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A Systematic Review of LC-MS/MS-Based Panels for Detecting Illicit Drug Exposure in Neonates and Meconium: Current Gaps and Future Directions

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Abstract

Background: The use of illicit drugs during pregnancy is a significant public health problem and linked to adverse neonatal outcomes, such as low birth weight, preterm birth and neurodevelopmental abnormalities. To receive timely clinical intervention, it is important to detect in utero drug exposure accurately.

Objective: The purpose of this systematic review was to present a comprehensive overview of the existing LC-MS/MS-based methods for the detection of neonatal drug exposure, review the performance of the various matrices, and evaluate the coverage of the multi-class panel.

Methods: A detailed search of PubMed, Scopus, Web of Science, and Google Scholar was conducted for 2010-2026 published articles. A total of 20 studies involving meconium, umbilical cord tissue, placenta and neonatal urine were included. Data were collected for analytical platforms, validation parameters (LOD, LOQ, precision, accuracy), matrix comparison, and multi-class drug coverage. A narrative synthesis of the SWiM guidelines was conducted. A custom Analytical Quality Assessment Checklist (CAQAC) was developed to evaluate methodological quality.

Results: Meconium was the most sensitive matrix for identification, more regularly than umbilical cord or urine. Increasing coverage over time was observed for multi-class LC-MS/MS panels, including emerging psychoactive substances. Standardization of validation and harmonized panels was indicated by analytical heterogeneity across studies. New technologies, such as UHPLC-QTOF and dual-mode LC-MS/MS, led to more sensitive and faster data analysis.

Conclusions: LC-MS/MS is a powerful and flexible method for screening neonatal drug exposure. The use of standardized, high-throughput multi-class panels is recommended for increased reproducibility and early detection of prenatal drug exposure.

Keywords: Prenatal exposure; Meconium; Umbilical cord tissue; Analytical validation; Toxicology

Introduction

Neonatal exposure to illicit drugs is a major public health and clinical problem, as in utero exposure has been linked to poor neonatal outcomes such as low birth weight, preterm delivery, neurodevelopmental anomalies, and increased risk of neonatal abstinence syndrome (NAS) (Patrick et al., 2012). Maternal self-report or maternal urine testing are traditionally used to identify maternal substance use during pregnancy but are limited by underreporting and short detection windows, inconsistent sensitivity and specificity, and missed opportunities for detection and clinical interventions for maternal exposure (González-Colmenero et al., 2020).

In the neonatal field, various biological matrices have been examined to optimize the detection of prenatal drug exposure, such as urine, hair, oral fluid, and amniotic fluid; however, the majority of these matrices have limited detection windows and are impractical for collection close to the time of birth (Ostrea Jr, 1999). The first fecal material excreted by newborns is meconium, which has been found to contain xenobiotics and their metabolites that can be deposited during later stages of gestation, usually the second and third trimesters of pregnancy (Bearer, 2003). Meconium collection is non-invasive, it can obtain enough sample size, and the metabolic profile of meconium has a relatively longer detection window than that of neonatal urine or blood, and this avoids the false negative result in the conventional screening approach (Ostrea, 1995). Retrospective clinical studies have shown the value added by screening for meconium to uncover prenatal drug exposure cases that would not be detected by routine clinical assessment (Bordin et al., 2025).

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Traditionally, meconium has been analyzed by immunoassay or gas chromatography-mass spectrometry (GC-MS); however, liquid chromatography with tandem mass spectrometry (LC-MS/MS) is the method of choice for confirmation in complex matrices such as meconium and umbilical cord tissue (Bordin et al., 2025). In addition to being cross-reactive and prone to high false positive rates, immunoassays are limited to detecting and confirming parent drugs and metabolites for a limited number of therapeutic and illicit compounds, whereas LC-MS/MS can be used to detect and confirm parent drugs and metabolites for a much wider spectrum of therapeutic and illicit compounds. The analytical benefits are particularly significant when considering that a variety of drugs, such as stimulants, opioids, cannabis, benzodiazepines, and novel psychoactive substances (NPSs), are becoming more common in prenatal exposure settings (Concheiro & Huestis, 2018).

In addition, umbilical cord tissue has been investigated as an alternative neonatal matrix, as it is readily available at birth, easy to collect, and sensitive to drugs used within the last few months of the mother's pregnancy (Montgomery et al., 2006). Comparative studies indicated that the qualitative results are comparable, but the quantitative results vary, with differences in the recoveries and/or matrix effects of the different analyses, hence the need for optimized and robust analytical panels for multiple matrices.

Although LC-MS/MS is becoming more common for neonatal toxicology, there are a number of concerns regarding the design of panels, matrix selection, sample preparation and comparability of results between various laboratories. The complexity of the matrices of meconium and umbilical cord, and methodological variations in extraction methods, chromatographic conditions and the number of analytes targeted, continue to hinder clinical interpretation and inter-study comparisons. Furthermore, the emergence of novel psychoactive substances (NPS) (also known as new psychoactive drugs) and other non-traditional drug classes underscore the importance of multi-analyte screening methods of drugs other than those found on traditional drug panels.

