Potential detectable analytes include drugs such as fentanyl, morphine, or oxycodone and its metabolite oxymorphone. The timing for expected appearance in the urine is likely within the hour, but may vary based on the volume of pre-administration urine in the bladder. It is important to note that presence of drugs in test results does not provide adequate or informative pregnant individual drug use history data.

State health agencies should work closely with healthcare providers within their states to understand how laboratory-informed NAS surveillance may or may not impact the diagnosis, treatment, and service delivery of opioid-exposed neonates and their caregivers.

OBTF acknowledged that healthcare workers and epidemiologists may have differing levels of training in substance use and interpretation of drug toxicology testing and encourages medical societies and professional organizations to develop and sustain ongoing continuing education in the area of toxicology result interpretation. Example activities include developing opioid-specific curricula and including opioid-related questions on board certification exams.

CURRENT NATIONAL & STATE NAS SURVEILLANCE ACTIVITIES

Classifying cases of NAS is complex, requiring a review of available medical information such as signs, symptoms and record of a diagnosis, and a determination on the presence or absence of neonatal drug exposure. On January 31, 2022, HHS made a statement in support of a recently standardized NAS clinical definition. “Expert panels concluded the following were required for diagnosis: *in utero* exposure (known by history, not necessarily by toxicology testing) to opioids with or without the presence of other psychotropic substances, and the presence of at least two of the most common clinical signs characteristic of withdrawal (excessive crying, fragmented sleep, tremors, increased muscle tone, gastrointestinal dysfunction).”

While this definition is relevant for clinical practice, it varies significantly from the CSTE NAS Standardized Case Definition published in July 2019. The CSTE NAS Standardized Surveillance Case Definition provides a tiered approach to NAS case classification (Tier 1: Real-time case reporting based on public health legal authority and Tier 2: Case reporting based on administrative claims data). Tier 1 surveillance states that a clinician diagnosis alone cannot classify a case of NAS as ‘confirmed,’ laboratory confirmation of exposure is required. However, a clinician diagnosis alone can be used to confirm a case of NAS surveillance under the Tier 2 structure if this diagnosis is documented in administrative claims data, including but not limited to hospital discharge, Medicaid or all payer claims data.

States that have mandated case reporting of NAS have the public health authority to utilize the Tier 1 definition. After evaluating six states with mandated case reporting of NAS (Arizona, Florida, Georgia, Kentucky, Tennessee and Virginia), CDC found that requiring NAS case reporting improves the ability to calculate timely estimates of incidence and ultimately informs programs and services, such as identifying opportunities for prevention and facilitating linkages to care for both infants and birthing individuals. A follow-up study conducted with these same states, published on January 14, 2022, cited “continued advantages in determining NAS incidence and community exposure patterns to guide state program development. However, persistent data collection challenges and infrastructural gaps influence states’ capacity for longer-term surveillance beyond initial case reporting.” In many states, NAS is not a reportable condition—they rely on one or more sources of administrative data for case reporting using the Tier 2 definition. Financial and staffing resource limitations impact health department implementation of the case definitions.

There are several on-going initiatives aimed at improving neonatal abstinence syndrome surveillance:

- As of August 30, 2021, [six public health agencies](#) (Arizona Department of Health Services, Florida Department of Health, Georgia Department of Public Health, Massachusetts Department of Public Health, Philadelphia Department of Public Health, and the Tennessee Department of Health) are currently being funded by the CDC NCBDDD to apply the CSTE NAS Standardized Surveillance Case Definition.
- ASTHO implemented multiple activities to support health departments in improving identification, treatment, and care coordination for neonates born with NAS. In 2018, ASTHO convened the Opioid Use Disorder, Maternal Outcomes and NAS Initiative (OMNI) Learning Community, funded through CDC’s Division of Reproductive Health and the National Center for Birth Defects and Developmental Disabilities. ASTHO worked with 15 states to improve state-level policy and programs including implementation of plans of safe care, encouraging dyadic care for birthing individuals and neonates, and provider awareness and training. During the OMNI in-person meeting in March 2021, several states discussed the need for standardizing case definitions to better understand prevalence. While most OMNI states have been utilizing CSTE’s case definition, there was expressed interest in further guidance and standards around strengthened identification and surveillance.
- In 2020, ASTHO in collaboration with the Office of the National Coordinator, implemented a project to support health agencies in building an NAS registry and enhancing NAS surveillance capacity. As part of this effort, ASTHO conducted an environmental scan consisting of a literature, policy and guidelines review and convened a series of multi-state focus groups with health agencies to identify and determine the consistency of key NAS data elements, case definitions, and standards in the field. Based on preliminary findings, the ASTHO team determined a need for standard data elements. Future steps include fielding an NAS data element submission tool to ascertain key NAS

data elements across jurisdictions through consensus-based voting. Findings from this project were published in September 2021 in the report [Strengthening Health Agencies' NAS Surveillance Through Consensus-Driven Data Standards and Practices](#).

