

Neonatal Abstinence Syndrome in Kentucky

Annual Report on 2017 Public Health Neonatal Abstinence Syndrome (NAS) Reporting Registry



Kentucky Department for Public Health

Division of Maternal and Child Health

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Neonatal Abstinence Syndrome in Kentucky— Annual Report on 2017 Public Health Neonatal Abstinence Syndrome (NAS) Reporting Registry

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Executive Summary

According to the Public Health Neonatal Abstinence Syndrome (NAS) Reporting Registry, in 2017, there were 1,114 unduplicated cases with signs and symptoms of NAS among Kentucky residents; this accounts for 22.35 of every 1,000 live births. The rate has declined very slightly every year since 2015, although that may be due to underreporting, and is still much higher in Kentucky than most of the nation. Rates are highest in Appalachian areas of the state, in some areas reaching nearly 65 cases per 1,000 live births. Mothers of infants with NAS tend to have less education, be unmarried, and have more children, which may suggest lower socioeconomic status, a lack of social support, or reduced access to services.

The most frequent substances reported were buprenorphine (60%), heroin (17%), methadone (13%), all other opioids (40%), cannabinoids (25%), amphetamines including methamphetamine (23%), and benzodiazepines (15%). All other substances were used by less than 10% of women in the registry. Reported heroin use declined from 2016 to 2017, and fentanyl was added to the registry in 2017. Approximately 63% of cases in the registry used more than one type of substance during pregnancy. Among women with polysubstance use, the average number of substances used was 2.8.

Prenatal care is critical for these women to address substance abuse and other co-occurring problems, such as hepatitis C, which was reported in about 35% of this population. Compared to women whose infants do not have NAS, women in this population are more likely to utilize prenatal Women, Infants, and Children (WIC) services, but much less likely to obtain adequate prenatal care. Lower rates of health insurance coverage may explain part of this disparity, although nearly 85% of mothers whose infants have NAS have Medicaid at the time of delivery. Enrollment in and compliance with medication-assisted treatment (MAT) is one factor associated with more prenatal care. Using a proxy measure, nearly 50% of the women in the registry were estimated to be enrolled in MAT, with about 40% compliance.

Infants with NAS are twice as likely to have a low birth weight and three times as likely to be admitted to a neonatal intensive care unit. Tobacco and alcohol use co-occur with substance use at higher rates compared with the rest of the population, which could further affect the health and development of these infants. Infants with NAS had a longer delivery hospitalization: 12.5 days as compared to 3.8 days for infants without NAS. The recommended length of stay for infants at risk of NAS is four to seven days for assessment and clinical monitoring; about 75% of cases in the registry met that benchmark. Longer hospitalizations were even more common in the 53% of infants with NAS who required pharmacological treatment. Among this group, the most common treatment was morphine (79%), followed by clonidine (36%), buprenorphine (11%), and phenobarbital (9.2%); about 37% received multiple medications.

More than 80% of infants with NAS were referred to the Department for Community Based Services, and more than 75% of those cases were accepted. Data from other Kentucky programs indicates that NAS is a risk factor for abusive head trauma and unsafe sleep. Further studies are needed on maltreatment and mortality among NAS cases.

To prevent NAS, the Kentucky Department for Public Health recommends: encouraging MAT programs, implementing a Plan of Safe Care, encouraging education on abusive head trauma and safe sleep for parents, implementing safe sleep modeling by healthcare and childcare providers, increasing enrollment in services such as WIC and home visiting program, and improving access to long-acting reversible contraception.

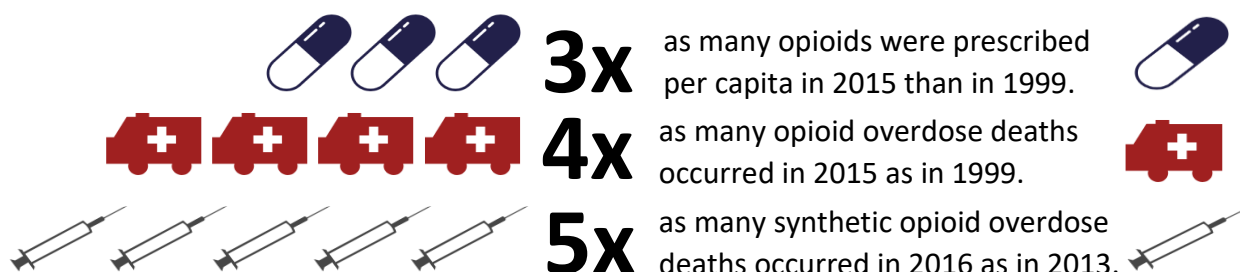
Background

The Opioid Epidemic

Across the United States (U.S.), there is growing concern about addiction and substance abuse, particularly focusing on the increased use of opioids in epidemic proportion. The problem is widespread and so severe that efforts are being directed to its control and prevention. This class of drugs is composed of narcotic substances that bind to receptors in the brain to produce pain relief, anesthesia, or euphoria (Hughes et al., 2016). Prolonged use of opioids, whether licit or illicit, can result in a need for increasing doses of medication to result in the desired effect (tolerance), contributing to fatal or non-fatal drug overdoses (ACOG, "Opioid," 2017).

Originally, opioids were derived from the opium poppy (opium and morphine). Later, semi-synthetic opioids (heroin, oxycodone, hydromorphone, hydrocodone, and buprenorphine) and synthetic opioids (methadone, fentanyl, tramadol, pethidine) were synthesized from the naturally occurring morphine, codeine, and thebaine, and were developed with the intent of increasing potency or decreasing potential for abuse, although no abuse-proof opioids have been developed (Hudak & Tan, 2012). For that reason, opioids are classified as controlled substances in the U.S. (Hughes et al., 2016).

In the U.S. between 1999 and 2015, the number of opioid overdose deaths increased from 8,050 to 33,091 (O'Donnell, Gladden, & Seth, 2017). Until about 2010, this increase was due to prescription opioid abuse. The amount of opioids prescribed (in morphine milligram equivalents per capita) increased from 180 in 1999 to 782 in 2010 (Guy et al., 2017). Since 2010, opioid prescriptions have declined slightly, and synthetic opioids, such as heroin and fentanyl, have been the driving forces behind overdose mortality (O'Donnell, Gladden, & Seth, 2017). Overdose deaths caused by synthetic opioids increased more than fivefold from 2013 to 2016 (O'Donnell, Halpin, Mattson, Goldberger, & Gladden, 2017). The rate of opioid overdose deaths grew more than 20% from 2015 to 2016, and at that time, about two-thirds of drug overdose deaths in the U.S. were due to opioids (Vivolo-Kantor et al., 2017).



Overdose fatalities only capture a small fraction of the problem caused by opioid abuse. Non-fatal opioid overdoses are also increasing rapidly, and can have consequences such as kidney failure, heart problems, nerve damage, and anoxic brain injuries (Clark, 2014). From 2012-2016, the rate of administration of naloxone (an overdose reversal medication) by emergency medical services providers increased by 75% (Cash et al., 2018). However, naloxone does not prevent these secondary consequences but is a lifesaving measure of last resort (Clark, 2014).

The 2018 Life in Rural America survey found that 25% of rural Americans believe that drug addiction and abuse is the biggest problem facing their local community. In rural Appalachia, that figure rises to 41%. When asked about the magnitude of the opioid epidemic in their community, 88% reported that it has remained about the same or gotten worse during the past five years (NPR, RWJF, Harvard, 2018). Among respondents 18-49 years old, 59% say they know someone who has struggled with opioid addiction.

2 out of 5

rural Appalachians believe that drug addiction and abuse is the biggest problem facing their community.



