APHL Opioids Biosurveillance Task Force

Model Opioids Biosurveillance Strategy for Public Health Practice

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APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES®

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INTRODUCTION

Over the past ten years, there has been a significant increase in opioid overdose-related deaths driven first by prescription opioids and then, more recently, a sharp rise in deaths from heroin and illicitly manufactured fentanyl and fentanyl analogs. Data from the National Center for Health Statistics (NCHS), US Centers for Disease Control and Prevention (CDC) data brief, Drug Overdose Deaths in the United States, 1999-2018[1] show each of these three waves of the opioid overdose epidemic. Additionally, non-fatal overdoses for all opioids increased significantly from 2016 to 2017. In 2017, the most recent year for which population-level estimates of non-fatal overdoses can be generated, 305,623 overdoses were opioid-involved, a 3.1% increase from 2016.[2] These data provide invaluable information public health professionals need to combat the opioid epidemic effectively in their jurisdictions. The US Department of Health and Human Services (HHS) has identified quality data as fundamental to addressing the opioid epidemic and has incorporated this concept into Strategy Two of its Five-Point Strategy to Combat the Opioid Crisis.[3]

Nationally, public health surveillance for opioid and other drug overdose events is conducted by both the CDC's National Center for Injury Prevention and Control (NCIPC)/Division of Overdose Prevention (DOP) and NCHS. More specifically, data are collected on fatal and non-fatal drug overdoses to track the opioid overdose epidemic from funded state and local public health partners to inform and target evidence-based prevention and response activities to reduce morbidity and mortality.

Data for fatal overdoses are derived from multiple sources including death certificates, medical examiner (ME)/coroner(C) reports, including death scene investigations, and detailed toxicology laboratory results identifying and confirming opioids. CDC collects these data through the State Unintentional Drug Overdose Reporting System (SUDORS) and the National Vital Statistics System. SUDORS is part of a national effort to collect comprehensive data on unintentional and undetermined intent drug overdose deaths in a timelier manner than traditional mortality data sources.

Surveillance of non-fatal opioid overdoses is dependent on data sources such as syndromic surveillance using emergency department (ED) and emergency medical services (EMS) records. Nationally, data about non-fatal overdoses of opioids and other drugs are captured through the Drug Overdose Surveillance and Epidemiology (DOSE) system, which leverages ED data from syndromic surveillance (e.g., CDC's National Syndromic Surveillance Program) and hospital billing data. Unlike fatal overdose surveillance, non-fatal overdose surveillance measures rarely include laboratory confirmation of the implicated substances, as clinical testing is often not required to treat overdoses.

In July 2019, the Council of State and Territorial Epidemiologists (CSTE) approved a standardized case definition for non-fatal opioid overdoses[4] in collaboration with federal, state, and local partners in epidemiology, injury prevention and laboratory science. This action ensures that designations of suspect, probable and confirmed cases will be assigned consistently by state, local and territorial health departments opting to use the case definition for local reporting requirements, resulting in data that is more comparable across jurisdictional lines. Note that the existence of these case definitions does not make either of these conditions nationally notifiable; the decision to report these cases is based on state public health reporting requirements.

Public health agencies require high-quality surveillance data upon which to determine the spatial and temporal extent of non-fatal overdoses and to inform public health interventions and decisions. The increased use of definitive (confirmatory) laboratory data that are sufficiently specific to identify the breadth of natural, synthetic and semi-synthetic opioids implicated in non-fatal overdoses, including the rapidly changing suite of novel fentanyl analogs, can help to achieve this goal. Public health laboratories working in partnership with state and local epidemiologists are uniquely poised to provide this critical missing information.

The APHL Opioids Biosurveillance Task Force (OBTF) Model Opioids Biosurveillance Strategy for Public Health Practice serves as guidance for public health agencies interested in developing and implementing an effective and impactful opi-

1 Ahmad F, Rossen L, Sutton P. Drug Overdose Deaths in the United States, 1999-2018. Provisional Drug Overdose Death Counts. US Centers for Disease Control & Prevention (CDC) National Center for Health Statistics; 2020.

2 Vivolo-Kantor AM. Nonfatal Drug Overdoses Treated in Emergency Departments — United States, 2016–2017. CDC MMWR Morb Mortal Wkly Rep; 2020.

3 Azar AM. Strategy to Combat Opioid Abuse, Misuse, and Overdose. Department of Health and Human Services; 2017.

4 Nonfatal Opioid Overdose Standardized Surveillance Case Definition. Council of State and Territorial Epidemiologists; 2019.

oids biosurveillance program in their jurisdiction. This document will provide the roles of key stakeholders, fundamentals of surveillance program design, legal and policy considerations and information on testing methods. Public health agencies should review this flexible model strategy in conjunction with other state and local laws, regulations and policies to develop plans specific to the needs of their jurisdictions.