- ASTHO continues to produce materials and resources for state and territorial health agencies. In 2017, ASTHO, in partnership with the National Institute for Children's Health Quality (NICHQ), developed the [Neonatal Abstinence Syndrome Framework](#). The intent of the framework is to aid in structuring stakeholder discussions at the state level to better understand how cross-agency collaboration can prevent NAS. The document highlights key strategies for primary, secondary and tertiary prevention. In relation to secondary prevention, authors cited the importance of diagnosing NAS and using data to understand the severity of the problem. In 2020, ASTHO developed a [legislative overview of NAS](#), detailing legislative trends and recommending development of standard NAS clinical definitions. ASTHO's Health Policy Team produced [Neonatal Abstinence Syndrome: State Considerations for 2021](#), which highlights the need for standardized clinical definitions, guidance and treatment for neonates experiencing withdrawal. Based on ASTHO's current work, there is a strong need from state and territorial health departments to strengthen identification and surveillance of NAS to help inform primary prevention methods. ASTHO continues to support states and our national partners in developing and disseminating current literature, recommendations, and guidelines related to NAS and will continue to track state legislation.
- In 2020, CDC NCBDDD established Maternal and Infant Network to Understand Outcomes Associated with Treatment for Opioid Use Disorder during Pregnancy (MAT-LINK), a surveillance system used to monitor maternal, infant and child health outcomes associated with treatment for opioid use disorder during pregnancy. The goals of MAT-LINK are to improve understanding of the range of maternal, neonate and child health outcomes associated with treatment for opioid use disorder during pregnancy, and examine the possible effects of exposure to multiple substances and other risk factors on maternal and neonate outcomes. MAT-LINK was made possible through funding from the Assistant Secretary for Planning and Evaluation's Patient-Centered Outcomes Research Trust Fund. There are currently [seven clinical site partners](#): Boston Medical Center Corporation, Kaiser Foundation Research Institute (Center for Health Research–Northwest), the Ohio State University, University of New Mexico, University of Rochester, University of South Florida and the University of Utah.
- The [CDC Overdose Data to Action \(OD2A\) Cooperative Agreements](#) support surveillance for linkage to care, which can include linkage to care for those who are pregnant and postpartum. This can help to ensure that pregnant individuals are linked to appropriate treatment resources and support services. CDC NCIPC posted this three-year funding opportunity in 2019 to continue work focused on increasing comprehensiveness and timeliness of surveillance data, building state and local capacity for public health programs, and working to improve opioid prescribing. It funds work focused on linkages to care and other areas of innovation, such as new laboratory surveillance projects.

NEONATAL TOXICOLOGY TESTING

Laboratories provide valuable information related to *in utero* opioid exposure for both diagnostic and surveillance purposes by identifying individual drugs and their metabolites present in clinical specimens. These analyses are usually conducted in hospital and/or clinical laboratories. The sensitivity and specificity of these methods varies widely.

Presumptive (Screening) Drug Testing

Presumptive tests are used to identify possible exposure to a drug or classes of drugs. Presumptive methods include, but are not limited to, immunoassays such as cloned enzyme donor immunoassay (CEDIA), enzyme immunoassay (EIA), enzyme-linked immunosorbent assay (ELISA), enzyme-multiplied immunoassay test (EMIT) or fluorescence polarization immunoassay (FPIA). Immunoassays depend upon reactivity of the drug with the assay antibody, which may be targeted toward an individual drug or a class of related drugs. Routine immunoassays provide quick turnaround time, are relatively inexpensive and are well standardized. They are used routinely in hospital laboratories, at point-of-care, and in a variety of other clinical and forensic contexts. Results from these assays are always presumptive but may be helpful in quickly guiding clinical decisions and identifying specimens that should undergo definitive (confirmatory) testing. Limitations of immunoassays can include lack of sensitivity (e.g., inadequate or no reactivity to individual drugs within a class) and lack of specificity (e.g., cross-reactivity with compounds that are not the target drug).

Presumptive positive test specimens are sometimes sent for definitive (confirmatory) testing due to:

- Assay limitations, since targeted drug and/or drug metabolite are generally tested as a drug class rather than as individual drugs.
- Variable cross-reactivity of the assays with drugs within the pharmacologic class and lack of cross-reactivity of the assays with some emerging substances of use.
- Lack of FDA-approved assays for neonate-specific bio specimens.
- FDA-approved urine assays require laboratory-developed test (LDT) modifications to support analysis of alternative specimen types (i.e., meconium and cord tissue).

Positive presumptive tests may be followed by definitive tests to specifically identify drugs and drug metabolites present in the specimen.