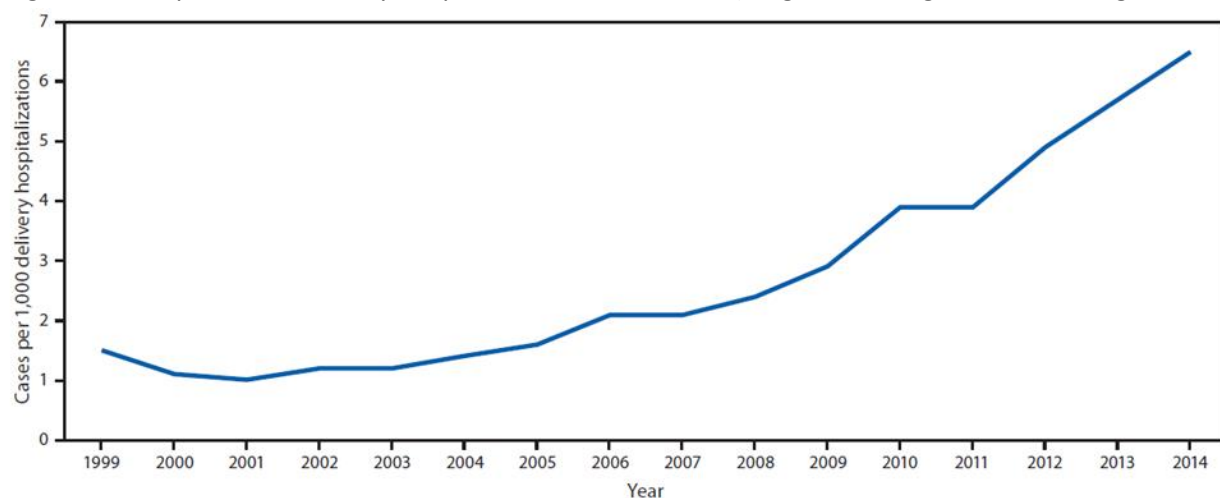
In a 2017 survey conducted by Foundation for a Healthy Kentucky, 16% of adults know someone who has experienced problems as a result of using heroin, up from 9% in 2013 (“Heroin,” 2018). In contrast, only 34% of Kentucky adults reported being prescribed prescription painkillers in 2017, as compared to 55% in 2011 (“Use and Misuse,” 2018). Furthermore, the percent of respondents who reported being prescribed more pills than they needed to control pain dropped from 10% to 6% during that same time period, mirroring the shift from prescription drug abuse to abuse of synthetic opioids.

Impact on Maternal and Child Health



The increase in opioid use is seen across many demographic groups, including women of childbearing age. The graph below shows the prevalence of opioid use disorder (OUD) per 1,000 deliveries across 28 states, including Kentucky (Haight, Ko, Tong, Bohm, & Callaghan, 2018). The rate in these states quadrupled between 1999 and 2014; in Kentucky, the change is even more dramatic: a 48-fold increase to 19 cases per every 1,000 deliveries (Haight, Ko, Tong, Bohm, & Callaghan, 2018).

Figure 1. OUD per 1,000 Delivery Hospitalizations, 1999-2014 (Haight, Ko, Tong, Bohm, & Callaghan, 2018)



* Prevalence numerator consisted of cases of opioid type dependence and nondependent opioid abuse based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes (304.00–304.03, 304.70–304.73, 305.50–305.53), and denominator consisted of delivery hospitalization discharges.

† Includes data from all states participating in HCUP each year (<https://www.hcup-us.ahrq.gov/partners.jsp?NIS>), weighted to produce national estimates. Rates before 2012 are weighted with trend weights, and rates after 2012 are weighted using original NIS discharge weights to account for the change in NIS design in 2012.

Higher rates of OUD translate into higher rates of maternal overdose. Although research in this area is limited, a large study from Massachusetts suggests that women with OUD have an elevated risk of overdose in the period from 7-12 months postpartum (Schiff et al., 2018). Of the women in the study who had overdosed, 25% had multiple overdoses during the year before and year after delivery. The availability of potent synthetic opioids (such as fentanyl) increases the risk of overdose, with potentially fatal consequences, after just one relapse into substance use (Schiff et al., 2018).

Neonatal Abstinence Syndrome

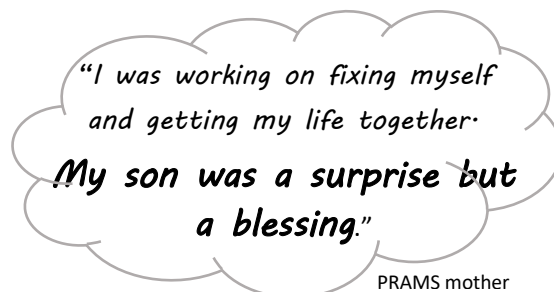
The effects of the opioid epidemic extend far beyond individuals with OUD, especially when women use substances during pregnancy. Neonatal abstinence syndrome (NAS) refers to a constellation of signs and symptoms at birth, due to the sudden discontinuation of substance exposure (Kocherlakota, 2014). Opioids, alcohol, barbiturates, benzodiazepines, caffeine, and selective serotonin reuptake inhibitors (SSRIs) are examples of substances that can cause NAS (Hudak & Tan, 2012). Many substances may be used legally and safely, and a diagnosis of NAS is not inherently indicative of illegal activity by the mother.

Although NAS is rarely fatal, it does cause irritability and discomfort in the infant. Signs and symptoms of NAS are similar to those of withdrawal in adults and include: restlessness, tremors, seizure, vomiting, fever, sweating, and slow apnea; these symptoms are often accompanied by a distinctive high-pitched cry (Hudak & Tan, 2012). Not all babies who are prenatally exposed to substances will experience withdrawal. Specific symptoms, as well as their severity and time of onset, vary based on the substance used. Use of multiple substances (polysubstance use) may also affect the severity of symptoms and treatment of NAS. Because symptoms are non-specific, maternal substance use history and toxicology screenings for both mother and infant are important in establishing in utero exposure.

The first line of treatment for NAS is non-pharmacological and includes comfort measures such as swaddling, rocking, and reducing environmental stimuli (Kocherlakota, 2014). More severe symptoms, as determined by the Finnegan Neonatal Abstinence Scoring Method, may indicate a need for pharmacological intervention. Treatment, whether pharmacological or non-pharmacological, may take place in a Neonatal Intensive Care Unit (NICU) but does not necessarily have to occur there.

Mirroring the patterns of OUD among women of childbearing age is the increasing rate of NAS. From 1999 to 2013, in a pooled sample of 28 states, the overall NAS incidence quadrupled from 1.5 cases per 1,000 births in 1999 to 6.0 per 1,000 births in 2013 (Ko et al., 2016). Kentucky had one of the highest rates, estimated at 15.0 cases per 1,000 live births in 2013 (Ko et al., 2016), and West Virginia, the only neighboring state included in the sample, had the highest rate of NAS at 33.4 cases per 1,000 live births (Ko et al., 2016). Due to families moving or seeking medical care across state borders, that elevated rate could have implications within Kentucky.

Data from the 2018 Kentucky Pregnancy Risk Assessment Surveillance (PRAMS) survey provides further insight into attitudes toward substance use during pregnancy, as women describe their struggles with addiction and their desire to do what was best for their baby. One mother said “need outweighed risk” in her decision to continue taking a specific



medication. Several mothers describe entering treatment programs when they found out they were pregnant. Pregnancy is a catalyst for changing health behaviors, when the desire to change meets the availability of services (Schiff et al., 2018).



Several mothers also described their frustrations: providers who did not understand or address their concerns, changes in pharmacological treatment for themselves or their children, the fear and uncertainties of pregnancy, difficulty breastfeeding, and separation during prolonged NICU stays. For the most part, however, women were grateful for what they see as a new, healthy beginning for their family.

