

Review of Scavenged Sampling for Sustainable Therapeutic Drug Monitoring: Do More With Less

Stef Schouwenburg, PharmD,* Robin F. J. van der Klip, MSc,* Tim J. L. Smeets, PharmD,*
Nicole G. M. Hunfeld, PhD,*† Robert B. Flint, PhD,*‡ Matthijs de Hoog, PhD,§ Henrik Endeman, PhD,†
Birgit C. P. Koch, PhD,* Enno D. Wildschut, PhD,§ and Alan Abdulla, PharmD*§

Purpose: Innovative and sustainable sampling strategies for bioanalytical quantification of drugs and metabolites have gained considerable interest. Scavenging can be stratified as a sustainable sampling strategy using residual material because it aligns with the green principles of waste reduction and sampling optimization. Scavenged sampling includes all biological fluids' (eg, blood, liquor, and urine) leftover from standard clinical care. This review elaborates on the past and current landscape of sustainable sampling within therapeutic drug monitoring, with a focus on scavenged sampling.

Methods: In February 2021, 4 databases were searched to assess the literature on the clinical use of innovative and sustainable sampling techniques without applying publication date restrictions. Studies reporting the clinical use of scavenged blood sampling and bridging studies of scavenged sampling and normal blood sampling were eligible for inclusion.

Results: Overall, 19 eligible studies concerning scavenged sampling were identified from 1441 records. Scavenged sampling is mainly applied in the pediatric population, although other patient groups may benefit from this strategy. The infrastructure required for scavenged sampling encounters several challenges, including logistic hurdles, storage and handling conditions, and documentation errors.

A workflow is proposed with identified opportunities that guide the implementation of scavenged sampling.

Conclusions: This review presents current evidence on the clinical use of scavenged sampling strategies. Scavenged sampling can be a suitable approach for drug quantification to improve dosage regimens, perform pharmacokinetic studies, and explore the value of therapeutic drug monitoring without additional sample collection.

Key Words: therapeutic drug monitoring, pediatrics, scavenged sampling, sustainable sampling, sampling strategies

(*Ther Drug Monit* 2022;44:215–223)

INTRODUCTION

Sample collection for therapeutic drug monitoring (TDM) is conventionally performed by venipuncture, which often involves a specific blood withdrawal for drug quantification purposes. Fortunately, given the global focus on sustainability, there is a growing shift from conventional blood collection to sustainable collection strategies. Accordingly, innovative and sustainable sampling strategies for the quantitative bioanalysis of drugs and metabolites have gained momentum.^{1–3} Sustainable sampling includes minimizing the total blood volume drawn and reducing material usage.

The current decade will see the dawn of “green” sustainable practice among hospital policy evolution.⁴ Several projects have attempted to reduce the carbon footprint and material spillage.⁵ Eventually, implementing sustainable techniques may lead to data set enrichment while applying patient-centric sampling and raising awareness among health care providers. Behavioral change and cross-sectional collaboration are the pillars of successful sustainable practice.⁶

Several sustainable sampling approaches have been introduced to reduce the number of samples or total volume of collected blood, which can be categorized into 3 main groups (Fig. 1): microsampling, sparse sampling, and scavenged sampling. First, microsampling embodies numerous techniques that require limited blood volumes (<50 μ L) to successfully quantify drug concentrations. The diverse microsampling techniques differ in the absorption matrix and/or method of analysis.⁷ The second approach is the use of sparse sampling, which aims to optimize sample collection. A small number of samples were collected from a large number of patients, which allows for flexibility in sampling times. Sparse sampling is extensively applied in pediatric population PK (popPK) studies because it corresponds with the ethical considerations regarding this

From the *Departments of Hospital Pharmacy and; †Adult Intensive Care, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands; ‡Department of Pediatrics, Division of Neonatology, Erasmus MC—Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, Netherlands; and §Department of Pediatric Intensive Care, Erasmus MC—Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, Netherlands.

Supported by the Erasmus University Medical Center Rotterdam, and no specific funding was received.

The authors declare no conflict of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.drug-monitoring.com).

Correspondence: Stef Schouwenburg, PharmD, Department of Hospital Pharmacy, Erasmus University Medical Center Rotterdam, P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands (e-mail: s.schouwenburg@erasmusmc.nl).