The scope of this systematic review is to consolidate the current LC-MS/MS methods available for the detection of neonatal exposure to illicit drugs, outline existing challenges in the field, and propose a direction for future developments, such as creating harmonized panels and an overall diagnostic framework. This review attempts to integrate analytical performance data, matrix comparisons and coverage of published panels to benefit both laboratory practice and clinical policy in neonatal toxicology.

Methodology

Study Design

The study was carried out as a systematic review and was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in order to ensure methodological rigor, transparency and reproducibility (Page et al., 2021). The primary goal was to identify, review and synthesize studies employing LC-MS/MS-based panels that identified prenatal drug exposure in neonates, with particular emphasis on the matrices used (meconium, umbilical cord tissue, placenta and neonatal urine). The review emphasized analytical performance and methodological quality of LC-MS/MS panels to identify current challenges and future directions in neonatal toxicology.

Data Sources and Search Strategy

A comprehensive literature review was conducted in databases like PubMed, Scopus, Web of Science, and Google Scholar for papers published between 2010 and 2026. Search terms included both controlled vocabulary and free text terms related to the neonatal drug exposure and analytical methods: "neonate" or "newborn," "drug exposure" or "illicit drugs," "meconium" or "umbilical cord" or "placenta," "LC-MS/MS" or "tandem mass spectrometry," with Boolean operators +AND+ and +OR+ to maximize the sensitivity and specificity of the search. Reference lists of relevant studies and of previous systematic reviews were hand-searched. This comprehensive search resulted in articles containing analytical methods, validation data, comparisons of matrixes, and multi-class panels.

Inclusion and Exclusion Criteria

Research articles were selected based on pre-defined criteria. Inclusion criteria included original research identifying the analysis of neonatal matrices for the detection of illicit or controlled drugs using LC-MS/MS, analysis of meconium, umbilical cord tissue, placenta or neonatal urine, reporting at least one of the following validation metrics: LOD, LOQ, linearity, precision and accuracy, and studies reporting a matrix comparison or multi-class panel coverage. Exclusion criteria were: case reports, conference abstracts, or editorials with no analytical content; studies based on immunoassays or

GC-MS without LC-MS/MS; review articles (for cross-referencing only); and non-human or in vitro studies.

Study Selection

All titles and abstracts were screened for relevance by two independent reviewers, then all were screened for eligibility through full-text review. All discrepancies were addressed by discussion, and if they could not be resolved, a third reviewer made the final decision. A PRISMA flow diagram was used to illustrate the selection process and the number of studies identified, screened, assessed for eligibility, and included. This process allowed for an open and repeatable selection of studies for review.

Data Extraction

Relevant data from each study were collected using a structured spreadsheet. Information retrieved consisted of study characteristics and details (author, year, country, sample size, neonatal matrix), analytical details (target analytes, extraction method, LC-MS/MS instrumentation, chromatographic conditions), method validation (LOD, LOQ, linearity, precision, accuracy, matrix effects), comparative analysis (positivity rates across matrices), multi-class panel coverage and gaps/recommendations reported by the authors. This standardization enabled a consistent assessment in different studies, and it helped to compile tables and figures for analytical performance, matrix, and coverage of drug panels.

Data Synthesis

A formal meta-analysis could not be conducted because the matrices and analytes varied, and because the study design and analytical technique varied. Hence, a Synthesis Without Meta-analysis (SWiM) approach was used (Campbell et al., 2020). Studies were classified based on the type of matrix, the range of drug classes covered, and the analytical method employed and the important quantitative data, including LOD, LOQ, and positivity rates, were presented in tables and figures. The narrative synthesis method was used to identify methodological trends, matrix performance differences, multi-class panel coverage and areas where new methods may be developed, thus revealing current gaps and opportunities in the standardization of neonatal LC-MS/MS toxicology.

Quality Assessment

There are limitations in traditional quality assessment methods used in clinical diagnostic or observational studies for assessing the analytical rigor of LC-MS/MS toxicology panel development (Lisboa et al., 2010). Thus, a Custom Analytical Quality Assessment Checklist (CAQAC) was created for this review, which includes important aspects of method validation, including LOD, LOQ, precision, accuracy, sample preparation, and reporting transparency (See supplementary Table 1). This is in line with principles in the literature of the mass spectrometry community for evaluating and reporting analytical methods, which highlight complete reporting of instrumentation and validation parameters for fitness for purpose and repeatability (Magnusson, 2014). The requirement for domain-specific quality criteria has also been emphasized in neonatal LC-MS/MS studies, which require customized assessment criteria due to the complexity of the matrix and performance of the multi-class panel.

Results

The PRISMA flow diagram displays the process for identifying, screening, assessing, and including studies in this PRISMA Review. A total of 1362 records were identified using a database search at the start. Records were removed prior to screening due to duplication (n = 358), automation tools that did not mark the records (n = 258), and other (n = 176). After this removal process, 572 records were screened. The records screened out were 198 due to failing initial screening.