Methodology

In 2013, the Kentucky General Assembly enacted Kentucky Revised Statute (KRS) 211.676, establishing NAS as a reportable disease. Mandatory statewide reporting to the Public Health NAS Reporting Registry (from here on, "the NAS Registry") began on July 15, 2014. The NAS Registry collects information from Kentucky hospitals on Kentucky resident children who experience signs and symptoms consistent with NAS, and who have a confirmed or suspected history of prenatal substance exposure. Case reporting is not tied to any specific International Classification of Disease (ICD-9 or ICD-10) code.

KRS 211.678 outlines the confidentiality requirements of the registry. To prevent the unauthorized release of protected health information (PHI), Kentucky Department for Public Health (KDPH) staff follow all state and federal laws, such as Kentucky's Personal Information Security and Breach Investigation Procedures and Practices Act (KRS 61.931-.934) and the Health Insurance Portability and Accountability Act (HIPAA). To this end, 1) reporting occurs through a secure fax line, 2) the online database is housed on secure servers, 3) hard copy reports are locked in a filing cabinet, and 4) data are suppressed for small numbers.

KRS 211.678 also calls for an annual report including aggregated statistical data analyses. This report includes Calendar Year 2017 births. Cases were linked to the Certificate of Live Birth to obtain prenatal and perinatal information. Cases were excluded if they were not Kentucky residents, were not born in 2017, or were reported as not having signs and symptoms consistent with NAS. Duplicate cases were also removed from the dataset. These duplicates occur when multiple hospitals report the same case (for example, if the infant was transferred to another facility for higher level care).

Results are expressed as number of cases or rates of the estimated prevalence of NAS per 1,000 live births. Prevalence is calculated as follows:

$$\frac{\text{Number of cases} \times 1,000}{\text{Total number of live births}}$$

Analyses with less than five (<5) cases in any category are suppressed. Categories with 5-19 cases may not be suppressed, but should be interpreted with caution; rare outcomes may lead to unstable estimates.

Unless otherwise stated, all figures and tables show unduplicated case counts of Kentucky residents for birth year 2017. Data are from the NAS Registry and the Office of Vital Statistics and numbers are preliminary.

Limitations

The NAS Registry is a passive surveillance system, which has several inherent limitations. Reporting practices between hospitals or individual hospital employees may not be consistent. Reporting based on symptoms instead of diagnosis codes has helped reduce this problem, although differences still exist. Education and technical assistance also help to minimize variation.

Cases that are reported too soon could be missing information about test results and Department for Community Based Services (DCBS) determinations. Only about 1% of cases were submitted on the first day of life, so it is a rare occurrence. Delayed reporting could also negatively affect data quality. For 2017 cases, 43% were reported more than 30 days after birth. The average time to submission was 67 days.

When reporting cases, hospitals often include any maternal history or positive toxicology screen during pregnancy. There is no mechanism to differentiate the details of timing and intent of substance use, which primarily affects data on polysubstance use and Medication-Assisted Treatment (MAT).

Finally, Kentucky resident births that occur at facilities outside of Kentucky and are not transferred to a Kentucky hospital are not reported to the NAS Registry. This issue could be pronounced near state borders, in areas that are served by Cincinnati Children's Hospital Medical Center, Monroe Carell Jr. Children's Hospital at Vanderbilt, and Cabell Huntington Hospital.

Data and Results

Kentucky Incidence Over Time

Table 1 shows the increase in NAS cases from 2000 to 2017. The numbers shown were derived from the Kentucky Injury Prevention Research Center (KIPRC) based on hospital claims discharge codes as well as from the NAS Registry. The trend of NAS in Kentucky is as or more pronounced than in much of the U.S., as the number of cases of NAS increased nearly 20-fold in the decade between 2000 and 2010. In the following four years, the number of cases nearly tripled. Overall in the 14-year time period of KIPRC data shown below, the number of NAS cases annually increased more than 55-fold. Due to differences in methodology, KIPRC data cannot be directly compared to the NAS Registry data, but for years when data are available from both sources, the case counts are within a reasonable margin of error.

In 2017, there were 1,114 unduplicated cases reported to the NAS Registry. This indicates a slight decrease from previous years (1,354 cases in 2015 and 1,257 cases in 2016). Even when adjusted for population, a slight trend remains (24.3, 23.0, and 22.4 cases per 1,000 live births in 2015-2017, respectively). Further study will be needed to determine if the decrease is attributable to underreporting by hospitals or if there is actually a significant downward trend in the occurrence of NAS. Although that possibility is encouraging, Kentucky rates still remain elevated far above the nation.

Table 1. Kentucky Resident Cases of NAS, 2000-2017

Kentucky Resident Cases of NAS, 2000-2017		
Source	Year	Cases
Hospital Discharge Data (KIPRC)	2000	19
	2010	379
	2014	1,060
Public Health NAS Reporting Registry	2015	1,354
	2016	1,257
	2017	1,114

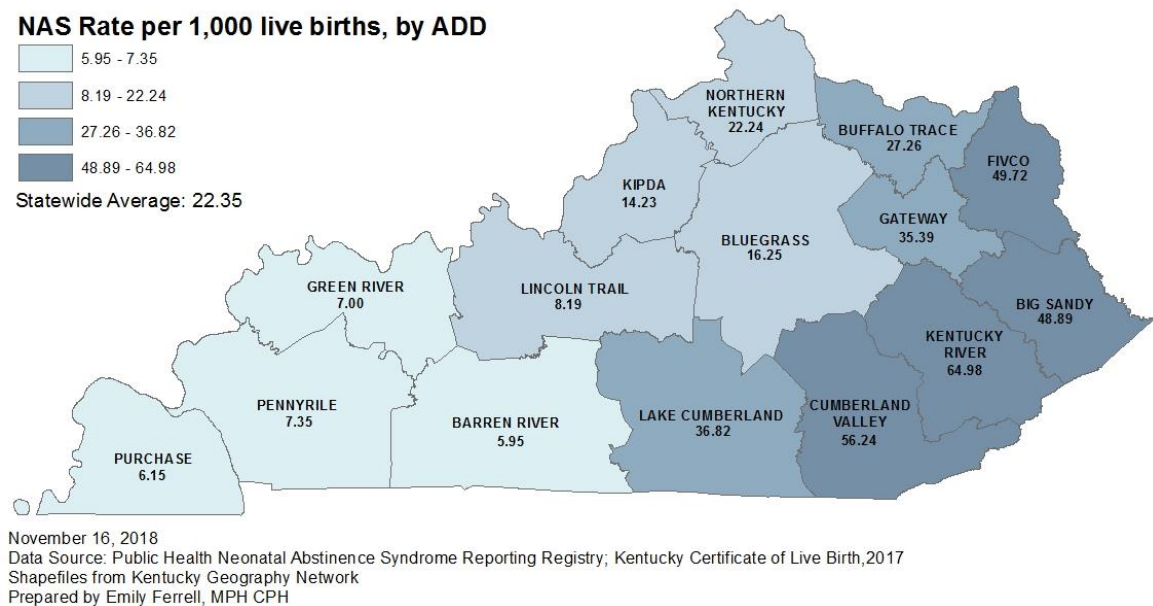
Table notes for historical data (2000, 2010, 2014): Data from Slavova, 2015; KIPRC, 2018. NAS is defined by KIPRC as ICD-9-CM codes 779.5 and V3x, or ICD-10-CM codes P96.1 and Z38. The U.S. transition to ICD-10-CM occurred on October 1, 2015. Years represent date of admission, not discharge.

Table notes for registry data (2015, 2016, 2017): Public Health Neonatal Abstinence Syndrome Reporting Registry. Numbers are preliminary and may change based on reporting practices of individual hospitals.