THE ROLE OF LABORATORY DATA IN OPIOID RESPONSE EFFORTS

Laboratories from multiple sectors across the United States, such as clinical, public health and forensic science, contribute to our understanding of the opioid epidemic and play a vital role in response efforts. Working with partners in healthcare and public health, laboratories provide data that inform clinical case management and supplement case ascertainment efforts. Additionally, forensic laboratories provide drug product and paraphernalia data to inform surveillance efforts. Laboratory data may provide additional context for risk factors associated with non-fatal opioid overdoses by identifying and/or measuring the concentrations of drugs and their metabolites detected in patient specimens at the time of overdose or hospital presentation.

When analyzed in aggregate, laboratory data provide evidence of the presence of specific drugs in the individuals suspected of experiencing drug overdoses and indicate, on a population basis, which drugs are responsible. Laboratories may also identify new or novel opioid compounds circulating in their jurisdiction. In this way, laboratories play a crucial role in informing treatment decisions, guiding public health surveillance, and ultimately facilitating overdose cluster response efforts.[5]

Hospital, commercial, forensic and public health laboratories offer testing services that, together, support the framework for reliable laboratory evidence that informs opioid response efforts. Laboratories vary in size as well as the complexity of test options. For clinical pathology support, hospital laboratories provide routinely-ordered tests whereas clinical reference laboratories provide expanded options for tests less frequently ordered. For toxicology services, clinical toxicology specialty laboratories and forensic toxicology laboratories provide medical and forensic support, respectively.

Hospital Laboratories Supporting Emergency Departments

Hospital laboratories frequently perform presumptive drug tests (screens) on clinical specimens from patients presenting to the Emergency Department (ED) with symptoms of opioid overdose. Presumptive tests such as immunoassays indicate the possible, but not definitive, presence of drugs or drug metabolites. Immunoassays are sensitive and cost-effective presumptive (screening) tests that are crucial to the management of patient care as the test results can be rapidly available. Although sensitive, these presumptive drug tests are not particularly selective, and some may be designed to detect classes of structurally similar drugs. Immunoassays are typically manufactured as test kits available for purchase from vendors who have received approval after review of test characteristics and approval by the US Food and Drug Administration (FDA). Modifications or additions to the test panels require extensive research and development followed by FDA consent before distribution and use. This regulatory burden assures that the assay meets the manufacturers' claims for sensitivity and specificity, but it does not allow for a nimble response to the evolving list of novel opioid compounds and fentanyl analogs. It should be noted that early in the opioid epidemic, the inability of hospital laboratories to detect fentanyl via immunoassay was hindered by the lack of an FDA-approved fentanyl drug test. The first urine enzyme immunoassay received 510(K) clearance on June 14, 2017.[6]

By design, immunoassays are intended as an initial drug test and require additional definitive (confirmation) laboratory-based drug tests to provide evidence to confirm the presence and identity of specific opioid drugs, drug metabolites, or other drug compounds. Since definitive (confirmatory) drug testing is costly and frequently not available in time for ED-provided patient care, presumptive-positive clinical specimens from non-fatal overdoses are rarely confirmed in-house or forwarded to reference laboratories for additional definitive analysis.

5 Stopping the Opioid Epidemic: Integral Role of Clinical Laboratories. American Association of Clinical Chemistry; 2019.

6 Immunalysis SEFRIA Fentanyl Urine Enzyme Immunoassay, Immunalysis Fentanyl Urine Calibrators Section 510(k) Substantial Equivalence Determination. DJG, DLJ, 21 CFR 862.3650 Jun 14, 2017 p. 13.

Clinical Reference Laboratories

Clinical reference laboratories may have increased capacity to identify opioid and other drug analytes in recent years. In addition to performing presumptive (screening) and definitive (confirmation) drugs of abuse testing, some clinical reference laboratories also have extensive experience performing therapeutic drug monitoring. Definitive (confirmation) methods include chromatography with mass spectrometry (liquid chromatography-mass spectrometry [LC/MS, LC/MS/MS], gas chromatography-mass spectrometry [GC/MS, GC/MS-MS]) and results may be reported as qualitative (identification only) or quantitative (identification and concentration). Providers may order definitive (confirmation) drug testing with or without reflexing upon prior presumptive-positive (screen-positive) drug test results. For both unambiguous identification and quantitation, suitable reference standards must be available.

Definitive (confirmation) methods require suitable reference standards to ensure unambiguous identification and accurate quantitation. Given the extensive method validation requirements for including additional analytes in the test panel, clinical reference laboratories may not include emerging fentanyl analogs or other types of novel psychoactive substances in their test menus.

Clinical Toxicology Specialty Laboratories

Clinical toxicology specialty laboratories provide enhanced mass spectrometry services and other highly specialized testing to analyze therapeutic drugs and drugs of abuse in clinical specimens. These laboratories can identify a wide range of analytes, including synthetic fentanyls and other novel synthetic and semi-synthetic opioids. Depending upon the analyte, quantitative results may be available. These laboratories are often charged with conducting therapeutic drug testing on a variety of clinical matrices (whole blood, plasma or serum) for opioid analytes as well as other drugs such as anticonvulsants, antidepressants, antipsychotics, anxiolytics, immunosuppressants and stimulants. Clinical toxicology laboratories often work closely with providers to use laboratory data to guide therapeutic drug use, palliative care and treatment for overdoses or accidental poisoning. More recently, given the potential for opioids addiction, there is an increased use of clinical toxicology laboratories by pain management clinicians to assure that patients comply with the use of prescribed drugs and abstain from the use of non-prescribed illicit drugs.