This was followed by the retrieval of 374 reports. However, 189 reports could not be retrieved, leaving 185 reports for full-text eligibility assessment. Several criteria required reports be excluded during the eligibility assessment process, such as non-comparative study design (n = 87), insufficient outcome data reported (n = 51), and ineligible study design (n = 27). Following the application of all inclusion/exclusion criteria, 20 studies were finally included in the systematic review, as shown in Figure 1.

Study Characteristics and Analytical Methods

Overall, the 20 studies reviewed examined neonatal matrices such as meconium, umbilical cord tissue, placenta, and neonatal urine for the detection of various illicit drug exposures, as well as those that included the use of LC-MS/MS or other high-resolution technologies (Table 1). Meconium (14 studies) and umbilical cord tissue (8 studies) were the most frequently analyzed matrices, while placenta and urine were less frequently analyzed. A wide range of analytes was included, including

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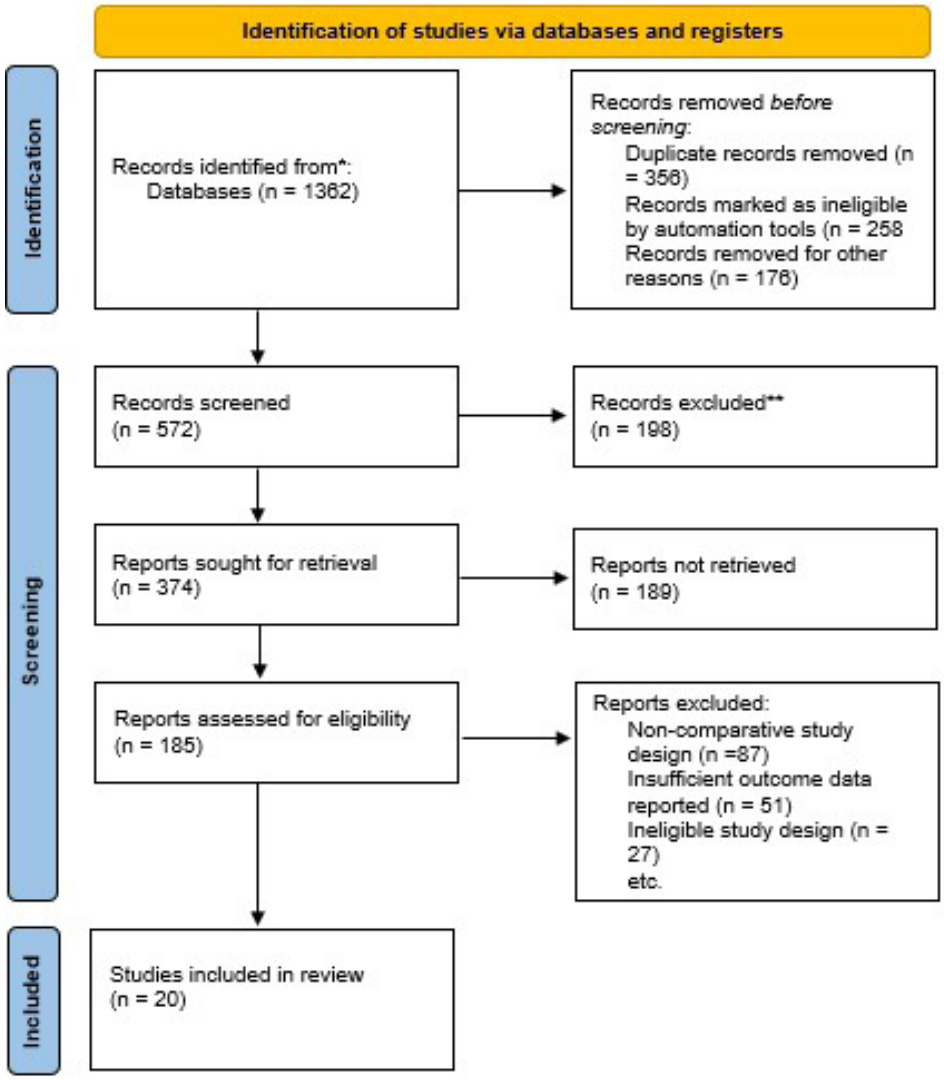

Figure 1. A PRISMA flowchart

different types of drugs, such as amphetamines, opioids, cannabinoids, benzodiazepines, antidepressants, and novel psychoactive substances, highlighting the dynamic nature of neonatal drug testing. Most analytical platforms were triple quadrupole LCMS/MS; some used UHPLC-QTOF or LDTD-MS/MS for greater sensitivity and speed.

Analytical Validation Parameters

It was reported that five primary studies had key validation metrics, such as LOD, LOQ, linearity, precision, and accuracy (Table 2). The values of LOD were between 0.2 ng/g and 50 ng/g, with LOQ values ranging from 0.6 ng/g to 2,000 ng/g, showing significant variability in sensitivity across different analytical platforms and matrices. A trending line plot of LOD and LOQ across these studies is presented in Figure 2 to show the variation in analytical sensitivity, and the effect that methodological differences have on the detection limits. The results highlight the need for optimizing the methods for each specific matrix for accurate identification of prenatal drug exposure.