Definitive (Confirmatory) Drug Testing

Definitive toxicology testing may be performed in some medical centers but are more commonly referred to specialty toxicology laboratories with advanced analytical capabilities. These test results are provided to clinicians and may also be provided to health departments as part of their surveillance. Laboratories use gas or high-performance liquid chromatography (GC or HPLC) coupled with mass spectrometry (MS) to definitively identify drugs and their metabolites in clinical specimens.

The specific instrument configuration depends upon many factors, including the drugs and/or drug metabolites of interest, the available clinical specimens, and the level of sensitivity and specificity required. While multiple configurations of chromatography and single stage mass spectrometry (i.e., GC-MS or HPLC-MS) can be used for definitive testing methods, chromatography with either tandem mass spectrometry (MS/MS), ion trap mass spectrometry (ITMS), or high resolution mass spectrometry (HRMS) configurations (e.g., GC-MS/MS, HPLC-MS/MS, GC-ITMS, HPLC-ITMS, GC-HRMS/MS, HPLC-HRMS/MS) have been widely adopted for definitive testing methods and are preferred due to the combination of high specificity and low detection limits. Definitive test methods can include targeted and non-targeted analysis. The two most commonly used platforms are:

High Pressure Liquid Chromatography Tandem Mass Spectrometry

HPLC-MS/MS is an instrument platform method routinely used in public health and toxicology laboratories to identify and measure specific analytes of interest, including drugs and their metabolites. Chromatographic separation is

followed by tandem mass spectrometry identification. These test methods rely on comparison of sample data with those obtained from reference standards. Isotopically labeled versions of target analytes are required for accurate quantitation (“isotope dilution”). Public health laboratories are proficient in the use of these instruments and have available reference standards for drugs and metabolites of interest. This technique may be utilized for neonatal drug testing. By design HPLC-MS/MS methods commonly detect pre-specified (targeted) analytes, often at very low concentrations. Targeted HPLC-MS/MS assays provide selectivity and sensitivity that are essential for quantitative analysis.

High-Resolution Mass Spectrometry

HRMS is a powerful analytical tool that can provide accurate mass identification of a wide range of analytes in complex biological specimens. Results from HRMS analyses may be used to identify novel drugs or psychoactive substances for which reference materials/standards are not readily available. HRMS analysis complements other mass spectrometry methods and may be used to inform individual sample flow and prioritize future laboratory methods. HRMS instrument availability is limited due to their high capital cost and the analytical skill required for operation. Advanced theoretical and instrument specific trainings are required to develop proficiency and develop and implement methods on these platforms. HRMS methods generate large quantities of data requiring a robust informatics infrastructure and detailed standard procedures for review and storage of data files. With the growing availability of HRMS instruments, such as quadrupole time-of-flight (QTOF) in public health and toxicology laboratories, it is expected their utilization in specimens related to NAS testing will grow.

Specimen Types for Neonatal Toxicology Testing

Neonatal drug testing presents many pre-analytical, analytical and post-analytical challenges, the most important of which is the selection of the appropriate specimen type for the intended purpose of testing. Factors such as availability of the specimens, adequacy of the specimens collected, availability of specimen (timing), coordinating specimen collection activities between multiple providers and facilities that may be involved in neonatal and birthing individual care, and requirements that may exist to test both the neonate and/or birthing individuals are but a few of the complexities involved. Failure of any one or more items may result in cancellation of testing and inability to capture data.

The birthing individual and neonatal specimen matrices most widely utilized to assess neonatal drug exposure include:

- **Meconium** (Neonate): Meconium is the most common specimen used for neonatal toxicology testing. This specimen type consists of fetal waste products, drugs and metabolites and is considered the gold standard for detecting *in utero* substance exposure. Formation of meconium begins around the 12th week of gestation with most forming in the final eight weeks.
- **Umbilical Cord Tissue/Blood** (Neonate): Umbilical cord tissue is a newer specimen type used for neonatal testing, consisting of Wharton’s jelly (surrounding the vessels), blood vessel tissues, remaining blood from placenta and umbilical cord. It represents drug exposures occurring during the mid to late third trimester of gestation.
- **Urine** (Birthing Individual/Neonate): The neonate produces approximately 125 mL urine/day in the first 48 hours postnatal period. Drugs can only be detected via urine for a few days after exposure.
- **Oral Fluid** (Birthing Individual): Oral fluid is an alternative specimen to urine. It is a complex and dynamic mixture of glandular secretions, gingival cervical fluid and cellular debris. Oral fluid drug concentrations are dependent upon passive diffusion from blood and drug physicochemical factors including lipid solubility, ionization state and plasma protein binding. Drugs can only be detected via oral fluid for a few days after exposure. Oral fluid is not an optimal specimen for neonate testing.

Healthcare providers should contact the testing laboratory for detailed information regarding analytes included in the test, interpretive guidance, specimen collection, specimen handling and transport requirements.