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

subpopulation.⁸ Finally, scavenged sampling involves the use of residual material of all biological fluids (eg, blood, liquor, urine, or saliva), which are leftover from the standard clinical practice.⁹ Importantly, scavenged sampling does not carry any extra burden or risks for the patient. It should be noted that in all 3 sustainable sampling approaches, the measurement of different components using a multianalyte assay involves additional advantages with respect to sustainability.

The objective of this review is to highlight the past and current landscape of the application of sustainable sampling within TDM, with a specific focus on scavenged sampling. We discuss the promising future of scavenged sampling methods, given their broad applicability, and provide a framework to stimulate sustainability. Furthermore, the authors elaborate on the prospects and broader implications of the scavenged sampling strategies.

METHODS

A literature search was conducted in February 2021, without restrictions on the publication date. Four databases were searched to assess reports on the clinical use of innovative and sustainable sampling techniques: Embase, MEDLINE All Ovid, Web of Science Core Collection, and Cochrane Central Register of Trials. Original research articles were eligible for inclusion when reporting the use of scavenged blood sampling and/or bridging studies designed to demonstrate the equivalence of scavenged sampling and scheduled blood sampling. The exclusion criteria were non-English articles, conference abstracts, letters to the editor, no full-text availability, animal studies, and in vitro studies. Validation of quantitative laboratory techniques and review articles was also excluded, but references in reviews were screened for relevant articles not identified by the search strategy. Then, articles from the databases were imported into a

reference manager (Endnote 20 X9®), and a previously described inclusion strategy was used.¹⁰ Titles and abstracts were screened independently by 2 reviewers (S.S. and R.K.). Disagreements were resolved by reaching a consensus. If the 2 assessors failed to reach a consensus, a third investigator (A.A.) was consulted. The following data were extracted from each included study: author, year of publication, type of study, study drugs, drug class, age category, number of samples and percentage of scavenged samples, main conclusions, and limitations.

SEARCH RESULTS AND SELECTION OF ARTICLES

Figure 2 presents a flowchart of the selection process for this review. The initial search resulted in 1441 records. Detailed research terms can be found in **Supplemental Digital Content 1** (see **Supplementary Material Table S1**, <http://links.lww.com/TDM/A529>). After eliminating duplicates and screening titles and abstracts, 23 articles were eligible for full-text assessment. Eventually, 19 of the 23 studies were included; 4 studies that did not meet the inclusion criteria were used to support the concept of scavenged sampling.^{8,9,11–31} Table 1 presents the characteristics of the 19 included studies. Table 2 presents the outcomes and limitations of included studies as described by the authors. Studies were reviewed in the chronological order of the year of publication, considering the evolving knowledge of scavenged sampling.

Application of Scavenged Sampling

Over the years, several studies have been conducted on the application of scavenged sampling, with reference to different drug classes (Table 1). New sustainable sampling strategies are of particular interest in pharmacokinetics and pharmacodynamic (PKPD) research and routine TDM. Most included articles (13 of 19) examined antibiotics. Other investigated drug classes were antimycotics, antivirals, antiarrhythmics, and opioid

SUSTAINABLE SAMPLING	DEFINITION	PROCEDURES	BIOLOGICAL MATRICES
Microsampling	A multitude of sampling techniques requiring limited blood volume	<ul style="list-style-type: none"> • Dried blood/plasma spot • Volumetric absorptive • Solid-phase microextraction • Capillary microsampling 	<ul style="list-style-type: none"> • Blood • Serum • Plasma • Saliva • Liquor • Urine
Sparse sampling	Collection of small number of samples from a large number of study participants	<ul style="list-style-type: none"> • Sample strategy optimization by reducing sampling 	
Scavenged sampling	The use of residual material from biological fluids left over from standard clinical care	<ul style="list-style-type: none"> • Clinical chemistry analysis • Microbiology tests • Point of care tests 	

FIGURE 1. Overview of sustainable drug monitoring methods.