Matrix Comparison and Detection Rate

Comparative analyses across matrices showed differences in positivity rates by drug class and matrix (Table 3). Overall, detection was increased for most analytes in meconium, while umbilical cord tissue and urine were slightly less sensitive for certain opioids and cannabinoids. The positivity rates for each matrix are displayed in Figure 3 and demonstrate that the sensitivity

Table 1: LC-MS/MS Methods by Matrix and Analytes

Author & Year	Matrix	Drug Classes / Analytes	LC-MS/MS Method / Instrument	Notes
(Ristimaa et al., 2010)	Meconium	Amphetamines, MDMA, morphine, codeine, 6-MAM, oxycodone, methadone, tramadol, buprenorphine, norbuprenorphine, THC-COOH	LC-MS/MS triple quadrupole; LC-TOF/MS	77 compounds detected; clinical relevance
(Marin et al., 2014)	Umbilical cord	57 drugs & metabolites	LC-TOF/MS	Cutoffs 1–40 ng/g; cannabis detection limited
(Prego-Meleiro et al., 2017)	Meconium	THC, OHTHC, THCCOOH, diOHTHC, CBN, CBD, THC/THCCOOH glucuronides	LC-MS/MS MRM	19 specimens; phase I & II metabolites
(López-Rabuñal et al., 2019)	Meconium	Synthetic cathinones	LC-MS/MS	28 specimens; Oasis MCX extraction
(López-Rabuñal et al., 2020)	Meconium	14 benzodiazepines, 15 antidepressants	LC-MS/MS	4 specimens; separate gradients
(Pandya et al., 2023)	Meconium & UC	32 analytes, 6 drug classes	LC-MS/MS semi-quantitative	4036 paired specimens
(Colby et al., 2019)	Meconium & UC	Multiple drug classes	LC-MS/MS	501 neonates; discordant detection
(Scroggin & McMillin, 2018)	Meconium	Cocaine, PCP, barbiturates	LC-MS/MS	51 samples; linearity $R \geq 0.995$
(Haglock-Adler et al., 2016)	Umbilical cord	Multiple drug classes	LC-MS/MS	514 samples; reduced runtime
(Jensen et al., 2019)	Meconium & UC	THC, THCA, 11-OH-THC, CBN, CBD	LC-MS/MS	46 paired samples
(Palmer et al., 2017)	Meconium & UC	Amphetamines, cannabinoids, opioids	LC-MS/MS	2072 neonates; retrospective analysis
(Colby, 2017)	Meconium & UC	Multiple drug classes	LC-MS/MS	Sensitivity comparison
(Kelly et al., 2008)	Meconium	Amphetamines	LC-APCI-MS/MS	LOD 1.25–40 ng/g
(López-Rabuñal et al., 2021)	Meconium	137 drugs of abuse	UHPLC-QTOF	Semi-quantitative; 30 specimens
(Brown et al., 2024)	Urine & Meconium	Methamphetamine, cocaine, cannabinoids, opioids, oxycodone, PCP	LC-MS/MS	1424 neonates

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Cont. Table 1

Author & Year	Matrix	Drug Classes / Analytes	LC-MS/MS Method / Instrument	Notes
(De Castro et al., 2013)	Placenta & UC	Opiates, methadone, amphetamines, cocaine	LC-MS/MS	Linear 1–5 to 100–500 ng/g
(Nelson et al., 2022)	Umbilical cord	Levamisole, xylazine, lidocaine, caffeine	LC-QTOF	Rapid analysis, 48 s per sample
(Jones et al., 2025)	Umbilical cord	EtG & co-exposure	LDTD-MS/MS	12,995 specimens; 238 EtG positive
(Jones et al., 2009)	Umbilical cord	Amphetamine, methamphetamine	LC-MS/MS	Linear up to 100 ng/g; LOD 0.2 ng/g
(Bavlovič-Piskáčková et al., 2026)	Meconium	Amphetamines, synthetic cathinones	Electromembrane extraction + UHPLC-MS/MS	50 mg sample; LOQ 2 ng/g

Table 2: Analytical Parameters (LOD, LOQ, Linearity, Precision, Accuracy)

Author & Year	Matrix	LOD (ng/g)	LOQ (ng/g)	Linearity Range (ng/g)	Precision (%CV)	Accuracy (%)	Notes
(Prego-Meleiro et al., 2017)	Meconium	1–2	4–10	4–400	<15.6	93.9–109	Phase I & II cannabinoids
(López-Rabuñal et al., 2019)	Meconium	0.5–1	1–2	LOQ–200	0–10	87.3–97.8	Synthetic cathinones
(López-Rabuñal et al., 2020)	Meconium	1–20	5–20	LOQ–400	0–14.6	90.6–111.5	BZDs & ADs
(Scroggin & McMillin, 2018)	Meconium	10–50	25–2000	20–5000	<11	84–100	Cocaine, PCP, barbiturates
(Jones et al., 2009)	Umbilical cord	0.2	0.6	0–100	NR	NR	Amphetamines

for the matrix of meconium is consistently higher than for other matrices. These observations align with the fact that meconium is still considered to be the most reliable matrix for retrospective detection of prenatal drug exposures because of the extended window of time of accumulation in utero.