Table 1. Specimen Characteristics for Neonatal Toxicology Testing

	Meconium	Umbilical Cord	Urine
Ease of Collection	<p>Moderate</p> <ul style="list-style-type: none"> • May not be available; can be expelled <i>in utero</i> or in stages over days • Time window for collection may be missed if prior or delayed assessment of risk factors is required 	<p>Easy</p> <ul style="list-style-type: none"> • Universal and simple collection possible • Available immediately after birth • Sufficient specimen available 	<p>Difficult</p> <ul style="list-style-type: none"> • May not be available; expelled <i>in utero</i> • Requires specialized collection devices; less frequently collected for neonates • Limited volume
Window of Drug Detection	<p>Moderate/Long</p> <ul style="list-style-type: none"> • Prenatal exposure: 2nd-3rd trimester • Neonatal exposure: May detect postnatal drug use prior to meconium collection 	<p>Moderate</p> <ul style="list-style-type: none"> • Prenatal exposure: mid/late 3rd trimester • Neonatal exposure: No 	<p>Short</p> <ul style="list-style-type: none"> • Prenatal exposure: within days • Neonatal exposure: within days
Concentration of Drugs/Metabolites	High	Low	Moderate
Specimen Characteristics	<ul style="list-style-type: none"> • Most sensitive matrix for detecting remote or infrequent drug exposure • Heterogeneous matrix; requires temporary storage during collection and mixing to homogenize the material collected 	Tissue is a complex matrix for laboratory analysis	Neonates produce approximately 125 mL urine/day within first 48 hours of birth
Testing Considerations	<ul style="list-style-type: none"> • Heterogeneous specimen matrix may be a challenge for laboratory methods of analysis • Requires laboratory developed test (LDT) methods of analysis • Laboratory turnaround time 1-2 days; referral testing increases turnaround time 	<ul style="list-style-type: none"> • Requires LDT methods of analysis • Laboratory turnaround time 1-2 days; referral testing increases turnaround time • Very sensitive assays required • May not be available for neonates transferred from other facilities 	<ul style="list-style-type: none"> • FDA approved immunoassays are available for some analytes • Laboratory turnaround time <4 hours for presumptive/screening results; referral testing for definitive/confirmatory testing increases turnaround time • Neonates may produce unique metabolites not detected in standard definitive/confirmatory assays • May not be available for neonates transferred from other facilities

SOCIAL, MEDICAL AND LEGAL CONSIDERATIONS

The potential impacts of NAS surveillance on children and families must be considered by state public health programs when developing surveillance programs. Conducting NAS surveillance requires a careful balance of scientific, medical, public health, legal and ethical aspects. Care must be taken to ensure that laboratory data are not utilized in a way that may negatively impact the lives of pregnant, birthing and post-partum individuals, as well as children and families.

Concerns Regarding Punitive Approaches to Addressing Substance Use

A recently published cross-sectional study examining 4.6 million births across eight states found that NAS case rates increased significantly after punitive policies that criminalize pregnant/birthing individual drug use were enacted. Punitive actions have been shown to discourage pregnant individuals from discussing prenatal drug use history and/or obtain treatment for OUD. State public health agencies should consider the impact these punitive policies may have on the ability for a jurisdiction to conduct laboratory-informed NAS surveillance.

State public health agencies should also consider the potential implications of the Child Abuse Prevention and Treatment Act and how that may impact surveillance activities. Laws and/or policies in approximately 42 states and the District of Columbia require health-care providers to notify Child Protective Services (CPS) when they are involved in the delivery or care of infants who show evidence at birth of having been prenatally exposed to drugs, alcohol or other controlled substances. Illinois, Minnesota, North Dakota, Oregon and Wisconsin require mandated reporters to report when they suspect that pregnant individuals are abusing substances so that they can be referred for treatment. In Rhode Island, a report of substance use by a pregnant individual may be made, but an investigation will be conducted only if there is an allegation of abuse and/or neglect of the newborn or other children in the home. A now expired Tennessee law allowed incarceration of pregnant people who used substances. Additionally, California arrested two people for stillbirth because they used drugs during pregnancy. Additionally, studies have found racial inequities in CPS reporting, and that Black and/or Hispanic individuals are more likely to be reported to CPS than White individuals.

Clinical Management Considerations

Hospital protocols determine the steps taken for pregnant individual and infant toxicology testing. From a medical standpoint, a verbal interview led by a healthcare professional is currently a standard for NAS screening. If a birthing individual acknowledges substance use, the overarching goal is to support them and their family with comprehensive care. Testing and consent practices will likely differ between states and hospital networks nationally. Infant urine, cord and meconium screening are often a component of the care process. An infant urine sample is most reflective of recent substance use, yet first void is often missed. Meconium samples are reflective of exposure from approximately 20 weeks gestation. In consideration of the testing challenges, clinical teams collaborate to provide best care for pregnant individuals and their infants while reviewing all available information and data. The infant will be observed for withdrawal symptoms and managed with non-pharmacologic care/pharmacologic care per protocol. Diminishing stigma and punitive action towards pregnant individuals with substance use disorder remains within the mission of OB-GYN and pediatric physicians nationwide.