TABLE 1. Characteristics of Included Studies Investigating Scavenged sampling

Author	Year	Objective	Drug	Drug Class	Age	Samples (% Scavenged)
Wade ¹⁴	2008	Development of a popPK model	Fluconazole	Antimycotic	PNA 16 (1–88) d	357 (39)
Cohen-Wolkowicz ⁹	2012	Development of a popPK model	Metronidazole	Antimycotic	GA <26: 53 (7–97); GA 26–29: 32 (0–97); GA 30–32: 33 (8–71) d	116 (90)
Cohen-Wolkowicz ¹⁵	2012	Development of a popPK model	Piperacillin	Antibiotic	PNA 17 (1–77) d	211 (96)
Zhao ¹⁶	2014	Development of a popPK model and evaluation of a dosing regimen	Ciprofloxacin	Antibiotic	PNA 27 (5–121) d	430 (38)
Leroux ¹⁷	2015	Comparison of 3 popPK models	Ciprofloxacin	Antibiotic	PNA 27 (5–121) d	430 (38)
Zhao ¹⁸	2015	Evaluation of a popPK model	Teicoplanin	Antibiotic	8.1 (0.5–16.9) yr	143 (14)
Germovsek ²¹	2016	Development and evaluation of a popPK model	Gentamicin	Antibiotic	PNA 6 (1–78) d	483 (53)
Leroux ¹⁹	2016	Development of a popPK model	Cefotaxime	Antibiotic	PNA 9.0 (0.0–69.0) d	185 (100)
Momper ²⁰	2016	Development of a popPK model and creation of a dosing regimen	Fluconazole	Antimycotic	PNA 23 (3–47) d	604 (61)
Chen ²³	2018	Evaluation of a dosing regimen with a popPK model and the penetration of cefotaxime in cerebrospinal fluid	Cefotaxime	Antibiotic	PNA 20 (3–88) d	97 (69)
Dallefeld ²²	2018	Development of a popPK model	Amiodarone	Antiarrhythmic	PNA 40.0 (20.0–171.0) d	315 (22)
Dong ²⁴	2018	Evaluation of a popPK model	Ganciclovir	Antiviral	PNA 20.0 (3.0–70.0) d	51 (100)
Hahn ²⁵	2019	Demonstration of the influence of genotype on the PK of morphine	Morphine (+genotyping)	Opioid	PNA 14 (1–212) d	85 (100)
Tang ²⁶	2019	Development of a popPK model and creation of a dosing regimen	Amoxicillin	Antibiotic	PNA 7.0 (1.0–37.0) d	224 (100)
Shi ³⁰	2020	Development of a popPK model and creation of a dosing regimen	Cefoperazone	Antibiotic	4.9 (2–10.8) yr	NA (99 pts) (100)
Tang-Girdwood ²⁹	2020	Demonstration of feasibility scavenged samples in a popPK model	Cefepime, meropenem, and piperacillin	Antibiotic	12.7 ± 8.3 (SD) yr	138 (100)
Wang ³¹	2020	Development of a popPK model and creation of a dosing regimen	Ceftriaxone	Antibiotic	0.94 (0.10–1.99) yr	169 (100)
Wu ²⁷	2020	Development of a popPK model and creation of a dosing regimen	Amoxicillin	Antibiotic	1.0 (0.09–2.0) yr	62
Zhao ²⁸	2020	Development of a popPK model and creation of a dosing regimen	Cefepime	Antibiotic	PNA 8 (1–25) d	100

agents. The first study reporting the use of scavenged sampling only applied the method to some of the samples. However, in more recent studies, the percentage of scavenged samples increased to 100% among all obtained study materials.

Scavenged sampling is mainly applied to infants and neonates (15 of 19). On the one hand, this may result from the new legislation regarding the permitted burden because

of sampling; by contrast, this could be attributed to the improved performance of assays that necessitate a smaller sample volume for quantification.³² Because the use of residual material reduces the required volume of biological fluids and an additional invasive procedure, this sustainable approach can also be of added value in other patient groups.