Kentucky Incidence by Geography and Demography

Compared to the rest of the nation, nearly all areas of Kentucky have elevated rates of NAS. However, there are also large discrepancies within Area Development Districts (ADDs) across Kentucky, with rates ranging from 6.0 to 65.0 cases per 1,000 live births. NAS disproportionately affects rural areas, and in Kentucky, the rate of NAS in rural counties is more than twice as high as the rate in semi-rural or urban counties. Although there are rural areas throughout the state, the Appalachian region in particular has high NAS rates, as shown in Figure 2. This pattern echoes the concerns expressed in the 2018 Life in Rural America survey. When comparing this map to geographic patterns of opioid prescription rates in 2017, both show peaks in Appalachia (CDC, “U.S. County Prescribing Rates,” 2017). However, opioid prescription rates are also high in Western Kentucky, a trend that is not reflected in the NAS rate; factors accounting for this difference will need to be explored.

Figure 2. NAS Rate Among Kentucky Residents by ADD, 2017



Mothers of NAS cases (compared to mothers of infants without NAS) were significantly more likely to be Non-Hispanic White, consistent with the demographics of the Appalachian region of Kentucky where NAS is most common. The differences in education, marital status, and parity are shown in Figures 3-5. Overall, mothers of infants with NAS tended to have less education, be unmarried, and have more children. All three of those factors may indicate lower socioeconomic status, and may also contribute to less social support or comfort navigating the healthcare system. In Kentucky, nearly three out of every five women who gave birth in 2017 had greater than a high school education, which includes any coursework from a post-secondary institution. Among mothers of babies with NAS, less than two out of every five mothers had greater than a high school education. Women whose infants had NAS were three times more likely to be unmarried than married, in contrast to women whose infants did not have NAS, the majority of whom (58%) were married. Less than one out five NAS cases was the first live birth to that mother, compared to about two out of five non-NAS cases. Identifying demographic patterns will identify at risk populations for designing interventions.

Figure 3. Education of Kentucky Resident Delivering Mothers by NAS Status of Child, 2017

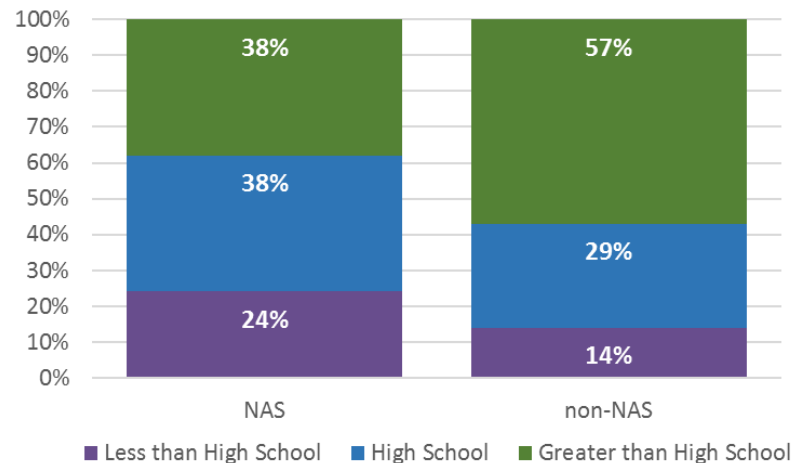


Figure 4. Marital Status of Kentucky Resident Delivering Mothers by NAS Status of Child, 2017

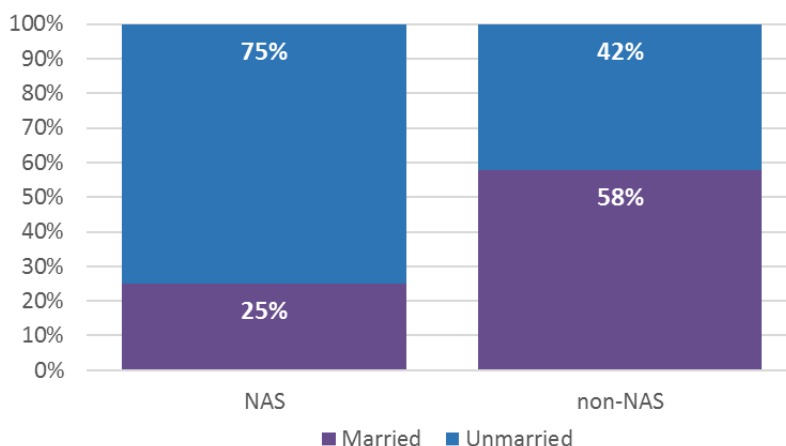
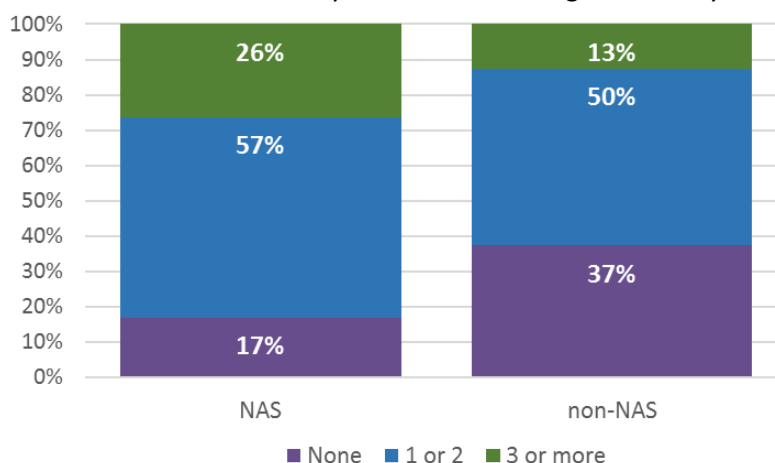


Figure 5. Parity or Number of Births of Kentucky Resident Delivering Mothers by NAS Status of Child, 2017



Frequent Substances Used

Table 2 includes all substances included in the NAS Registry (excluding tobacco and alcohol) by category, ranked from most to least commonly reported. Variation in hospital testing policies, type of sample (cord blood, urine, or meconium), ability of the substance to pass through the placenta, and half-life of the substance were adjusted for by considering a case a positive if there is any indication of substance use (maternal history, maternal toxicology screen positive, or infant toxicology screen positive). There were no substantial changes in the rankings of substances from last year's NAS Registry report.

The most common substance in the NAS Registry is buprenorphine, which is used in MAT to reduce withdrawal and cravings (SAMHSA, 2016). Buprenorphine is an opioid partial agonist, with effects that are similar to but weaker than other opioids, resulting in less potential for misuse (SAMHSA, 2016). While buprenorphine can cause NAS, its use as part of supervised MAT is preferable to untreated OUD during pregnancy. The rate of infants testing positive for buprenorphine has been rising since the inception of

the NAS Registry, from 30.7% in 2015 to 37.5% in 2016 and 41.7% in 2017. One possible explanation is increases in treatment programs and MAT providers for pregnant women.

The second most common reported substance was “other opioids.” Non-specific toxicology reports or maternal histories of opioid use make up the majority of this category, but oxycodone is a substantial contributor, as it was involved in one in ten cases in the NAS Registry. Fentanyl and tramadol were only reported for about one in every 100 cases, but fentanyl is a newly emerging public health threat.

Table 2. Frequency of All Substance Groups in the Public Health NAS Reporting Registry, 2017

Buprenorphine	60.05%		
Methadone	12.66%		
Heroin	16.52%		
All Other Opioids	39.86%		
Cannabinoid	24.78%		
(Meth)Amphetamines	23.07%		
Benzodiazepines	14.81%		
Cocaine	7.81%		
Gabapentin	7.45%		
SSRIs	2.33%		
Barbiturates	1.71%		
Tricyclics	1.35%		

Unspecified Opioids	34.11%
Oxycodone	10.59%
Fentanyl	1.17%
Tramadol	0.72%

Note: Numbers will not add to 100% as more than one substance can be reported per case and not all substances are shown in the table above. The category (Meth)Amphetamines includes any indication of use of methamphetamine and/or amphetamines. The category All Other Opioids includes any indication of use of codeine, fentanyl, hydrocodone, meperidine, morphine, oxycodone, tramadol, and/or other unspecified opioids.