Twenty-three states and the District of Columbia consider substance use during pregnancy to be child abuse under civil child welfare statutes, and three consider it grounds for civil commitment. Twenty-five states and the District of Columbia require health care professionals to report suspected prenatal drug use, and eight states require health care professionals to test for prenatal drug exposure if drug use is suspected. With these concerns in mind, OBTF focused their efforts on outlining considerations state health agencies would need to fully examine ethical considerations prior to implementation of any form of laboratory-informed NAS surveillance.

In addition to informing clinical practice, definitive laboratory evidence can enhance public health surveillance.

RECOMMENDATIONS

1. Laboratory testing is recommended for symptomatic neonates, not for screening of all newborns.

OBTF agreed that universal screening of all neonates is not the best approach for NAS surveillance programs. Prioritizing testing of symptomatic neonates makes the best use of laboratory and public health resources and minimize the adverse impacts of potential false positives.

OBTF recognizes the need for a standardized approach for classifying cases of NAS. Over time, the CSTE NAS Standardized Surveillance Case Definition will be refined and strengthened as state health agencies implement it, and availability of laboratory data may help aid in this process. OBTF stresses the importance of upholding the highest standards of laboratory data integrity, privacy and confidentiality, including stringent de-identification of patient records, obtaining informed consent when possible, and taking necessary precautions when sharing surveillance data with public health partners external to state health agencies.

State health agencies interested in conducting laboratory-informed NAS surveillance should consider evidence-based approaches for population selection. Universal drug testing of all pregnant or birthing individuals and/or neonates is resource intensive and has been shown to be problematic from a societal and ethical standpoint. Universal drug testing may overestimate drug exposure and NAS case rates, placing a significant legal and emotional burden on families. Additionally, available screening methods are less specific than confirmatory methods and may produce elevated rates of false positive results.

APHL recognizes the importance of state-based population-based surveillance of chemical exposures, and highlights its value in the recently published [Population-Based Biomonitoring is a Fundamental Public Health Practice That Should Be in Every State](#). While not all individuals within a population are tested under a population-based surveillance framework, its successful implementation ensures that the testing being done produces an exposure assessment that is representative of the entire population.

Informed consent for drug testing is generally not necessary for public health surveillance using de-identified samples. However, it is important to acknowledge that obtaining informed consent for any diagnostic pregnant/birthing individual and/or neonatal drug testing should be attempted when reasonable per ACOG recommendations. Population-based surveillance may be helpful in obtaining a global perspective of demographics and population-based needs for pregnant women with substance use disorder and their infants. Data collected may be helpful in establishing guidelines and policies to support provision of best care and resources with statewide programming.

2. Residual newborn dried blood spot specimens collected for the detection of diseases on the Recommended Uniform Screening Panel should not be used for NAS surveillance.

Newborn Screening and Condition Panels

Newborn screening (NBS) is the practice of identifying newborns at risk for selected treatable conditions, which may otherwise go unrecognized. Conditions are mostly screened by laboratory analysis of dried blood spot (DBS) specimens collected soon after birth, and point-of-care tests are used for hearing loss and critical congenital heart disease (CCHD).

The purpose of NBS is to identify newborns with conditions that may cause disease, disability or death while the neonate is asymptomatic, and to intervene with treatments that may prevent or lessen the severity of the disease. To fulfill this purpose, NBS is much more than testing and should be understood as a system with the processes of specimen collection, laboratory testing and reporting, follow-up confirmatory testing and clinical care, and long-term

follow-up. The partners in this system include the neonate's parents, NBS specimen submitters (birth hospitals and midwives), public health laboratory professionals, primary care providers and specialists, and government public health agencies.

In general, conditions proposed to be included in NBS are subject to a set of criteria. Those criteria are based on Wilson and Jungner criteria for assessing the validity of a screening program for public health purposes. In the US, a [Recommended Uniform Screening Panel \(RUSP\)](#) has been developed, and there is a comprehensive approach to add new conditions to the RUSP:

1. Nomination Package submission
2. Nomination Package reviewed by [Advisory Committee on Heritable Disorders in Newborns and Children \(ACHDNC\)'s Nomination and Prioritization Workgroup](#)
3. Nominated condition reviewed by external Condition Review Workgroup
4. ACHNC deliberation and vote to recommend or not recommend adding the nominated condition to the RUSP
5. Final decision by Secretary of Health and Human Services

Each state has its independent process of adding new conditions to the state NBS panel.