Multi-Class Drug Coverage

Coverage of drugs varied significantly between studies (Table 4). Several studies tested only a subset of drug classes, while others included multi-class panels that detected a maximum of 137 analytes, including novel psychoactive substances (NPS). A heatmap of the inclusion of drug classes by study is shown in Figure 4. In contrast, early studies rarely included benzodiazepines or antidepressants, and more recent studies included extensive multi-class panels, showing a growing trend toward broad-spectrum neonatal drug testing.

Emerging Techniques and Novel Approaches

A number of studies adopted novel analytical approaches that are achieved with greater sensitivity, throughput, and multi-class detection (Table 5). These were electromembrane extraction, UHPLC-QTOF and

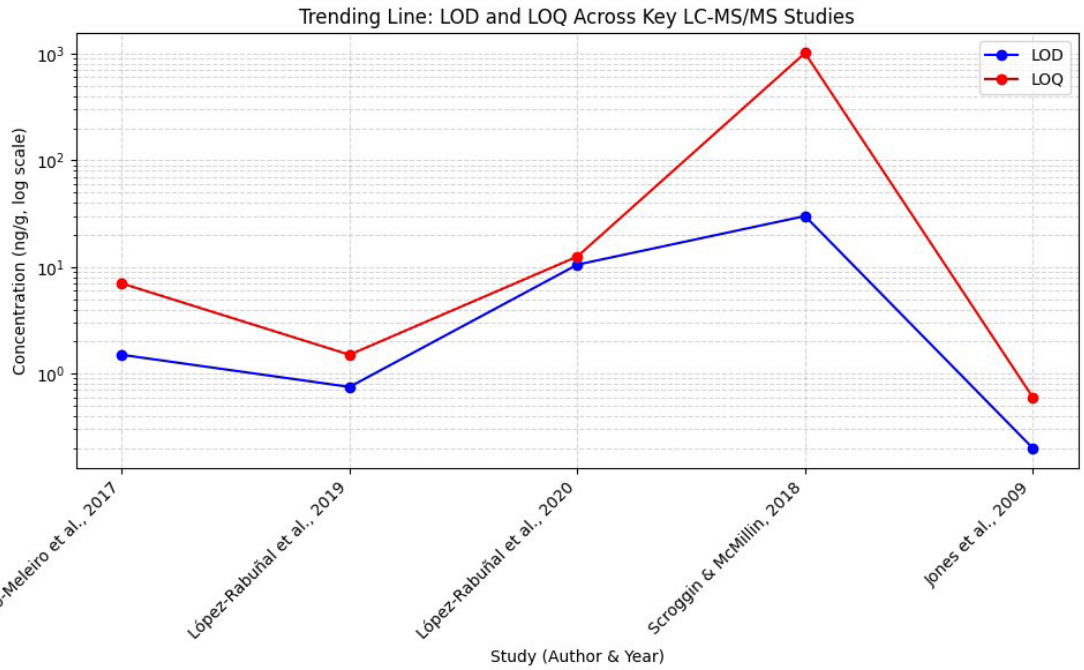

Figure 2. Trending line plot showing the limits of detection (LOD) and limits of quantification (LOQ) for key neonatal LC-MS/MS studies. LOD and LOQ values are shown in blue and red, respectively. The Y-axis is displayed using a logarithmic scale to allow for reporting of values over a broad range across matrices and analytical techniques.

Table 3: Comparative Detection (Meconium vs Umbilical Cord vs Urine)

Author & Year	Sample Size	Matrix Comparison	Positivity Meconium (%)	Positivity UC (%)	Notes
(Pandya et al., 2023)	4036 pairs	Meconium vs UC	Higher for most analytes	Higher except THC-COOH & cocaine	THC-COOH + opioids most common
(Colby et al., 2019)	501	Meconium vs UC	NR	NR	UC less sensitive for opioids
(Palmer et al., 2017)	2072	Meconium vs UC	21.3	29.2	Iatrogenic meds detected differently
(Brown et al., 2024)	1424	Urine vs Meconium	Equivalent	Equivalent	Methamphetamine, cocaine

single-injection dual-mode LC-MS/MS, all of which would enable fast analysis and minimize sample consumption. The trend in the field to move toward high-throughput, reproducible, and environmentally friendly analytical processes in neonatal toxicology is illustrated by these methods.