A quarter of the cases in the NAS Registry had exposure to cannabinoids. Across the U.S., cannabis is the most commonly used illicit drug, with about 7% of pregnant women and 12% of non-pregnant women self-reporting use in the past month (McCance-Katz, 2018), which likely represents only about half of all users (Garg et al., 2016). One factor in the frequency of cannabis use is a perception of safety. Several Kentucky PRAMS participants described smoking marijuana while pregnant, and all said that they felt it was safe and possibly even helpful for anxiety, depression, and morning sickness. One participant wrote:

“Man made drugs hurt babies. They say marijuana also hurts babies but I think that it's natural and it shouldn't be treated the same.”

The American College of Obstetricians and Gynecologists (ACOG) discourages marijuana use during pregnancy due a lack of studies on its safety (ACOG, “Marijuana,” 2017). Current research does not indicate that cannabis leads to NAS, but it has been associated with significantly increased likelihood of using other substances, including tobacco, alcohol, and opioids (Passey, Sanson-Fisher, D’Este, & Stirling, 2014).

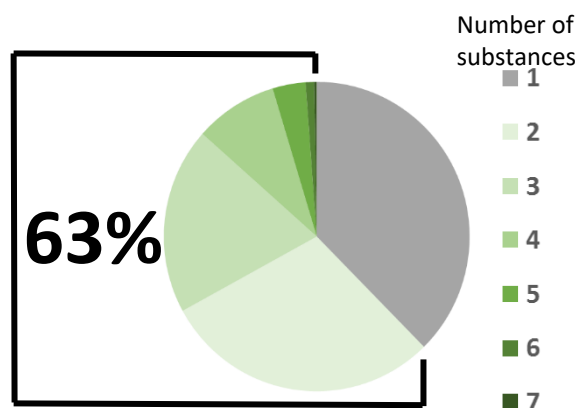
Amphetamines including methamphetamines, benzodiazepines, heroin, methadone, and oxycodone were used by 10-25% of women whose babies were in the NAS Registry. Having so many substances that are commonly used is an indication that women are using more than one substance. From 2016 to 2017, the overall frequency of heroin use decreased from 20.4% to 16.52%.

SSRIs, barbiturates, and tricyclics are among the least-frequently reported to the NAS Registry (all reported in less than 5% of included cases). SSRIs and tricyclics are types of prescription anti-depressants. Barbiturates are a class of central nervous system depressants that can be used to treat anxiety, seizures, and sleeplessness (Hughes et al., 2016). Due to the potential for abuse, barbiturates are generally falling

Figure 6. Frequency of Polysubstance Use

out of favor when there are safer alternatives, such as benzodiazepines (Hughes et al., 2016; NIMH, 2016). These substances may be underreported to the Public Health NAS Registry due to a focus on opioids.

Approximately 63% of cases in this dataset had polysubstance use, which in this report means use of substances from more than one type or category (see Table 2), excluding tobacco and alcohol. In this report, using multiple substances during pregnancy, even if not concurrently, is considered polysubstance use. About 29% of women used two types of substances and about 34% used three or more types of substances. The average number of substances used among women with polysubstance use was 2.8.



Polysubstance use is not often compatible with responsible prescribing practices, due to dangerous pharmacological interactions, and it is often indicative of OUD. Polysubstance use may contribute to more severe or increased duration of NAS symptoms. Both illicit drugs, such as cocaine (Hudak & Tan, 2012), and prescription medications, such as SSRIs (Kaltenbach et al., 2012) and benzodiazepines (Hudak & Tan, 2012), can be associated with worsened NAS symptoms among women also using opiates. Data from the NAS Registry showed a slight, non-significant increase in length of stay (LOS) for infants who were exposed to more than one substance.

Nearly half (48.37%) of the women had a prescription for MAT, which would include buprenorphine and methadone. Less than 10% of women had prescriptions for treatment of pain or of psychiatric disorders (9.16% and 3.35%, respectively). Prescriptions for pain medications would include the “All Other Opioids” category, as well as gabapentin. Prescriptions for psychiatric disorders would primarily fall into the categories of benzodiazepines, SSRIs, and tricyclics. The relatively low frequency of prescriptions aligns with the low frequency of reported use.

Prenatal Care

Infants with NAS differ from infants without NAS in healthcare utilization, from the time of conception onward. The prenatal period presents a unique window of opportunity for women to make many changes in their health and lifestyle, whether it is improving diet, managing a chronic condition, obtaining psychiatric care, or beginning treatment for an OUD (ACOG, “Opioid,” 2017). ACOG recommends women with OUD have prenatal screenings for hepatitis B, HIV, chlamydia, gonorrhea, syphilis, tuberculosis, and Hepatitis C (ACOG, “Opioid,” 2017).

In about 6% of pregnant women with hepatitis C, the infection passes to the baby (CDC, “Hepatitis C,” 2017). Among Kentucky women who had live births without NAS in 2017, 1.7% were diagnosed with hepatitis C; among mothers of NAS cases, this rose 20 times to 34.6%. Among women with polysubstance

Hepatitis C is **20x** more common in mothers of NAS cases.

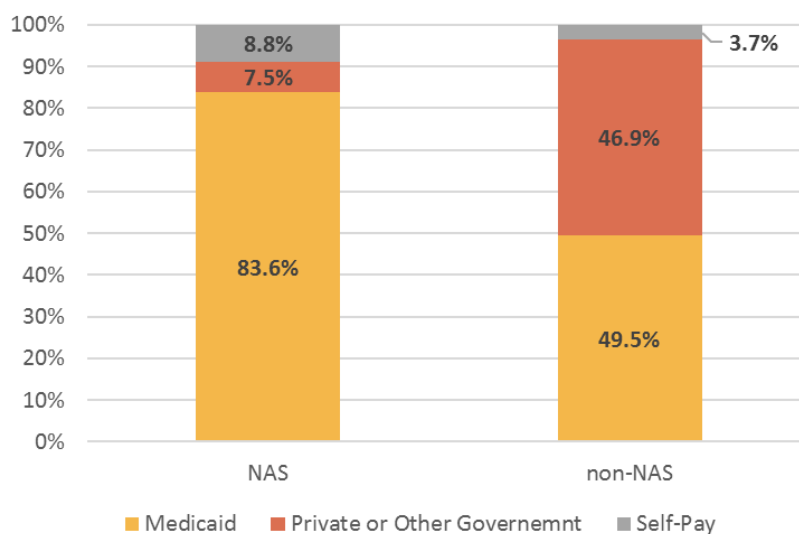
use, it is 38.6%. These concerns led KDPH to request voluntary reporting of hepatitis C in December 2013 and mandatory reporting in February 2015. In April 2018, Senate Bill 250 was signed into law. This bill added universal screening of pregnant women for hepatitis C to KRS 214.160.

About three out of every five mothers whose infants had NAS received prenatal services through the Women, Infants, and Children program (WIC). That rate is nearly 1.5 times higher than women whose infants do not have NAS (60.9% and 43.0%, respectively). Enrollment in WIC can ensure proper nutrition for an infant who is at risk of feeding difficulties, provide assistance with breastfeeding, and serve as a point of contact where women can be referred to additional services.

Although prenatal care is crucial, particularly for this population, only 48.6% of mothers in the NAS Registry received a number of prenatal care visits that was at least adequate (Kotelchuck index), compared to 75.3% of mothers who did not have infants with NAS. Almost all pregnant women in Kentucky receive some prenatal care, but mothers of infants with NAS were at least five times more likely to have no prenatal visits than mothers of infants without NAS (7.9% and 1.4%, respectively).

Disparities in insurance type and status, shown in Figure 7, give one possible explanation for prenatal care utilization. More than twice as many deliveries of infants with NAS were paid out-of-pocket as opposed to deliveries of infants without NAS (8.9% versus 3.7%).