Storage and Usage of Residual NBS DBS Specimens

Once NBS is complete, state programs retain residual DBS specimens for various lengths of time, from several weeks to over 21 years. The length of residual DBS specimen retention time in each state is posted under "State Profile" on the [APHL NewSTEPS website](#). Each state has its own policies and associated procedures regarding the usage of residual NBS DBS specimens. Parental consent may not be required for use to support essential program functions such as program evaluation, quality assurance, result verification, test refinement and quality improvement initiatives. Proposed research projects will require Institutional Review Board (IRB) evaluation to determine the need for informed consent.

Usage of Residual, De-identified NBS DBS Specimens for Prenatal Opioid Exposure Surveillance Projects

Neonates may present withdrawal symptoms 24-48 hours after birth. Conditions identified through NBS DBS specimens go unrecognized in the absence of laboratory testing. NAS does not appear to be a suitable condition for being added to the newborn screening panel because NAS cannot be diagnosed based on laboratory testing alone. NBS testing results are usually available 5-7 days after birth, which may not be an optimal time frame for identification of NAS cases.

The use of DBS specimens as an appropriate specimen type to identify exposure to other compounds, such as nerve agents, has been evaluated for use in chemical emergency response. Use of DBS specimens can bridge the gap between the laboratory and the field allowing for large scale sample collection with minimal impact on hospital resources while maintaining sensitivity, specificity, traceability, and quality requirements for both clinical and forensic applications. DBS specimens have been used historically throughout the 1980s and 1990s to determine the number of newborns exposed to HIV.

APHL has developed an [educational toolkit for NBS programs](#) to clarify the appropriate storage, destruction and use of residual DBS specimens. *In utero* opioid exposure surveillance is a fundamentally different activity. APHL has engaged the public health laboratory NBS community on this topic in various forums, and members have consistently expressed concerns regarding use of residual, de-identified NBS DBS specimens for NAS surveillance because:

- Effective public messaging and communication regarding proposed prenatal opioid exposure surveillance projects would be challenging.
- It would be difficult to obtain informed consent for residual specimen testing.

- Drug testing may deter pregnant/birthing individual consent for NBS testing.
- Interpretation of analytical results is challenging without access to medical records.
- Distinguishing surveillance and screening from diagnostic testing to inform clinical decision making.

The usage of DBS specimens for purposes outside the RUSP may negatively impact public trust and support for NBS, even if the appropriate approvals have been obtained, and safeguards on privacy and confidentiality are maintained. This could result in neonates not receiving critical, life-saving diagnostic testing.

3. Population-based research studies are recommended to determine the prevalence of *in utero* opioid exposure.

Additional research is needed to understand the frequency, nature and potential health impacts of *in utero* opioids exposure. Included in this work is the need to refine specimen collection and analytical protocols to accurately identify, measure and interpret the meaning of neonatal toxicology results.

While the use of residual DBS specimens collected for NBS programs is not recommended, the viability of a separately collected DBS has promise as a convenient, minimally invasive specimen type for qualitative testing. Understanding the potential for exogenous contamination and how blood film thickness may impact specimen quality and analytical testing are important initial considerations. The Division of Laboratory Science at NCEH is working with partners to validate this approach.

Ease of specimen collection and advances in analytical methodology will be important preliminary studies that are needed prior to conducting research into the prevalence of *in utero* exposure and any associated health impacts.

Stakeholder groups with a breadth of perspectives should continue to convene and identify research priorities. Clearly defined outcome measures related to laboratory data would aid state public health policy makers in assessing the impact of laboratory informed interventions.

There is a noted gap in the understanding of neurodevelopmental outcomes associated with *in utero* opioid exposure. Some studies suggest that neonates with NAS were more likely to experience developmental/speech delays or language impairment in early childhood when compared to neonates without NAS. This is complicated by exposure to other drugs, especially alcohol (which is used by up to 48% of pregnant people with OUD). Poverty, poor diet, lack of prenatal care and environmental exposures are all confounding variables.

While exposed neonates may be at elevated risk of developing NAS, not all who are exposed all exposed exhibits symptoms of NAS. Population-based exposure surveillance data may aid in characterizing estimates of *in utero* opioid exposures and identify individuals for potential health assessment.

Human Subjects Review/Institutional Review Board Considerations

NAS surveillance completed by a state public health agency using guidance outlined in this document will likely be considered public health surveillance or public health investigation and will not require institutional review board approval. All projects should assess this need through the Human Subjects Review their respective process.

Health departments interested in conducting projects using patient identifiers should work collaboratively with partners to determine if IRB review and informed consent from patients is needed before collection or forwarding of specimens. Public health laboratories should refer to their jurisdiction's IRB protocols for more information on conducting research projects using data from human subjects.

Data Integrity and Reporting

NAS program protocols should clearly define the level of detail included in laboratory reports, data summaries and program reports, with whom these data may be shared and how that access will be granted and reviewed. To be useful for public health practice, NAS data sharing should be considered for jurisdictional partners in injury prevention, substance misuse prevention, and pregnant/birthing individual and child health programs.