Gaps and Future Directions

In spite of the progress, the review showed that there was still a long way to go in terms of methodology (Table 6). These encompass decreased sensitivity of umbilical cord tissue for some analytes, few multi-class validations, and the non-standardization of analytical procedures in different laboratories. The synthesis underscores the importance of a standardized cutoff, multi-class panels and automated workflow to facilitate inter-study comparison and facilitate reliable detection across all neonatal matrices.

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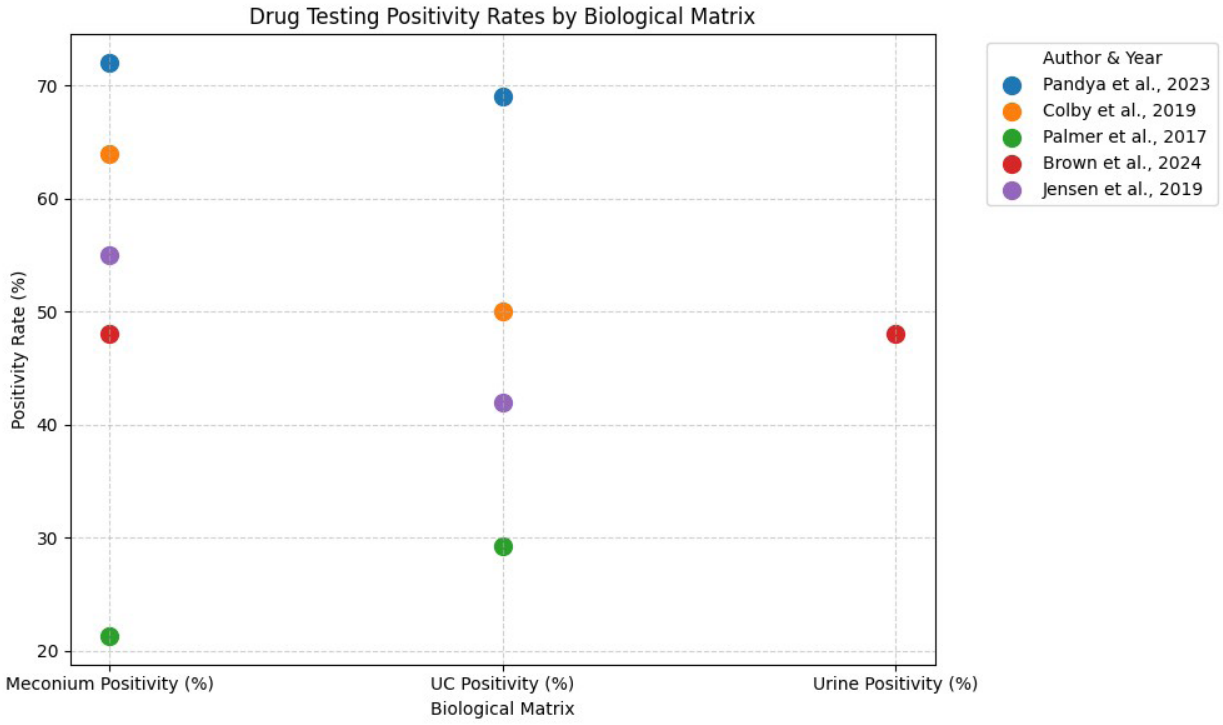

Figure 3. Neonatal drug positivity rates across all included studies are shown in a scatterplot by matrix (Meconium, Umbilical Cord, Urine). The colors of the points show the type of matrix tested and the number of analytes tested, with each point representing a study's reported positivity result for one or more analytes.

Table 4: Multi-Class Drug Coverage

Author & Year	Amphet-amines	Opioids	Canna-bis	Benzodi-azepines	Antide-pressants	NPS / Synthetic Cathinones	Other
(Ristimaa et al., 2010)	✓	✓	✓	–	–	–	Local anesthetics, nicotine, sedatives
(López-Rabuñal et al., 2019)	–	–	–	–	–	✓	–
(López-Rabuñal et al., 2020)	–	–	–	✓	✓	–	–
(Prego-Meleiro et al., 2017)	–	–	✓	–	–	–	–
(Bavlov-ič-Piskáčková et al., 2026)	✓	–	–	–	–	✓	–