Forensic Toxicology Laboratories

Forensic toxicology laboratories focus on the detection and quantitation of drugs in human specimens, particularly associated with death investigations. They typically provide presumptive (screening) and definitive (confirmation) drug testing (whether therapeutic or illicit) that helps medical examiners or coroners investigate the causes of fatal overdoses. These laboratories are generally publicly funded by state, county, tribal or city governments. The capabilities and scope of testing of forensic toxicology laboratories and the use of their results by coroners and medical examiners may vary from jurisdiction to jurisdiction. These laboratories are expected to meet high standards of legal defensibility, as results are critical for medico-legal investigations, including the cause-of-death determinations. Forensic toxicology laboratories and forensic evidence (pills and powders found at the scene of suspected overdose deaths) testing laboratories play a critical role in ascertaining fatal overdose cases. Forensic laboratories play a crucial role in opioids biosurveillance by maintaining close communication with PHLs and informing them of novel opioids identified through testing of seized drugs circulating in their jurisdiction. Forensic toxicology and seized drug testing laboratories may also be referred to as forensic drug chemistry, police or crime laboratories, or by a name unique to their jurisdiction.

Forensic toxicology laboratories can test for a wide variety of compounds. However, they focus on the individual patient or decedent, not biosurveillance for public health practice.

Public Health Laboratories

Public health laboratories (PHLs), working at the state, local and territorial levels, perform testing for public health surveillance, identification of emerging threats, and the detection of infectious and environmental diseases. These laboratories are staffed by highly trained scientists that use sophisticated instrumentation to monitor and detect a wide range of diseases, disorders and chemical agents. In close collaboration with state and local health departments and federal agencies (e.g., CDC, DHS, EPA, FDA, FBI), they form the backbone of several laboratory networks.

Every state, territory and the District of Columbia has a PHL that is responsible for its jurisdiction. Local PHLs, ranging in size from large metropolitan laboratories to smaller county or regional laboratories, may specialize in one area of practice, and may not be termed as 'PHLs,' regardless of their ability to perform complex testing and contribute to public health surveillance. Additionally, PHLs strive to improve their operational and technical capacity by sponsoring specialized training events, providing updates on health threats to their communities, sharing information on best practices, and developing and refining test methods.[7]

PHLs help to inform interventions aimed at addressing the opioid epidemic by testing clinical specimens collected from patients who have suffered a non-fatal overdose. This approach has been termed, "opioids biosurveillance of non-fatal overdoses." Biosurveillance involves the use of definitive test data to confirm and supplement overdose case ascertainment and clinical management efforts in collaboration with epidemiologists, hospitals, and clinicians. PHLs have the potential to inform interventions by linking laboratory results with existing drug use surveys, prescription drug monitoring and hospital discharge data.

Building upon the infrastructure and expertise gained through participation in the Laboratory Response Network for Chemical Threats (LRN-C) and the National Biomonitoring Network, state PHLs have the advanced analytical capability necessary to implement opioids biosurveillance. In addition to specialized instrumentation and training, scientists in PHLs have developed critical relationships with epidemiologists, public health toxicologists, clinicians in acute care settings and medical toxicologists at poison control centers—all of which are necessary for the success of biosurveillance programs.

At this time, many PHLs are using Traceable Opioid Material (TOM) Kits as reference materials for clinical testing of a suite of standard and newly emerging opioid compounds as well as novel fentanyl analogues. TOM Kits are products that provide reference materials for all US laboratories to use for compound identification and confirmation purposes. CDC directed the development of the TOM kits with input from the US Drug Enforcement Agency (DEA) and the National Forensic Laboratory Information System. They are available free of charge to laboratories meeting DEA controlled substance registration requirements. As of April 22, 2020, two TOM Kits are available for use; Fentanyl Analog Screening and Emerging Panel (FAS) and Opioid Certified Reference Material (CRM) kits. Together, these kits enhance laboratory capacity by enabling scientists to identify over 230 opioid compounds and fentanyl analogs.[8]

Recognizing that many overdoses are associated with poly-substance use and the rate of development for novel fentanyl analogs and synthetics is rapid, states are also exploring qualitative, non-targeted drug testing of clinical specimens. This technique requires expensive high-resolution mass spectrometry instruments (such as quadrupole time-of-flight or QTOF), highly skilled analysts and a laboratory data system capable of managing enormous quantities of data. PHLs have begun using this technology with training support from APHL and CDC.

Many PHLs are leveraging funding for biosurveillance activities through the CDC Overdose Data 2 Action (OD2A) cooperative agreement,[9] as well as other federal and state funding streams.

7 About Public Health Laboratories. Association of Public Health Laboratories.

8 Traceable Opioid Material (TOM) Kits to Improve Laboratory Detection of Synthetic Opioids in the US. US Centers for Disease Control and Prevention; 2020.