TABLE 2. Outcomes and Limitations of Included Studies Investigating Scavenged sampling

Author	Year	Drug	Outcomes	Limitations Identified by the Authors
Wade ¹⁴	2008	Fluconazole	Identical concentrations in PK samples are observed in scavenged samples	Minimal bias introduced and slight underestimation of concentrations.
Cohen-Wolkowicz ⁹	2012	Metronidazole	Lower concentrations of 30% (CI: 10%–42%) are observed with scavenged samples	Bias introduced and underestimation of concentrations. Higher variability because of higher documentation errors in relation to sampling or dosing times and storage and handling.
Cohen-Wolkowicz ¹⁵	2012	Piperacillin	Scavenged samples had a 2–10-fold lower concentration; therefore, it is not useful for unstable drugs without rigorous measurements.	Higher variability because of higher documentation errors in relation to sampling or dosing times and storage and handling.
Zhao ¹⁶	2014	Ciprofloxacin	A popPK model and a dosing regimen of ciprofloxacin is established with scavenged samples	No limitations regarding scavenging methods.
Leroux ¹⁷	2015	Ciprofloxacin	A popPK model and a dosing regimen is established with scavenged samples	Evaluation of density of sampling and drug stability.
Zhao ¹⁸	2015	Teicoplanin	A popPK model for teicoplanin is developed with scavenged samples	No limitations regarding scavenging methods.
Germovsek ²¹	2016	Gentamicin	With the use of mechanistic covariates, the predictions of gentamicin were unbiased	Effects of scavenging and time registration on sampling not evaluated.
Leroux ¹⁹	2016	Cefotaxime	A popPK model and a dosing regimen for cefotaxime is established with scavenged samples	Introduced under prediction of variability.
Momper ²⁰	2016	Fluconazole	PK parameter estimates were not biased, and visual predictive check demonstrated adequate concentrations with scavenged samples	No limitations regarding scavenging methods.
Chen ²³	2018	Cefotaxime	Studying antimicrobials in CSF is promising with scavenged samples	No limitations regarding scavenging methods.
Dallefeld ²²	2018	Amiodarone	Scavenged material is an efficient way to develop a popPK model	No limitations regarding scavenging methods.
Dong ²⁴	2018	Ganciclovir	Ganciclovir dosage individualization with scavenged samples is a suitable clinical method	No evaluation of scavenging was performed.
Hahn ²⁵	2019	Morphine (+genotyping)	The influence of genotyping on the PK of morphine is demonstrated with scavenged samples	No limitations regarding scavenging methods.
Tang ²⁶	2019	Amoxicillin	A dosing regimen for amoxicillin is established with scavenged samples	No limitations regarding scavenging methods.
Shi ³⁰	2020	Cefoperazone	A dosing regimen for cefoperazone is established with scavenged samples	No limitations regarding scavenging methods.
Tang-Girdwood ²⁹	2020	Cefepime, meropenem, and piperacillin	Scavenged sampling is feasible to examine the variability of drug concentrations for future drug monitoring	Potential for low residual blood volumes. Unknown effect of storage and handling on the stability of the quantified drug.
Wang ³¹	2020	Ceftriaxone	A dosing regimen for ceftriaxone is established with scavenged samples	No limitations regarding scavenging methods.
Wu ²⁷	2020	Amoxicillin	A dosing regimen for amoxicillin is established with scavenged samples	No limitations regarding scavenging methods.
Zhao ²⁸	2020	Cefepime	A dosing regimen for cefepime is established with scavenged samples	No limitations regarding scavenging methods.

CI, confidence interval; PK, pharmacokinetic. CSF, cerebrospinal fluid.