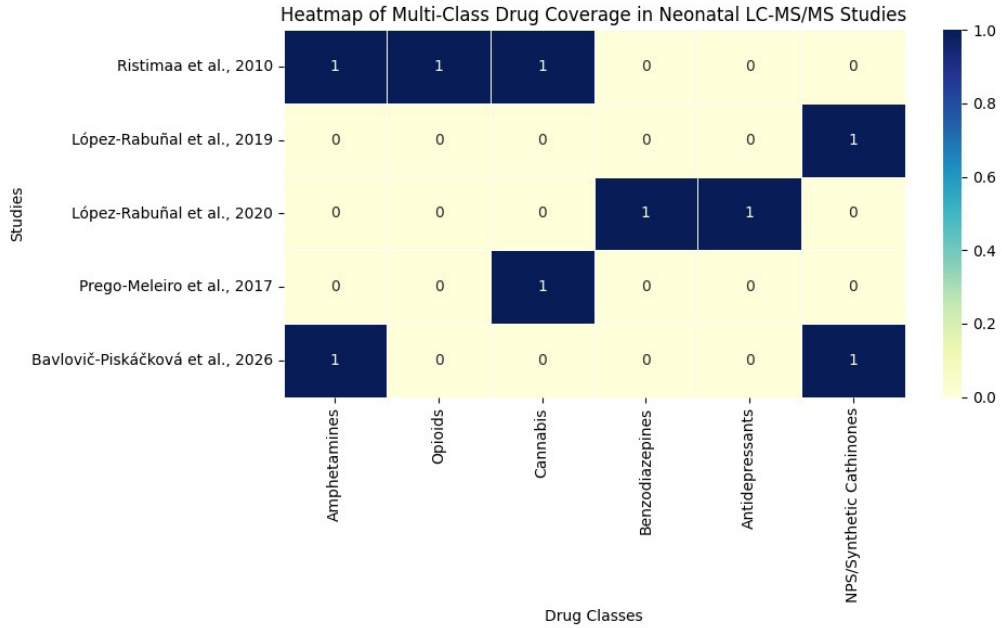

Figure 4. Heat map of multi-class drug coverage in included LC-MS/MS studies. Each row is from a different study, and each column is a different class of drugs (Amphetamines, Opioids, Cannabis, Benzodiazepines, Antidepressants, NPS/Synthetic Cathinones). The cells are shaded to show whether the drug class was present in the study panel (dark) or not (light).

Table 5: Emerging / Novel Techniques

Author & Year	Matrix	Technique / Improvement	Notes
(Bavlovič-Piskáčková et al., 2026)	Meconium	Electromembrane extraction + UHPLC-MS/MS	50 mg sample; LOQ 2 ng/g; green chemistry; high reproducibility
(Haglock-Adler et al., 2016)	Umbilical cord	LC-MS/MS single injection dual mode	55% faster; maintained specificity; 514 samples
(López-Rabuñal et al., 2021)	Meconium	UHPLC-QTOF	137 NPS and drugs; semi-quantitative; 30 specimens

Table 6: Key Gaps and Future Directions

Author & Year	Gap Identified	Matrix / Drug Class	Suggested Future Direction
(Pandya et al., 2023)	UC less sensitive for some analytes	UC vs Meconium	Improve UC sensitivity; standardize cutoffs
(Colby et al., 2019)	Discordance in detection	UC vs Meconium	Standardize matrices & panels
(Bavlovič-Piskáčková et al., 2026)	Limited multi-class validation	Meconium	Expand validation to broader panels; automation
(Brown et al., 2024)	Urine vs Meconium differences for minor analytes	Urine / Meconium	Confirm equivalence in larger cohorts

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To sum up, meconium continues to be the most sensitive and widespread matrix for drug exposure screening in neonates, LC-MS/MS panels are becoming available to screen for multiple drug classes, and new analytical methods are making screening more rapid and reproducible. Nonetheless, variability of analytical approaches and panel coverage points to the need for standardized, validated multi-class LC-MS/MS approaches for clinical and public health use.

Discussion

This systematic review is designed to critically evaluate twenty studies employing LC-MS/MS-based techniques for the detection of prenatal drug exposure in neonates. The overall synthesis indicates that the meconium is the most sensitive and is the most broadly used matrix, and has an exposure window even longer than umbilical cord tissue or neonatal urine. Meconium was always positive for opioids, amphetamines and cannabinoids, as these three classes of drugs were known to be present in meconium across the studies included (Colby et al., 2019; Pandya et al., 2023; Ristimaa et al., 2010). This aligns with the previous analytical toxicology literature in which the use of meconium in retrospective exposure analysis was pointed out as valid (López-Rabuñal et al., 2020; Prego-Meleiro et al., 2017).

Umbilical cord tissue has logistical benefits, since it is readily retrievable from a birth and can be collected without any disturbance, but some studies have found a slightly lower sensitivity when analyzing certain drug types, such as opioids and THC metabolites (Jensen et al., 2019; Palmer et al., 2017). The differences could be due to matrix-specific incorporation and metabolic factors, reinforcing the need for matrix validation prior to using cord tissue as a substitute for meconium for clinical and/or forensic purposes. Notably, some studies found they could detect the same select analytes in both matrices, indicating that cord tissue could be used when meconium collection is not completed, as an alternative (Brown et al., 2024; Colby et al., 2019).

There were large variations between studies in analytical validation parameters. The limits of detection and limits of quantification also had a wide range from 0.2 ng/g to 50 ng/g (LOD), and 0.6 ng/g to 2,000 ng/g (LOQ) (Jones et al., 2009; Scroggin & McMillin, 2018). This variability is due to the differences in instrumentation, sample preparation and method optimization in different laboratories. The scope of the multi-class panels also differed significantly, from focusing on a single drug class to wider panels that contained more than 130 analytes covering synthetic cathinones, opioids, cannabinoids, and benzodiazepines (Bavlovič-Piskáčková et al., 2026; López-Rabuñal et al., 2019). At the same time, greater panel width became a desire and the need for identification of additional substances in the neonatal population grew, with sensitivity and specificity of assays maintained over time.