Figure 7. Insurance Type at Time of Delivery, by NAS Status, Kentucky Residents, 2017



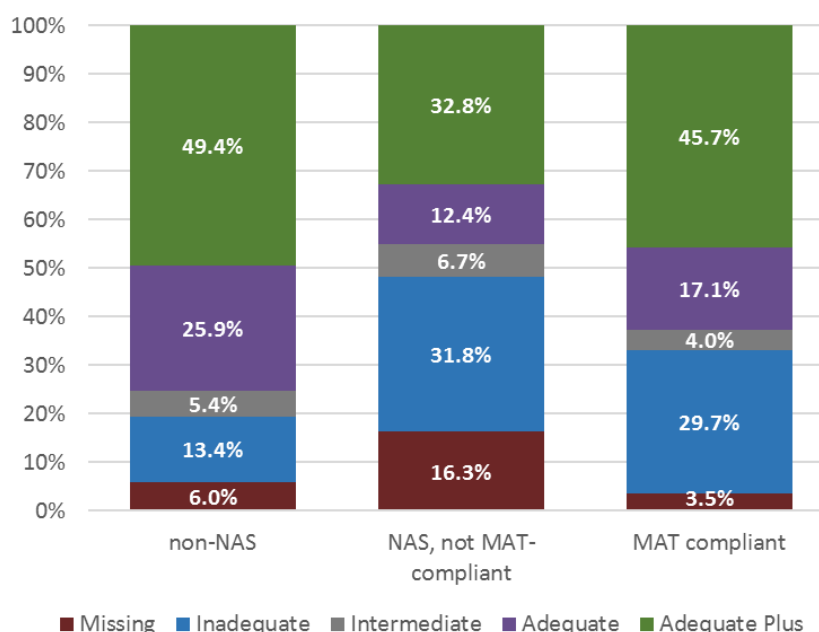
With approximately 84% of babies with NAS having Medicaid, as opposed to about 50% of the non-NAS population, Medicaid organizations are positioned to ensure appropriate follow-up for affected infants to avoid preventable, costly outcomes in the future.

Another factor in prenatal care utilization is enrollment in and compliance with MAT (Figure 8). MAT uses therapy approaches in addition to medications such as buprenorphine, methadone, or naltrexone. Methadone and buprenorphine are used for replacement therapy and should not be taken in combination with other opioids. Naltrexone is an opioid receptor agonist that is used to block opioid highs (Schuckit, 2016). It is not used to treat physiological opioid dependence, but can be used to help maintain opioid

abstinence during the rehabilitation process (Schuckit, 2016). Women who were compliant with MAT were much more likely to have prenatal care that was at least adequate, as compared to women who were not compliant with MAT. This could indicate that women in MAT are more likely to seek prenatal care when becoming pregnant, or that pregnant women receiving prenatal care are more likely to enroll in MAT. Regardless, increased interactions with the healthcare system encourages other interactions.

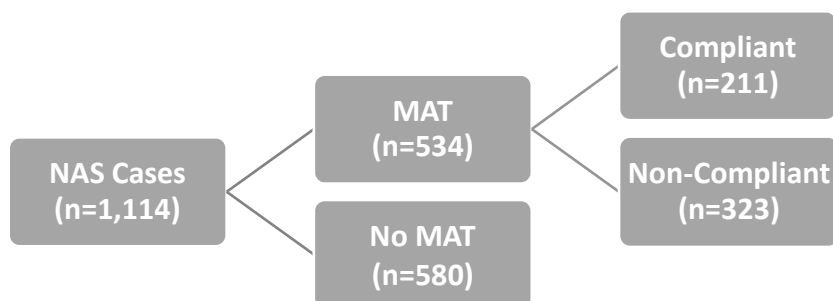
In this report, MAT is defined as having a valid prescription for replacement therapy. Compliance was defined as having no indication of using amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, gabapentin, heroin, or any other opioid.

Figure 8. Adequacy of Prenatal Care, by NAS and MAT Compliance, Kentucky Residents, 2017



In the 2017 cohort, nearly half of the mothers were enrolled in MAT, and about two out of every five of those were compliant. A limitation of this data is the use of proxy measures, as the registry is unable to determine if the mother is actually compliant with the MAT program. Low rates of compliance are echoed by the high rate of polysubstance use among women in MAT, which was not significantly different than the rate among women who were not in MAT. As non-compliance translates to ineffective treatment, this is an area that should be addressed.

Figure 9. Number of Cases in NAS Registry, by MAT Participation and Compliance

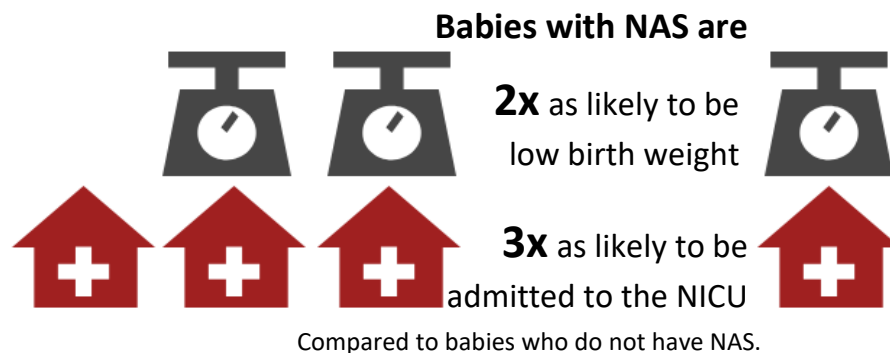


A common misconception, even among providers, is that the drugs used for MAT will not result in NAS. Data from the NAS Registry showed no significant differences in frequency of pharmacological treatment for NAS symptoms or in the average LOS, when stratified by MAT status or compliance. Perpetuating misinformation can lead to distress, mistrust, and ultimately non-compliance. A mother provided this statement to Kentucky PRAMS (verbatim):

“When I found out I was pregnant, I began a Subutex program because I had heard the baby would not withdrawal or have any problems. I also knew the Subutex would keep me away from other drugs. I learned when I had her, some babies there is no guarantee. If I would've know it would hurt my baby, I wouldn't have taken it. I would've found another treatment for my addiction.”

Newborn Outcomes

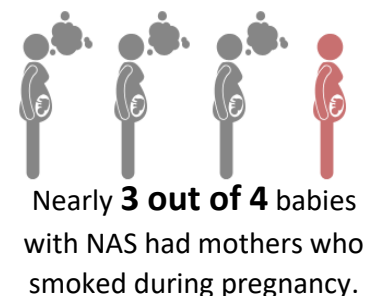
Compared to infants without NAS, infants with NAS are slightly more likely to be born preterm (less than 37 weeks gestation) and twice as likely to be low birth weight (LBW), defined as less than 2,500 grams.



Co-occurring factors, such as smoking, may confound these results, although some studies have suggested that LBW among substance-exposed infants was largely due to underlying social, behavioral, and biomedical factors (Schempf & Strobino, 2008). Symptoms of NAS such as vomiting and diarrhea, which can lead to difficulties feeding and gaining weight (Hudak & Tan, 2012), further increase the health risks and challenges associated with preterm and low birth weight.

In the wake of the opioid epidemic, alcohol and tobacco are often overlooked although both have negative effects if used during pregnancy, including developmental delays and preterm birth (Bishop et al., 2017). The effects may last a lifetime. Both substances can cause withdrawal-like symptoms in infants (Hudak & Tan, 2012) and may worsen NAS. Use of alcohol and tobacco during pregnancy has also been associated with use of other illicit substances, including marijuana (Passey, Sanson-Fisher, D’Este, & Stirling, 2014).