9 Overdose Data to Action. US Centers for Disease Control and Prevention; 2019.

OVERALL OPIOIDS BIOSURVEILLANCE PROGRAM DESIGN

The prevalence of opioids use and misuse and the consequent incidence of non-fatal and fatal overdoses can differ dramatically between states or even within counties or cities. Moreover, individual public health surveillance systems have evolved in a variety of ways, based on the scope and scale of the problem in the jurisdiction and the resources available. Understanding current systems for opioids biosurveillance in a jurisdiction is essential to ensuring the proposed biosurveillance program will complement existing systems and avoid unnecessary competition for resources and jurisdictional conflicts.

To understand where gaps exist and how to address them, the following components should be explored in an environmental scan of a jurisdiction's resources for opioids surveillance:

- Systems in place for medical examiners' and/or coroners' investigations of fatal overdoses (e.g., overdose fatality reviews)
- Epidemiological infrastructure
- Current reportable condition regulations
- EMS notification of opioid-related overdoses
- Hospital ED-based reporting systems for drug/opioid overdoses
- Law enforcement and forensic toxicology laboratory drug identification reporting
- Community groups and activities such as overdose prevention coalitions, safe injection sites and syringe exchange programs
- Local and national poison center data

These data sources do not typically provide definitive laboratory identification of the substances implicated in non-fatal overdoses. PHLs, with their expanded testing capabilities and integration within the public health system, provide unique opportunities to gather critical information and inform the development of public health policy, intervention and practice.

There are additional factors to consider before developing and implementing a biosurveillance program for non-fatal opioid overdoses. The program design should consider the specific objectives of the program, available technical and financial resources, public health authority, and specific questions to be answered and/or public health interventions to be evaluated. This flexible model strategy provides state, local, tribal and territorial health departments a framework for developing a jurisdiction-specific plan.

Value of Biosurveillance

There is a critical lack of laboratory data that definitively identify the substances that result in overdose and cause individuals to seek life-saving medical treatment, unless the overdose becomes fatal. As the opioid epidemic persists, communities are tasked with developing effective public health surveillance and intervention strategies aimed at curtailing opioid overdoses and other adverse outcomes. Lack of laboratory evidence of opioid exposure and identification of novel fentanyl analogs constitute a significant gap in the surveillance infrastructure at state and local levels. Biosurveillance, the analysis of clinical specimens such as blood and urine, provides important exposure information not available in existing epidemiological, EMS and seized drug data sets.

Objectives of Biosurveillance

The primary objective of non-fatal opioid overdose biosurveillance is to fully utilize the unique aspects of laboratory results to inform overall efforts to reduce opiate overdoses and substance use disorders. These overall objectives include:

- Rapidly identifying the causes of non-fatal opioid overdoses and clusters to implement immediate prevention and control measures and provide treatment referrals to prevent additional overdoses;
- Estimating the magnitude of the problem and tracking longitudinal trends, including changes in the epidemic between and within states;
- Identifying high-risk areas and sub-groups of the population, such as pregnant women, substance-exposed infants and other sub-groups with service needs that differ from the general population;
- Providing context to further evaluate the impact, effectiveness and scale of interventions, including the widespread availability of naloxone, mental health promotion and services, prescription drug monitoring programs (PDMPs), medication-assisted treatment (MAT), linkage to care or treatment, efforts to reduce stigma and improve care-seeking behaviors, and overdose prevention programs such as needle exchange/syringe service programs and safe injection facilities;
- Providing enhanced information to improve the allocation of resources for clinical, prevention or treatment services;
- Investigating novel exposure pathways, previously unknown overdose scenarios and the emergence of novel opioids; and
- Enhancing efforts to prevent opioid overdoses.

Limitations of Biosurveillance

When de-identified specimens are collected as part of a biosurveillance program, the privacy of the patient and confidentiality are more easily maintained. However, knowledge of other drug exposures such as pharmaceuticals used for routine therapeutic and medical purposes is lost. Care should be taken not to assume that all detected drugs and drug metabolites are associated with illicit use or as contributing to the patient's overdose. These interpretive limitations increase as analyte lists expand beyond the panel of opioids and fentanyl analogs suggested for inclusion in biosurveillance.

Legality of Specimen Collection

Separate from emergency investigations, public health agencies have broad powers that enable them to investigate disease, outbreaks and other public health threats, including those that are new or emerging. Some jurisdictions that require reporting of certain health conditions and diseases also mandate reporting of non-fatal overdoses. These provisions may be part of the broader regulations for "reportable diseases" and outbreak investigations, or they may be stand-alone regulations.

Some states have cited their public health investigation authority to require reporting of hospital laboratory drug data and request submission of residual clinical specimens to the PHL for further analysis. The APHL OBTF believes that most opioids biosurveillance projects will be characterized as either public health investigation or surveillance and will fall within the legal authority of the public health department to implement.