New analytical platforms such as UHPLC-QTOF, dual-mode LC-MS/MS and electromembrane extraction improved throughput, reduced sample size, and enhanced the reproducibility (Haglock-Adler et al., 2016; López-Rabuñal et al., 2021). The innovations suggest the potential for increased resolution and automated platforms for routine neonatal screening and forensic toxicology. Nevertheless, there are methodological issues, such as sample preparation, extraction efficiency, and chromatography, that make it difficult to achieve comparability and interpretation of quantitative results across studies.

While much progress has been achieved, there are still some areas that require attention. Results are not easily comparable across studies because there is no standardization of analytical procedures, unreliability of reporting of validation results and inconsistencies of multi-class panel coverage. Some examples include the limited number of matrices reported in previous studies and the absence of reporting on matrix effects for emerging drug classes, or a more recent publication, which details the method validation, but sometimes reports only a few matrices (López-Rabuñal et al., 2020). Such differences highlight the importance of harmonized protocols, standardized thresholds, and comprehensive validation procedures to enhance the accuracy and consistency of detection and between-study reproducibility.

Overall, the data show that LC-MS/MS is a sensitive, specific, and flexible screening tool for neonatal drug exposures. The specimen of choice for retrospective detection is meconium, and the umbilical cord has some practical collection advantages. New analytical tools are enhancing the field of testing, as are multi-class panels, but until these are standardized and fully validated, they may not be interpreted or used uniformly in the clinic. The observations highlight the need for continued innovation, inter-laboratory cooperation, and the development of common analytical approaches to improve the practice of neonatal toxicology medicine.

Limitations

The findings of this systematic review are limited and should be considered within the scope of the following limitations. The studies evaluated were extremely diverse in their methodology, including LC-MS/MS instrumentation, sample processing technique, and validation parameters (LOD, LOQ, precision, and accuracy). The variability limited quantitative comparisons of studies and necessitated a narrative synthesis approach. Moreover, sample size ranged widely between the small group involved in method development and the large population-based studies, which could affect the extent to which the results can be generalized and how reliable the comparisons are. Differences in detection rates were also found between matrix; the detection rates of umbilical cord tissue and urine for some analytes were variable, whereas those of meconium were consistently higher, due to differences in the incorporation of the drug into the tissues. Finally, the comparability was hampered by non-standardized reporting of multi-class panel coverage and analytical validation in laboratories, and this underscores the need for harmonized protocols for neonatal LC-MS/MS studies.

Future Recommendations

Several recommendations can be proposed based on the critical synthesis of the studies included. From the critical synthesis of the studies included, several recommendations can be proposed for the progress of neonatal LC-MS/MS screening. First, it is necessary to have a standardized protocol for validation and reporting to allow for reproducibility and inter-laboratory comparability. Analytical rigor will be enhanced if LOD, LOQ, linearity, precision and accuracy are reported for each matrix of interest consistently. Second, it is required to have prospective studies that directly compare several neonatal matrices on the same analytical conditions to define the matrix-specific performance characteristics and optimize selection for clinical and forensic applications. Third, the addition of emerging psychoactive substances, synthetic opioids and clinically relevant metabolites to multi-class panels will increase detection breadth and will reflect current trends in the use of substances. Fourth, automation and high throughput, such as UHPLC-QTOF or dual mode LC-MS/MS, can improve the efficiency, reduce variation and support clinical routine applications. Finally, future research should aim to establish correlations between analytical findings and neonatal clinical outcomes to reinforce the clinical translation-relevance of screening with LC-MS/MS and to assist clinical decision making.

Conclusion

This systematic review demonstrates the potential of LC-MS/MS as a powerful and sensitive analytical tool for the detection of drugs in the fetal period. Meconium is the most sensitive matrix for retrospective exposure assessment, and umbilical cord tissue is an attractive matrix for sampling immediately after delivery. The evolution of multi-class LC-MS/MS panels over the years has increased the ability to detect a broad range of substances, including emerging drugs of abuse. Despite these, methodological variation, issues with reporting validation, and variations in panel coverage are significant hurdles to comparability between studies and to the transfer of findings to the clinical setting. The development and validation of procedures, multi-class panels, and high-throughput analytical workflows will be significant for advancing neonatal toxicology, improving confidence in drug exposure detection, and providing early detection of in utero drug exposure.

Declarations

Ethics Approval and Consent to Participate: This systematic review does not involve direct participation of human subjects or primary data collection. Ethical approval was not required for this review. All included studies have been conducted in accordance with ethical standards and guidelines of their respective institutions.

Consent for Publication: As this review involves secondary data analysis, consent for publication was not required. All authors have consented to the publication of this review.

Availability of Data and Material: The data supporting the findings of this review are included in the articles retrieved and cited within the review. Further details on specific datasets are available from the original studies upon request.

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