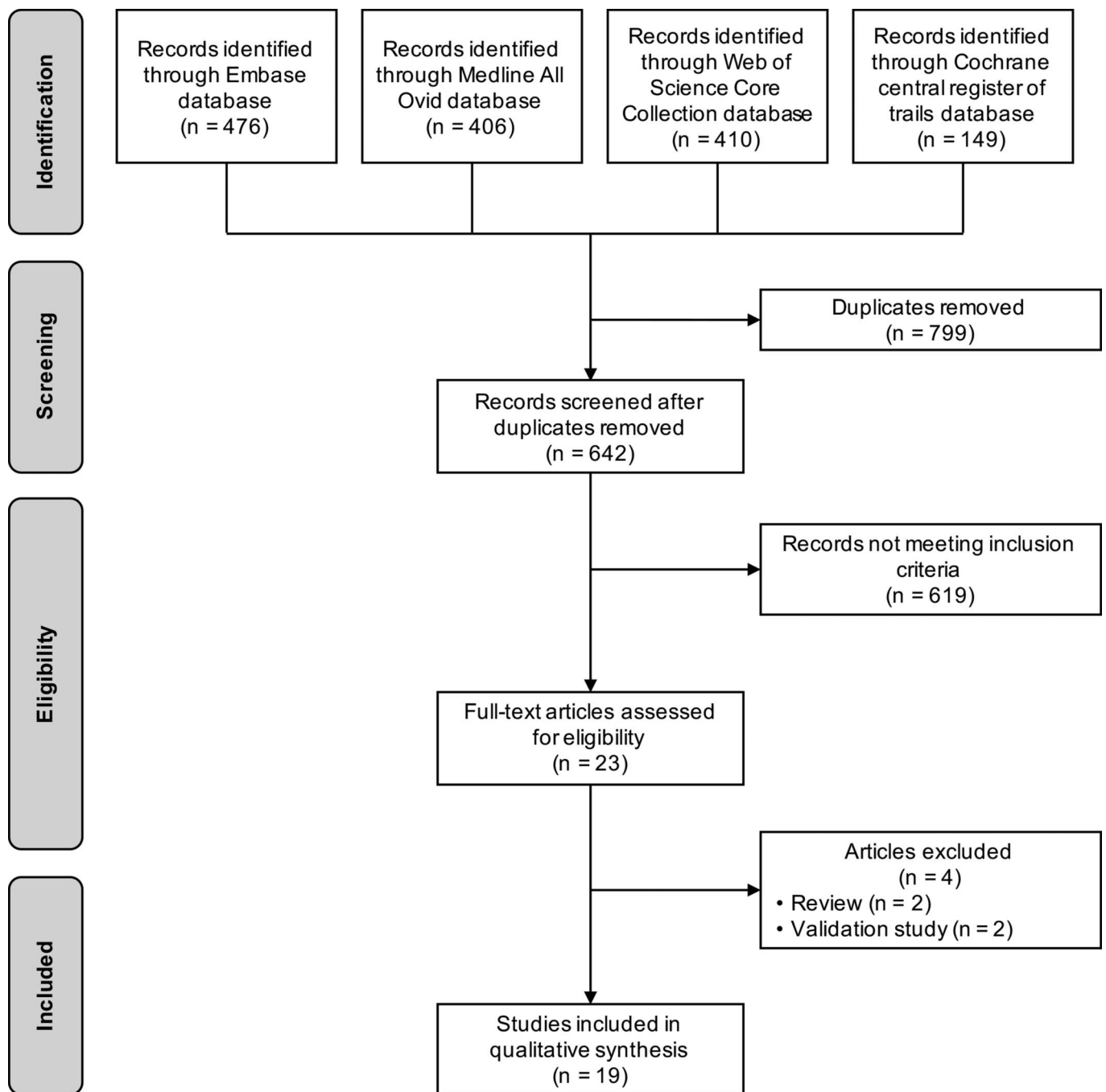


FIGURE 2. Flowchart of the selection process.

Several bridging studies have compared the statistical performance of using scavenged versus scheduled sampling. Scavenged sampling has proven to be an efficient strategy to collect data for developing popPK models. In addition, numerous studies have proposed adapted dosing regimens without any limitations regarding the scavenged sampling strategy.^{16,18,20–22} Moreover, some studies only used scavenged samples and concluded that the strategy was suitable for establishing popPK models.^{19,24–28,30,31}

Wade et al (2008) first mentioned scavenged sampling while developing a popPK model for fluconazole in young infants.¹⁴ Paired samples presented nearly identical concentrations when comparing plots for observed versus predicted concentrations. The investigators concluded that scavenged sampling introduced a minimal bias of 4% (95% confidence interval [CI] [–11%–2%]) and slightly underestimated the concentrations of fluconazole.¹⁴ Two studies by the same research group developed popPK models for metronidazole and piperacillin.^{9,15} Evaluation of the bias introduced in the

final popPK model by scavenged metronidazole samples demonstrated a 30% (95% CI: 10%–42%) underestimation of metronidazole concentrations. The authors concluded that scavenging is a viable sampling strategy to describe metronidazole PK parameters; however, a larger number of samples should be collected to precisely estimate the amount of bias introduced by scavenged samples. In addition, patients displayed a 2–10-fold lower piperacillin concentration in observed nonpaired scavenged samples when compared with previously conducted research, possibly because of scavenging.^{15,33,34} Leroux et al (2015) compared 3 different ciprofloxacin popPK models based on their sampling strategy, either based on scavenged samples leftover from routine biochemical testing, scheduled samples, or on a mix of both sample types.¹⁷ Clinical applicability of scavenged sampling was confirmed because the results demonstrated similar predictive performance between models.¹⁷