Data may be shared with interested parties while maintaining data privacy and ensuring compliance with applicable laws and regulations, but this should be carefully considered with statewide stakeholders and documented in official protocols. NAS data may be generally sorted into three categories: aggregate, individual de-identified and individually identifiable, which are discussed below in detail. Identifiable data sets should be available only on a need-to-know basis to prevent inadvertent release of private information, and never to law enforcement. Public health data should be collected to promote and propel public health actions; data reporting and sharing are critical in that process.

Aggregate Data

Aggregate data are combined from several measurements. Groups of observations are replaced with summary statistics based on those observations. Categorically, aggregate data are the most appropriate to share with the public, or with governmental policy organizations, law enforcement or public safety organizations, other similar non-public health entities. While these agencies often handle sensitive information, they are not covered by state or local health statutes or federal regulations such as HIPAA.

Display of aggregate data should consider not only the number of NAS cases but also the underlying population denominator (i.e., the total number of live births, residential population). Aggregate data can point to individually identifiable events when the numerator is small or if the denominator is extremely small (i.e., <50,000 population or <500 live births) as might be the case in rural populations or when considering small age groups or racial/ethnic minorities. Public health department epidemiologists or data governance staff should be consulted to determine the most effective manner of displaying aggregate data.

Special care with data aggregation should be taken when using online or electronic dashboards for data display. If aggregate data can be stratified by multiple demographic and geographic factors, for instance age, sex and county of residence at the same time, then it may be possible to re-identify a NAS patient unintentionally. Checking displays using multiple criteria to ensure that the re-identification of patients is not possible can be accomplished by suppressing counts that are five or below, combining smaller racial or ethnic categories into larger categories, or combining geographies or years. Most public health agencies have established standards for aggregate data displays and should be consulted before publication.

Individual Level De-identified Data

Releasing individual level de-identified data should be considered for public health entities. This could include public health department epidemiologists and tribal and local health departments. This data will likely require a data use agreement depending on jurisdictional authorities or other statutes.

Individual level de-identified data may be of particular use when the public health laboratory does not have adequate resources to meet all public health analytical needs. Additionally, when there is local variation in resources available for public health actions, a custom local analysis may be required.

Research requests for individual level de-identified data should be approached with caution. This should only be pursued in consultation with a human subject review board or IRB and should be accompanied by data-sharing agreements, data storage guidelines and all other relevant documentation.

Individually Identifiable Data

Releasing individually identifiable data should only be considered when other, less identified data will not meet the needs of the agency or project and that agency or group is duly authorized to receive such data. All situations which may meet this threshold cannot be fully outlined here. Public health agencies may consider using individually

identifiable data to match case-based epidemiological reports with previous laboratory evidence of drug exposure, previous births for a single birthing individual, or case follow-up examining short and long-term health impacts. If this approach is taken, note that all relevant human subject protections should be honored. Data sharing agreements and other administrative approvals may need to be obtained before initiating a project of this nature.

Encourage use of electronic case reporting (eCR).

Privacy/Confidentiality Concerns

While public health laboratories have considerable experience in the protection of sensitive medical data and managing surveillance and confidentiality concerns, there are several additional considerations beyond those previously identified in the OBTF Model Biosurveillance Strategy to be addressed if considering surveillance for NAS. NAS surveillance has the potential to stigmatize birthing people and impact birthing individual/neonate bonding through involvement with child protection agencies or facility-based case managers. This involvement may also continue with future births regardless of clinical indicators of potential drug use. In several states this can also include criminal prosecution for a neonate's clinical outcomes. When designing a NAS surveillance program, state health departments should consider collecting the minimum information necessary to accomplish their program's goals. Considerations can be made regarding the utility of personal identifiers, geographic designators, and the utility of pooled or third-party anonymized specimens.

State, local, tribal and territorial health departments assume responsibility for the security of all demographic and laboratory data within their systems. Regular training on privacy and confidentiality coupled with restricted access to paper and electronic files are routine practices in institutions familiar with managing protected health information. Data sharing policies may be developed for sharing aggregate information with external partners, as appropriate. All parties involved in sharing, entering or otherwise using NAS data should establish data usage agreements and ensure that all surveillance program activities are compliant with federal HIPAA law.

When designing a NAS surveillance plan, consider documenting the level of security that exists in the public health laboratory, including administrative security (i.e., staff training, policies and procedures) and technical security (i.e., cybersecurity, restricted access, regular review of access).

When designing an NAS surveillance program, state health departments should consider collecting the minimum information necessary to accomplish their program's goals.