In 2016, about 7.2% of pregnant women smoked in the U.S., which is less than half of Kentucky’s rate (18.4%) (Drake, Driscoll, & Matthews, 2018). Data from the 2017 Kentucky Certificate of Live Birth, show that 17.1% of women whose babies did not have NAS reported smoking during pregnancy. That figure increases to 73.5% for women whose babies have NAS. Self-reported smoking data from the Certificate of Live Birth is usually an under-representation of actual prevalence, but it is higher than

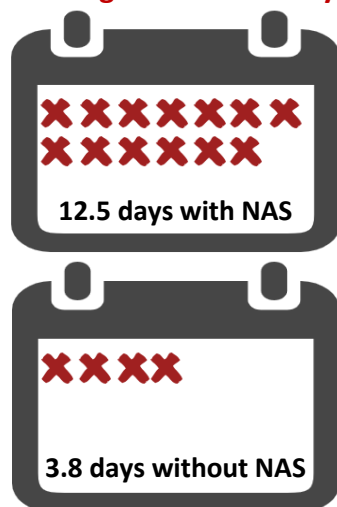


the 67.4% reported to the NAS Registry. This discrepancy may be caused by the question wording or other data collection factors.

The prevalence of alcohol use during pregnancy is not well-known, as social taboos lead to reluctance in self-reporting in medical or legal records, such as the birth certificate. In 2017, the reported rate in Kentucky was less than 0.5%. Despite this stigma and low reporting, drinking alcohol during pregnancy is not uncommon. Data from an anonymous national survey found that about 10% of pregnant women admitted to drinking alcohol in the past 30 days (CDC, 2015). In the NAS Registry, 5.1% of women reported drinking during pregnancy. This is six times higher than these same individuals reported on vital records, indicating that the registry might be a more accurate source for this variable.

With NAS as a consideration, the delivery hospitalization is often more complicated. In 2017, less than 10% of newborns were transferred to the NICU, according to data reported on the Kentucky Certificate of Live Birth. This number climbs to upwards of 30% for newborns with NAS. Whether or not they are admitted to the NICU, NAS cases have a much longer LOS post-delivery: 12.5 days versus 3.8 days. NAS cases utilize an increasing amount of healthcare resources: about 4.0% of total NICU days nationwide were attributed to NAS in 2013, versus about 0.6% in 2004 (Tolia et al., 2015).

Average LOS at delivery

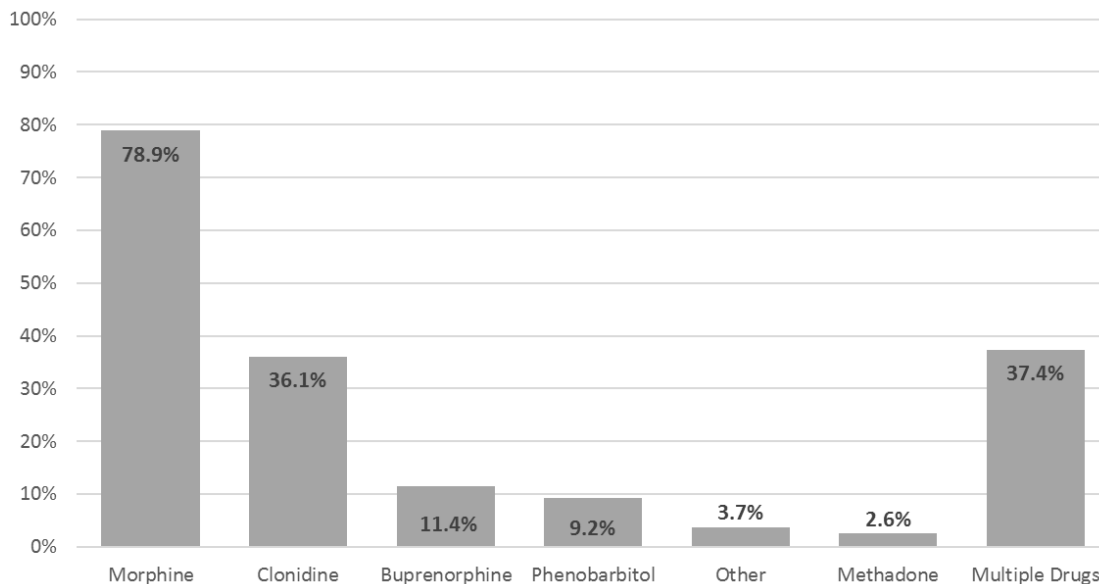


A long LOS may be beneficial or even crucial for NAS cases. Symptoms of NAS begin around 24-72 hours after birth for most opioids, although genetic, environmental, and pharmacological factors can influence that (Kocherlakota, 2014). According to 2017 data from the NAS Registry, the average age at onset of symptoms is 23.5 hours, although a very broad range of times was reported. Nearly 10% of cases in the registry were asymptomatic until more than 48 hours after birth. For this reason, it could be dangerous to discharge infants with a history of maternal substance abuse within two or three days of life, because they may have a later onset of NAS symptoms, especially with long-acting medication used in MAT. The American Academy of Pediatrics (AAP) (Hudak & Tan, 2012) and the World Health Organization (2014) both recommend observing these infants in the hospital for four to seven days post-delivery. In this dataset, 75.5% of NAS cases had hospital stays of at least four days, which rose to 90.0% for cases that received pharmacologic interventions.

Infants receiving pharmacological interventions for symptoms of NAS tend to have a much longer LOS than those who receive comfort (non-pharmacological) care only (only 19.4 days compared to 6.7 days). Overall, 53% of infants with NAS received pharmacologic treatment, using a variety of medications, sometimes in combination. Nearly four out of every five infants treated received morphine. This is consistent with previous studies of prescribing practices (Hudnak & Tan, 2012). All other medications were administered to <40% of infants who received pharmacological interventions. Clonidine was used in 36.1% of these cases, although there are few studies evaluating its use to alleviate NAS symptoms in infants (Hudak & Tan, 2012). Randomized trials have shown its effectiveness as an adjunct to morphine in NAS treatment. Studies have shown that buprenorphine is well-tolerated but causes only insignificant reductions in treatment duration and LOS (Hudak & Tan, 2012). It was prescribed to 11.4% of babies who received pharmacologic treatment, even though there is a lack of large randomized trials for newborns, or reports on its effect on long-term outcomes. Studies of phenobarbital, singly or in combination with

morphine, have demonstrated mixed results for efficacy, and phenobarbital is generally recommended as a second-line option when morphine has been unsuccessful in treating symptoms (Hudak & Tan, 2012). Less than 10% of cases in this sample received phenobarbital.

Figure 10. Frequency of Medications Administered to Treat NAS, Kentucky Residents, 2017



When considering pharmacological treatments for NAS, the first concern is that treatment should be both safe and effective for infants. The AAP Committee on Drugs and Committee on Fetus and Newborn states:

“Withdrawal from opioids or sedative-hypnotic drugs may be life-threatening, but ultimately, drug withdrawal is a self-limited process. Unnecessary pharmacologic treatment will prolong drug exposure and the duration of hospitalization to the possible detriment of maternal-infant bonding. The only clearly defined benefit of pharmacologic treatment is the short-term amelioration of clinical signs” (Hudak & Tan, 2012)

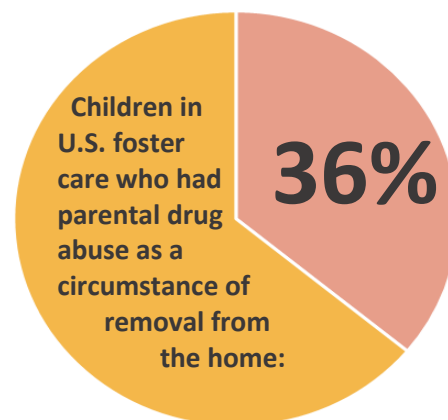
Breastfeeding is one non-pharmacologic intervention that may be associated with a reduction in the severity of NAS symptoms (Hudak & Tan 2012). ACOG recommends breastfeeding, unless contraindicated, in women who are stable on opioid agonist treatment, provided the mother is not using any other illicit substances (ACOG, “Opioid,” 2017). The AAP does caution that close supervision and follow-up is necessary in order for safe breastfeeding to occur (Behnke & Smith, 2013). According to Kentucky Live Birth Certificate data, just over a quarter of mothers whose infants have NAS plan to breastfeed, compared with nearly three-quarters of mothers whose infants did not have NAS. Among mothers whose infants have NAS, about 24% actually initiate breastfeeding.