Statutory and regulatory authority is highly variable by jurisdiction; public health departments should be familiar with local laws and statutes that may apply to opioids biosurveillance. PHLs should consider consulting a legal or regulatory liaison within their agencies to clarify the legal authority to request laboratory data and/or specimens from hospitals and to obtain assistance with formulating the initial request.

If a state or jurisdiction lacks the statutory or regulatory authority to collect specimens for opioids biosurveillance or if the scope of the project includes a research component, the program will require human subjects review and possibly institutional review board approval before implementation.

There are a number of considerations each jurisdiction should discuss with their legal or regulatory liaisons in regards to data sharing and specimen submission/testing arrangements (**Figure 1**). Jurisdictions are encouraged to develop detailed protocols and tailor them to federal, state, tribal, local or territorial laws. Examples of relevant laws include the

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule,[10] 42 Code of Federal Regulations (CFR) Part 2,[11] Clinical Laboratory Improvement Amendments (CLIA) regulations,[12] and state and local healthcare information privacy and disease reporting laws.

Figure 1. Discussion points with collaborators and legal counsel.

Program Objectives	Biosurveillance	Data Governance
What are the goals/objectives of your biosurveillance program? • Understand the prevalence of opioid misuse and incidence of overdoses in your community/state. • Identify high-risk populations for intervention and treatment. • Assess how well-implemented strategies are working. Thoroughly think through these topics prior to discussions with legal counsel.	Does the health department have the authority to collect and test biological specimens as part of a public health investigation? If yes, • Is this authority applied widely or just to infectious diseases? • Are non-fatal overdoses a reportable condition in your state? • Is Human Subjects Review recommended? Institutional Review Board approval required?	• PHLs receive, generate and manage confidential information and protected health data every day. • PHL staff adhere to strict policies limiting access to and sharing of protected health information. • Consider existing statutes and regulations that govern protected health information, noting that public health investigations are exempt from some HIPAA requirements.

Reaching Target Populations

This guide is focused on non-fatal opioid overdoses, though PHLs may choose to expand their biosurveillance programs beyond these case definitions due to their specific needs. Unique considerations exist for opioid testing and measuring exposures in pregnant women and neonates (e.g., child protective services, child custody, other domestic issues), as well as for certain professions.

Individuals presenting at acute care hospitals who show signs or symptoms compatible with a non-fatal opioid overdose[13] should be eligible for inclusion in the biosurveillance system. Generally, these patients do not receive opiate medications during pre-hospital or hospital treatment. However, when they do, any specimens collected after the application of these medications should not be included in the biosurveillance system.

In ideal circumstances, the state should strive for standardized statewide population representation in its biosurveillance program. This should include representation across geography, level of urbanization, gender, race/ethnicity and age. Additional key areas of representation may exist within a particular state, and these should also be considered where relevant.

Engaging Partners and Stakeholders

Effective biosurveillance programs are partnerships among experts in epidemiology, analytical chemistry, toxicology, informatics and clinical medicine. Each of these partners should have input into the program design and protocol development for the biosurveillance program.

Biosurveillance programs can build upon existing relationships and practices developed through the LRN-C and the National Biomonitoring Network. State PHLs and their public health partners should maximize community input into the program design, seeking counsel from substance abuse prevention programs, medical societies, medical examiners/coroners, epidemiologists, forensic toxicologists, state and local elected officials, and the regional poison control center. These trusted partners can facilitate relationships with emergency department personnel that are key to the success of the program. It is also critical to involve epidemiologists, opioid overdose prevention specialists and communication experts early in program design to clarify expectations and promote a common platform for internal information exchange and public messaging.

10 The Health Insurance Portability and Accountability Act of 1996. Pub. L. 104-191. Stat. 1936. Web. 11 Aug. 2014.

11 Clinical Laboratory Improvement Amendments. Sect. Title 42: The Public Health and Welfare, 42 CFR 493 1988.

12 Confidentiality of Substance Use Disorder Patient Records. Title 42: The Public Health and Welfare. Sect. Chapter 1 Oct 1, 2019.

13 Azar AM. Strategy to Combat Opioid Abuse, Misuse, and Overdose. US Department of Health and Human Services (HHS); 2017.

Obtaining Specimens

Each state laboratory has an LRN-C coordinator who provides outreach to the clinical community regarding signs and symptoms of chemical exposures and guidance on specimen collection, handling, and transport. These coordinators are familiar with local partners and may facilitate introductions crucial to the success of the project as well as advise on the collection and receipt of residual clinical specimens from individuals presenting with a non-fatal opioid overdose. The collection of specimens exclusively for biosurveillance is possible, but may be impractical and is not advised at this time.