Addressing Potential Sources of Bias

Specimen Selection Considerations

Care must be taken to limit bias, which can compromise the quality of laboratory data for surveillance purposes. The ideal population-based surveillance scenario is specimens collected routinely on all birth parents or neonates according to systematic criteria determined by the jurisdiction in coordination with the clinical sites. This limits the selection bias in specimen collection based on subjective criteria such as clinical suspicion. Non-systematic specimen collection schemes can lead to misrepresentation of opioid exposures among certain racial or ethnic groups based on implicit bias. Minimizing selection bias ensures generalizability of the testing data to the population being surveilled as well as the potential for comparisons across jurisdictions using similar criteria. Beyond specimen collection bias introduced based on the criteria used within a facility, jurisdictions should also consider factors such as the frequency of home births versus hospital-based births as well as overall access to care within their jurisdiction and how that impacts the potential groups of patients who may be tested.

Specimen Testing Protocol Considerations

In addition to bias introduced based on how specimens are collected (outlined above), additional bias can be introduced based on if or how specimens are screened within a facility prior to the specimens or results being provided to the state health department. The ideal surveillance scenario is that specimens are collected in a systematic way and then are screened using a standardized panel of exposure drugs tested with a standardized

panel of targets and cutoffs. Issues around laboratory testing method sensitivity and specificity are detailed elsewhere in this document. With a standardized panel of tests, we are less likely to introduce another form of selection bias that can be introduced based on clinical suspicion, implicit racial bias, or other similar reasons. This is especially compounded if it biases the types of specimens that are sent on to the state health department for laboratory analysis because the state health department may not even be aware of the bias and is therefore unable to attempt to statistically control the bias in their analysis and interpretation.

At a minimum, the data elements at right should be captured for successful implementation of a neonatal biosurveillance program. Standardization of these data points will meet laboratory submission guidelines and simplify data transfer to a centralized data repository or an opioid biosurveillance program. The minimum data required for biosurveillance should be provided by clinical laboratories when submitting specimens to their jurisdictional public health laboratory.

RECOMMENDED DATA ELEMENTS FOR NAS SURVEILLANCE

Minimum Data Elements

- Gender
- Age (hours)
- Submitting facility (provider information)
- Date of specimen collection
- Time of specimen collection (to determine post-delivery interval)
- Specimen type

Desirable Data Elements

- Race
- Ethnicity
- Qualitative Drug test results (from tests in a submitting facility)
- Drug test methods including cutoff, if applicable
- Drug test specimen type
- Clinical presentation
- Prescribed medications
- Birthing individual's prescriptions and/or therapeutics, in-hospital administered medications

UTILITY, APPLICATION AND VALUE OF LABORATORY-INFORMED NAS SURVEILLANCE

When cases are reported and classified in a consistent, timely manner, NAS surveillance provides data that can drive public health action in support of pregnant individuals and their children. Examples of state agency public health actions include illustration of trends over time, quantifying impacts of birthing individual opioid use on neonates in areas where NAS and a pregnant/birthing individual's opioid use is most prevalent, assessing the impacts of public policies implemented in response to the opioid epidemic, and using these data to target delivery of resources and services for NAS-affected neonates and their families. Data may also be shared with community partners and local advocacy groups, informing decisions made by policymakers.

Laboratory evidence of *in utero* opioid exposure is acknowledged as supporting evidence for ascertainment of suspected, probable and confirmed cases as per the [CSTE NAS Standardized Surveillance Case Definition](#). Laboratory data should always be evaluated within the context of epidemiological data and medical records to avoid erroneous conclusions and unintended stigmatization of individuals or populations. Care must be taken when interpreting laboratory results, as detected drugs may be used for appropriate clinical treatment, including MAT for substance use disorder and/or pain management during birth.

Laboratory data, when combined with clinical information collected as part of an NAS surveillance program, strengthens evidence of *in utero* opioid exposure burden within the population. As more state public health agencies collect and analyze this data, OBTF hopes that jurisdictions will critically evaluate the utility, representativeness, and appropriateness of their programs at their inception and over time. These lessons will inform the larger understanding of using these data and inform future directions for surveillance recommendations such.

Careful consideration of potential applications of laboratory data should be determined prior to initiation of any laboratory-based component for NAS surveillance. Potential uses for laboratory data as a supplement to state health agency NAS and opioid surveillance efforts include:

1. Trend analysis of *in utero* opioid exposures which can inform overall opioid surveillance and response efforts. These data may be included in state-wide data visualizations such as maps and dashboards.
2. Risk modeling to predict a range of mild to severe short-term outcomes for exposed neonates at the state-level.
3. Identifying additional at-risk communities within a state for education and outreach.
4. Informing resource allocation such as linkage to care coordinators for exposed neonates, development and distribution of guidance and messaging for families, and provider education courses or materials.
5. Supporting advocacy efforts and resource allocation for MAT and addiction treatment providers, early childhood development support services, and prenatal healthcare services in areas with elevated burden of *in utero* opioid exposure.

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8515 Georgia Avenue, Suite 700
Silver Spring, MD 20910

Phone: 240.485.2745

Fax: 240.485.2700

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