Outcomes Beyond Discharge

In addition to insurance, another reason that women with OUD have less engagement with prenatal care is fear of consequences, such as civil or criminal charges or reporting to DCBS. These fears are not baseless, as 23 states and Washington, DC, consider substance use during pregnancy to be child abuse; 24 states

and Washington, DC require suspected prenatal substance abuse to be reported to child welfare organizations (Guttmacher Institute, 2018).

As part of the Child Abuse Prevention and Treatment Act (CAPTA), states are required to have policies to notify their Child Protective Services (CPS) programs of substance-exposed infants. Nationwide, in Fiscal Year 2017, 96,000 children entering foster care had parental drug abuse as a circumstance of removal from the home (Children's Bureau, 2018). A recent national study of opioid prescriptions and child removals did not find an overall pattern using state-level data, but noted that the variation in state child welfare systems, access to health care and pharmaceutical services, and availability of illegal drugs all contributed to the complex association between the two (Quast, 2018).



According to the Cabinet for Health and Family Services (CHFS) standard of practice manual, a report regarding substance misuse may be accepted upon delivery of an infant when the infant has risk of harm because the caretaker engaged in a pattern of conduct that renders him/her incapable of caring for the immediate and ongoing needs of the child due to incapacity due to alcohol or other drug misuse (2018). Examples of this include: an infant born with non-prescribed drugs in their system or who is showing signs of withdrawal from non-prescribed drugs, or the caregiver is misusing substances, or their ability to care for the child is negatively impacted. In Kentucky, prenatal substance exposure is not classified as child abuse or neglect, but there are criminal statutes associated with exposing children to illegal drug activity (Children's Bureau, 2015). DCBS cannot accept a report of abuse or neglect on behalf of an unborn child, but providers are expected to report prenatal substance misuse and to ensure that the history is documented in the prenatal record. Of all infants in the NAS Registry, 82% were referred to DCBS; 76% of those were accepted. Among infants whose mothers were estimated to be compliant with MAT, 79% were referred to DCBS and 53% of those were accepted. With no additional risk factors, these infants do not meet grounds for acceptance by DCBS. A limitation of this report is that the DCBS data might be under-reported if the case is submitted to the NAS Registry prior to discharge.

The Child Fatality and Near Fatality External Review Panel (henceforth "the Panel") conducts comprehensive, multidisciplinary reviews of child fatalities and near fatalities with suspicion of abuse or neglect, to become aware of risk factors and systems issues and recommend prevention measures (2018). Of cases reviewed in 2016, 41% had substance abuse in the home and 36% had substance abuse by a caregiver; those patterns were similar in cases with abusive head trauma (AHT), but were substantially higher (65% and 58%, respectively) among cases with unsafe sleep (2018). Preliminary data for 2018 show that caregiver substance abuse was a characteristic in 46% of all cases reviewed by the Panel. The following case (F-13-17) reviewed by the Panel highlights some risk factors related to NAS and caregiver substance use:

"CPS received a report that the mother was using drugs and not able to care for her two-month old infant. The reporting source stated that when they went to the mother's home she was observed to have pill residue under her nose. The following day, when CPS and law enforcement visited the home, the mother appeared intoxicated but informed the officer the baby was not home. The mother agreed to let them enter her home, where the child was found deceased at the end of her bed. The mother did not even realize the child was in the home and stated she had not cared for

the infant in over 12 hours. The infant had been diagnosed with NAS at birth, the meconium was significant for methamphetamine, amphetamine, and THC. The infant had only been seen by a medical provider once since birth. The mother had a significant history with CPS related to drug use and neglect regarding the deceased child and sibling. Mother reported using drugs since she was a teenager and began using meth just prior to becoming pregnant with the victim. Mother reported using Subutex during her pregnancy and returned to using methamphetamine multiple times a day along with Suboxone purchased on the street after the child was born.”

From the 2016 data from Kentucky’s Sudden Unexpected Infant Death (SUID) Case Registry, 18% of SUID cases had NAS or a caregiver with substance use. As less than 3% Kentucky infants are reported to the NAS Registry, this data could indicate that NAS is a risk factor for SUID. There is currently not a known biological mechanism that would predispose NAS cases to SUID, and the scenario is further complicated by the contribution of caregiving or co-sleeping while impaired. As 2016 was the first year of data collection for the SUID Case Registry, further analysis will be done as data becomes available in the future.

A study from Australia found that infants with NAS were more likely to be hospitalized for assaults, maltreatment, and poisoning, and were overall more likely to die during hospitalization (Uebel et al., 2015). Research on this topic is limited, and further studies are warranted to assess the risk of maltreatment and mortality among NAS cases.

Conclusions and Recommendations for Prevention

NAS is just one facet of the opioid epidemic and cannot be addressed in isolation from larger systemic issues. Although the problem is daunting, prevention is possible. The following recommendations help address the underlying determinants of health to promote better outcomes for families and children.

Encourage MAT programs. MAT programs, especially those that incorporate comprehensive services to address the complex needs of the mother and family, can be very successful in addressing OUD, as illustrated by this success story of a Kentucky mother in MAT:

“I’m excited to report that she just received Drug Court Participant of the Month! Her case workers attended the [program] session yesterday because they are amazed at the progress she has made in just 3 weeks. The judge stated that if she continues the program for another 6 months and has clean screenings he will seriously consider permanency...She has since enrolled in GED courses, has an appointment with a new therapist in a few weeks, and is in the process of securing an apartment.”

All MAT providers need training in family-oriented protocols for counseling and behavioral therapy, which are crucial to the success of the treatment program.

Implement a Plan of Safe Care. Every infant prenatally exposed to drugs or alcohol should leave the hospital with an appropriate Plan of Safe Care. A Plan of Safe Care should address the services needed for the impacted child, caregivers, and OUD parent. KDPH has the community outreach structure in place to help bridge the widening gap between the need for and availability of programs.

Encourage education for parents on abusive head trauma and safe sleep. Due to the heightened risk for infant maltreatment and death among NAS cases, parents need to receive additional training and information on prevention. Birthing hospitals provide in-person, evidence-informed education regarding safe sleep and abusive head trauma prevention to parents, both antepartum and postpartum. Making this a universal practice will ensure that all parents of infants with NAS or prenatal substance exposure are reached. To that end, the Kentucky Hospital Association supports this practice.

Implement the practice of modeling safe sleep among healthcare and childcare providers. NAS cases have an increased risk of SUID, which may be reduced through medically appropriate safe sleep practices. Healthcare and childcare providers are uniquely positioned to encourage these practices through modeling, and should do so universally.

Increase enrollment in services such as WIC and HANDS (home visiting). Services that enroll mothers and families prenatally and throughout early childhood have unique opportunities for engagement. These programs should incorporate substance abuse education into curricula on healthy pregnancies, in addition to making referrals to counseling or treatment for women who are interested.

Improve access to long-acting reversible contraception (LARC). More than four out five NAS cases were not the first live birth to that mother, compared to about three out of five non-NAS cases. This demographic trend was noted last year in *Neonatal Abstinence Syndrome in Kentucky: Annual Report on 2016 Births*, with the additional context that nearly 90% of pregnancies among this population are unintended (Heil et al., 2011). This trend could indicate a need for more effective pre-conception counseling, including improved access to family planning among women of reproductive age who use opioids for any purpose. Women who are not utilizing reproductive health may be limited by socioeconomic factors and the cost of child rearing would be an increase in financial burden. LARCs should be available to all mothers during the intrapartum period.

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