Figure 2. Biosurveillance Strategies for Non-fatal Opioid Overdoses

Biosurveillance Strategy	Advantages	Limitations
Statewide Biosurveillance Entire geographic regions	• Identifies large overdose clusters • Elucidates trends in population-level data • Evaluates efficacy of policies and interventions	• Financial and human resource-intensive • Logistically complex • Insensitive to rare and emerging events
Targeted Biosurveillance Population of interest or entire geographic regions	• Targets high-risk or underserved populations • Informs community-level interventions • Evaluates efficacy of policies and interventions	• Inability to capture population-level data • Not generalizable to entire geographic regions
Pilot Biosurveillance Project Population of Interest (e.g., limited geographic region, hospital system)	• Refines protocols • Demonstrates proof of concept • Identifies opportunities for improvement in the overall project design	• Not generalizable to entire geographic regions or specific populations • Small sample size

Required Specimen Data

Each biosurveillance project will develop detailed protocols outlining the nature and specificity of the required data elements. Input from PHLs, epidemiologists and clinical partners will be required to ensure the protection of personal health information and confidentiality, and to meet regulatory requirements for testing and reporting.

At a minimum, the following data points (**Figure 3**) should be captured for successful implementation of an opioid 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 (elements 1-8 in Figure 3) should be provided by clinical laboratories when submitting specimens to their jurisdictional PHL. However, jurisdictions may elect to collect additional data relating to non-fatal opioid overdose (NFOO) specimens if they so choose.

Figure 3. Biosurveillance Specimen Submission Data Elements

Minimum Data Elements	
1	Gender
2	Age group
3	Three-digit zip code (patient's residence)
4	Submitting facility (provider information)
5	Date of specimen collection
6	Time of specimen collection
7	Specimen type
8	Medical record number or other patient identifying information

Desirable Data Elements	
A	Race
B	Ethnicity
C	Drug test results
D	Drug test methods
E	Clinical presentation
F	Pregnancy status

Privacy and Confidentiality Considerations

Public health laboratories are accustomed to handling sensitive data and managing surveillance and confidentiality concerns. However, opioids biosurveillance introduces unique considerations such as prosecution for drug use or possession. 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 opioids biosurveillance data should establish data usage agreements and ensure that all surveillance program activities are compliant with federal HIPAA law. Medical record numbers (MRNs) or other unique identifiers should be used in place of identifiable data because access to hospital data by the health department may put the patient in danger. Forensic toxicology laboratories may share information with public safety officials.

A biosurveillance plan should include a description of the level of security that exists in the PHL, including administrative security (staff training, policies and procedures) and technical security (cyber security, restricted access, regular review of access). Ideally, biosurveillance data from various jurisdictions would be combined in a secure, restricted-access national repository.

Human Subjects Review/Institutional Review Board Considerations

Opioids biosurveillance as defined in this model strategy will likely be considered to be public health surveillance or a public health investigation and thus will not require institutional review board approval. Health departments interested in conducting projects using patient identifiers should work collaboratively with partners to determine if review and informed consent from patients is needed before collection of specimens. PHLs should refer to their jurisdiction's Institutional Review Board (IRB) protocols for more information on conducting research projects using data from human subjects.

Specimen Testing Strategies

Each PHL will determine the appropriate testing algorithm for its respective biosurveillance program in collaboration with public health partners based on the specific program objectives, available analytical instrumentation and analyst skill level. The testing scheme will be detailed in the program protocols. Analytical methods of varying selectivity and specificity are available in the peer-reviewed literature and from partner organizations. Application notes from instrument manufacturers and from partner laboratories participating in the APHL Opioid Community of Practice may also be useful although they are not comprehensive sources. Individuals interested in joining the APHL Opioid Community of Practice should send contact the APHL Environmental Health program at eh@aphl.org.

Opioids biosurveillance must provide definitive laboratory information to aid in the early identification of emerging threats and novel substances. Testing may involve one or more of the following technologies: presumptive or definitive drug testing, targeted or non-targeted analysis.

Presumptive (Screening) Drug Testing

Presumptive (screen) tests are used to identify possible use or non-use of a drug or classes of drugs. Presumptive tests are commonly followed by definitive (confirmation) tests to specifically identify drugs and drug metabolites. Presumptive methods include, but are not limited to, immunoassays (CEDIA, EIA, ELISA, EMIT, FPIA). Presumptive (screening) immunoassays provide quick turnaround time and relatively low-cost methods. They are used routinely in hospital laboratories with individuals suspected of overdose. Results from these assays are always presumptive, but helpful in quickly guiding clinical decisions. Immunoassays depend upon cross-reactivity of the drug with the assay antibody. Limitations of immunoassays include lack of sensitivity (inadequate or no cross-reactivity) and false-positivity (lack of specificity).
Non-immunoassay presumptive (screen) methods include chromatography without mass spectrometry, chromatography without adequate mass spectrometry, and mass spectrometry without adequate chromatography resolution.

Presumptive (screen) testing has less utility in opioids biosurveillance due to:

1. Assay limitations, as opiates are generally tested as a drug class rather than as individual drugs,
2. Lack of cross-reactivity of the assays with novel fentanyl analogs and emerging substances of abuse, and
3. Lack of FDA-approved assays.

Where presumptive (screen) methods are not available or insensitive to the drug testing menu, mass spectrometry methods are the only alternative.