Clinical Accessibility of Scavenged Sampling

For most hospitalized patients, an abundance of biological material is retrieved through the standard of care, leaving the residual material unused. To successfully implement and accept scavenged sampling, we propose a workflow that illustrates the relevant phases (Fig. 3). First, the applicability of the strategy in specific research or clinical settings has to be determined. Multiple populations (eg, children, elderly, pregnant, and critically ill) may benefit from scavenged sampling. However, limited data are available regarding the application of this strategy in the adult population. Irie et al (2021) performed a PK study of favipiravir in patients with coronavirus disease 2019 (COVID-19) using stored residual serum samples from routine clinical practice.³⁵ Furthermore, various blood compounds of interest (drug, biomarker, and genetic material) may benefit from the scavenging strategy. Moreover, biomarker-guided strategies are of growing interest because of personalized treatment optimization for efficacy, toxicity, and antibiotic resistance risk.³⁶ For

the additional quantification of compounds of interest, scavenged sampling induces no additional burden on the patient.

Second, method validation is essential for the legitimate application of quantification techniques. This process starts with microsampling assay development, if not yet available. Head-to-head method comparison studies are required to validate the technique by comparing samples obtained by scavenging with the standard of care. Publication of information through open science principles may provide the foundation for the broader implementation of scavenged sampling by other research groups.

The third phase concerns the practical realization of scavenged sampling. The logistics operation required for the implementation of this strategy must overcome several challenges. First, it is crucial to identify possible barriers and hurdles by auditing current and future processes. Second, through educational meetings and presentations, personnel can be trained to assimilate the importance of the strategy and procedures required to gather the residual material. Third, clinical visibility and accessibility are important for implementing scavenged sampling in practice. Essentially, all 3 phases (applicability, validation, and realization) should facilitate a sustainable mindset in clinical care and research for patient burden, the way blood samples are obtained, and the sustainable handling of materials.

GAP ANALYSIS

The workflow of scavenged sampling can be divided into 4 main steps: sampling, registration, storage, and analysis of the sample material. Figure 4 shows an infrastructural workflow for scavenged sampling with key benefits, pitfalls, and opportunities indicated at different steps. In addition to the benefits of scavenged sampling, several challenges arise when using this strategy, as illustrated by the limitations addressed in the included reports (Table 2). Multiple studies have reported errors in the estimation of drug concentrations in scavenged samples.^{9,4,15} This is most likely because of the