Definitive (Confirmatory) Drug Testing

Laboratories use either liquid or gas chromatography coupled with mass spectrometry to definitively identify drugs and/or their metabolites in clinical specimens. The specific instrument configuration depends on several factors, including the compounds of interest, the available clinical specimens, and the level of sensitivity and specificity required. While several chromatographies and mass spectrometry definitive (confirmation) methods (such as LC/MS or GC/MS) can be used for opioids testing, tandem mass spectrometry with chromatography has been widely adopted and is preferred due to the combination of high specificity and low detection limits.

Targeted Analysis: Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS)

LC/MS/MS is a technique commonly used in PHLs and advanced toxicology laboratories to identify and measure analytes of interest, including drugs and their metabolites. There are many advantages to this technique, as it is used to target specific analytes of interest with great sensitivity. Optimized chromatographic separation is followed by tandem mass spectrometry identification. Results may be reported as qualitative or quantitative. 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"). Given the proficiency of LRN-C and state biomonitoring laboratories in the use of these instruments and the availability of reference standards for novel fentanyl analogs provided by the CDC Division of Laboratory Sciences, National Center for Environmental Health, this type of targeted testing is an integral component of biosurveillance testing.

The selectivity and sensitivity of these assays which are essential for quantitative and targeted qualitative analysis, also limit their utility in identifying unknown compounds. By design these methods look for specified analytes at very low levels.

Non-Targeted Analysis: High-Resolution Mass Spectrometry

Several PHLs have recently added high-resolution mass spectrometry (HRMS) to their analytical laboratories and are exploring how to utilize the power of this technology to screen clinical specimens and identify unknown drugs associated with intoxications. HRMS is a powerful analytical screening tool, as it can provide very precise identification of unknown compounds when operated in full scan mode. When identifications are verified with analytical standards, PHLs can provide partners with identifications of emerging analytes of concern such as synthetic fentanyls and other novel synthetic and semi-synthetic opioids. This information may be used to identify novel drugs or psychoactive substances, develop a baseline for emerging trends and prioritize these analyte targets during the analysis of future clinical specimens.[14]

Before implementation of HRMS methods for biosurveillance, analytical chemists must receive advanced theoretical and operational training for their specific instruments as well as, method validation and data analysis. HRMS methods generate large quantities of data requiring standard procedures for review and storage of data files and robust informatics infrastructure. It is advisable that all biosurveillance programs pilot test all phases of their project to identify opportunities to refine the pre-analytical, analytical and post-analytical phases of their projects.

HRMS complements targeted mass spectrometry methods and may be used to inform individual sample flow and prioritize future laboratory methods.

14 Metushi I. Performing drug screening through high resolution mass spectrometry in the clinical laboratory: to implement or not? American Association for Clinical Chemistry; 2017.

Data Reporting

Program protocols will 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, biosurveillance data will be shared with jurisdictional partners in injury prevention and substance misuse prevention. Ideally, jurisdictional biosurveillance data will be residing in the APHL Data Lake for approved use by federal public health partners and others with authorized access and a demonstrated business need.

Data may be shared with interested parties while maintaining data privacy and ensuring compliance with applicable laws and regulations. Biosurveillance data may be sorted into three categories: aggregate, individual de-identified and individually identifiable (**Figure 4**), which are discussed below in detail. Identifiable data sets should be available 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.

Figure 4. Categories of biosurveillance data

Description	Security	Audience/Utility	Data Sharing Considerations
Aggregate Data			
Groups of observations replaced with summary statistics based on those observations. Includes overdose cases (numerator) per a relevant population denominator (e.g., Total number of emergency room visits, population size, etc.)	Most secure way to share health-related data as there are no identifiable markers.	Most appropriate to share with the public, governmental policy organizations, law enforcement or public safety organizations, and other similar non-public health entities.	Consult public health department epidemiologists and data governance staff to discuss appropriate ways of displaying aggregate data.
Individual Level De-Identified Data			
Datasets grouped by patient using a unique identifier to distinguish patients from one another. Personally identifiable information (name, DOB, address, etc.) is stripped or otherwise removed.	Somewhat secure. May require data use agreements and data storage guidelines prior to sharing.	Approach requests for individual-level de-identified data with caution. Can be considered for public health entities, such as public health department epidemiologists, or tribal and local health departments.	Consult a Human Subjects or Institutional Review Board before fulfilling research-driven data requests.
Individually Identifiable Data			
Datasets grouped by patient using unique identifiers to distinguish patients from one another. Varying levels of Personally Identifiable Information (PII) are included in the dataset.	Not secure. Release of this data should only be considered when other, less identified data will not meet the needs of the agency or project.	Consider using individually identifiable data to match case-based epidemiological reports with laboratory evidence of drug exposure.	Data sharing agreements and other administrative approvals may need to be obtained before initiating a project of this nature.

Aggregate Data

Aggregate data are data combined from several measurements. When data is aggregated, groups of observations are replaced with summary statistics based on those observations. Categorically, aggregate data is the most appropriate to share with the public, governmental policy organizations, law enforcement or public safety organizations, and other similar non-public health entities. While these agencies often handle sensitive information in their own right, they are not covered in state or local health statutes or federal regulations such as HIPAA.[15]

15 Overdose Data to Action. CDC; 2019.

Display of aggregate data should take into account not only the number of overdoses but also the underlying population denominator, for example, the total number of emergency department visits, live births or residential population. Aggregate data can point to individually identifiable events when the numerator is small or if the denominator is extremely small (e.g., <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.

Figure 5. Minimum Data Elements to Include in the Laboratory Report

Specimen Collection Data	Specimen Analysis Data
• Laboratory name • Laboratory address • Specimen ID number • Specimen type • Collection date • Collection time	• Analyte • Analytical method • Result • Result units • Reporting limit units • Date of analysis • Time of analysis

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 an overdose patient unintentionally. It is worthwhile to check displays using multiple criteria to ensure that the re-identification of patients is not possible. This 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 type of data may 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 subjects review board or Institutional Review Board 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 laboratory evidence of drug exposure. If this approach is taken, note that all relevant human subjects' protections should be honored. Data sharing agreements and other administrative approvals will need to be obtained before initiating a project of this nature.

Evaluating Opioids Biosurveillance Programs

Health departments should consider short, medium, and long-term evaluation metrics as core components for assessing the success of their opioids biosurveillance program. Those currently developing the capability and capacity to identify natural, semi-synthetic and synthetic opioids in clinical specimens from individuals experiencing non-fatal overdoses can demonstrate success through the tracking of a number of input, activity, output and outcome metrics (**Figure 6**).

Note that evaluation metrics and time frames are highly dependent upon the needs and capacity of individual jurisdictions, however, these should be discussed early in the program development process, including input from all key stakeholders.

Figure 6. Logic model of anticipated outcomes of a successful opioids biosurveillance program.

Inputs	Activities	Outputs	Short-term Outcomes	Intermediate-term Outcomes	Long-term Outcomes
☐ **Laboratory & Surveillance Data** • Test results (PHLs, forensic toxicology) • Surveillance Sources (ED, EMS, National Syndromic Surveillance Program, hospital billing data, CDC Drug Overdose Surveillance and Epidemiology (DOSE) System) ☐ **Guidance & Regulations** • CSTE Nonfatal Opioid Overdose Standardized Surveillance Case Definition, July 2019 • Reportable condition requirements ☐ **Laboratory Capacity** • Adequate funding • Skilled workforce • Analytical instruments and supplies • Informatics capability ☐ **Partnerships** • Public health partners • State health officials • Public health, forensic, hospital and clinical laboratories • Public health departments • Public safety and elected officials	☐ **Determine Need** Conduct a needs assessment within the jurisdiction ☐ **Define the Program's Scope** Identify objectives and target populations ☐ **Implement the Program** ☐ **Collect Clinical Specimens** ☐ **Perform Laboratory Testing**	☐ **Established Program Objectives** ☐ **Identified Target Populations** • Geographic reach of biosurveillance project (e.g. town, city, state) • Identification of areas and subgroups of interest (e.g. those with Opioid Use Disorder (OUD) ☐ **Laboratory Testing** • Validated method • Demonstration of proficiency for target analytes • Quality management system • Report laboratory results (Individual and/or aggregate data) as appropriate	☐ **System and Partners** Expansion of coordinated efforts in key partners and stakeholders within the jurisdiction ☐ **Laboratory Capacity** Completed assessment of laboratory capability and capacity	☐ **Laboratory Capacity** • Consistent adherence to quality assurance/quality control processes • Development and validation of toxicological tests used to detect and characterize emerging drug threats • Workforce with technical expertise in confirmatory technology • Streamlined laboratory workflows for specimen receipt and processing ☐ **Identify Data-driven Interventions** Qualitative or quantitative data used to inform practice, decision-making or policy ☐ **Partnerships** • Development of new or reinvigoration of existing partnerships • Dissemination and promotion of success stories	☐ **Surveillance Capacity** • Consistent identification and characterization of opioid compounds and fentanyl analogs in non-fatal overdose patients • Reduced incidence of non-fatal opioid overdoses in target population(s) ☐ **Data-Driven Interventions** Refinement and evaluation of public health interventions and services in collaboration with partners

THE ROLE OF OPIOIDS BIOSURVEILLANCE IN NEONATAL ABSTINENCE SYNDROME: FUTURE CONSIDERATIONS

In 2016, the incidence of domestic Neonatal Abstinence Syndrome (NAS) cases was 6.7 per 1,000 in-hospital births. Rates were highest amongst American Indian/Alaska Native individuals (15.9 per 1,000) and non-Hispanic white individuals (10.5 per 1,000).[16] The APHL OBTF acknowledges the scope and magnitude of this syndrome, as well as the impact that opioids biosurveillance programs can have on NAS activities at the state and local level. A separate initiative will be launched in 2020-2021 in collaboration with a wide network of stakeholders to address this issue in more detail at that time. Further work will address the fundamentals of neonatal specimen collection, testing, results interpretation and implications of results to inform NAS surveillance activities.

16 Strahan AE, Guy GP, Bohm M, Frey M, Ko JY. Neonatal Abstinence Syndrome Incidence and Health Care Costs in the United States, 2016. JAMA Pediatr. 2020;174(2):200–2.

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