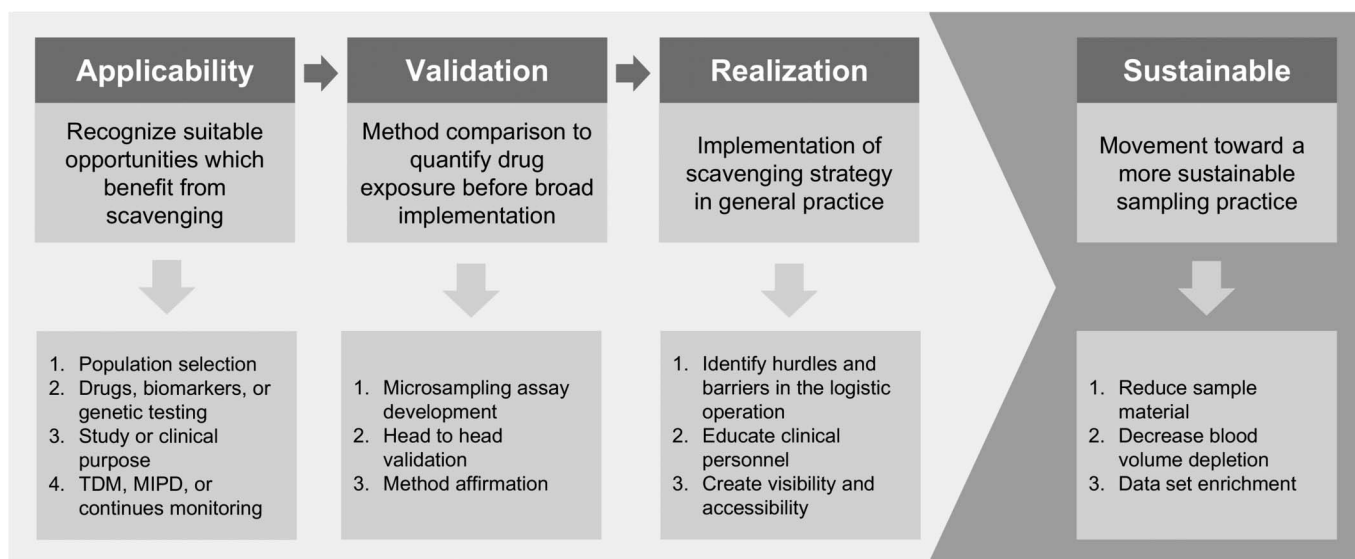


FIGURE 3. Schematic framework for implementation of innovative scavenged sampling strategy.

higher incidence of documentation errors of sampling and dosing times, improper storage and handling conditions before laboratory procedures, and model misspecifications. Model misspecifications emerge owing to the incorporation of biased coefficients and biased parameter estimations. In addition, it is important to consider the preanalytical stability of certain drugs because specific measures may be required during storage and handling procedures.¹⁵ Multiple freeze–thaw cycles owing to handling procedures may compromise the compound integrity because of sample degradation and/or precipitation.³⁷ Most studies do not elaborate logistic procedures for scavenged sampling (eg, materials and validation). Greater transparency and a detailed definition of handling would improve the infrastructure for the scavenged sampling approach.

Traditionally, blood is collected in various sampling tubes, such as ethylenediaminetetraacetic acid (EDTA) tubes and heparinized tubes.^{9,14,15,29} Heparin is known to form complexes with specific drugs and may complicate adequate drug quantification. In addition, Tang-Girdwood et al demonstrated a broad distribution of antibiotic-free concentrations, particularly toward the end of the dosing intervals.²⁹ However, the authors indicate that there are possibly multiple factors contributing to the wide variability in free concentrations, including pathophysiological changes because of critical illness and variable protein binding, as well as patient factors.

Quantification of the unbound drug concentration illustrates another challenge for drugs with a relatively high plasma protein–bound fraction. Quantifying free (unbound) drug concentrations demands a greater blood volume, potentially complicating the use of scavenged sampling. Tang-Girdwood et al reported a 10% occurrence of a low sample blood volume for quantifying the concentration of beta-lactam antibiotics.²⁹ Typically, scavenged sample preparation

requires sample dilution to ensure sufficient volume for quantification, thus elevating the lower limit of quantification with a consequent increase in measurement error. Quantitative techniques and materials (ie, syringes and containers) urgently need a further decrease in the volume required for the successful measurement of drugs and metabolites. Improved sampling techniques, assays, tube types, and priming substances will lead to a reduction in infrastructural pitfalls such as transportation, cooling requirements, material deposition, and the accompanying reduction in costs and footprint.³⁸

Compared with adults, blood sampling in pediatric patients is more challenging because of the increased impact of blood draws on volume depletion and the invasive burden. Pediatric blood sampling in clinical studies should not exceed 3% of the total blood volume during a 4-week period and should not exceed 1% at any single time.³⁹ Moreover, the actual physical condition of the child (sleep/activity, severity of anemia, and hemodynamic state) should permit blood sampling. Nevertheless, the rapid maturation and ontogeny of the smallest infants can only be described in a popPK model if sufficient concentrations have been incorporated, which generally requires more samples than in older infants or adults. Scavenged sampling techniques partially solve the previously mentioned obstacles in pediatric PKPD research and routine TDM because it makes the optimal use of all residual materials obtained through the standard of care. One opportunity for scavenged sampling lies in applying this strategy in other subpopulations, as mentioned previously.

By contrast, there are circumstances in which scavenged sampling is less applicable. First, the number of scavenged samples must be sufficiently large to account for the additional variability related to the scavenged sampling in the data set; this especially applies to dispersed scavenged time points added to an existing data set from the scheduled

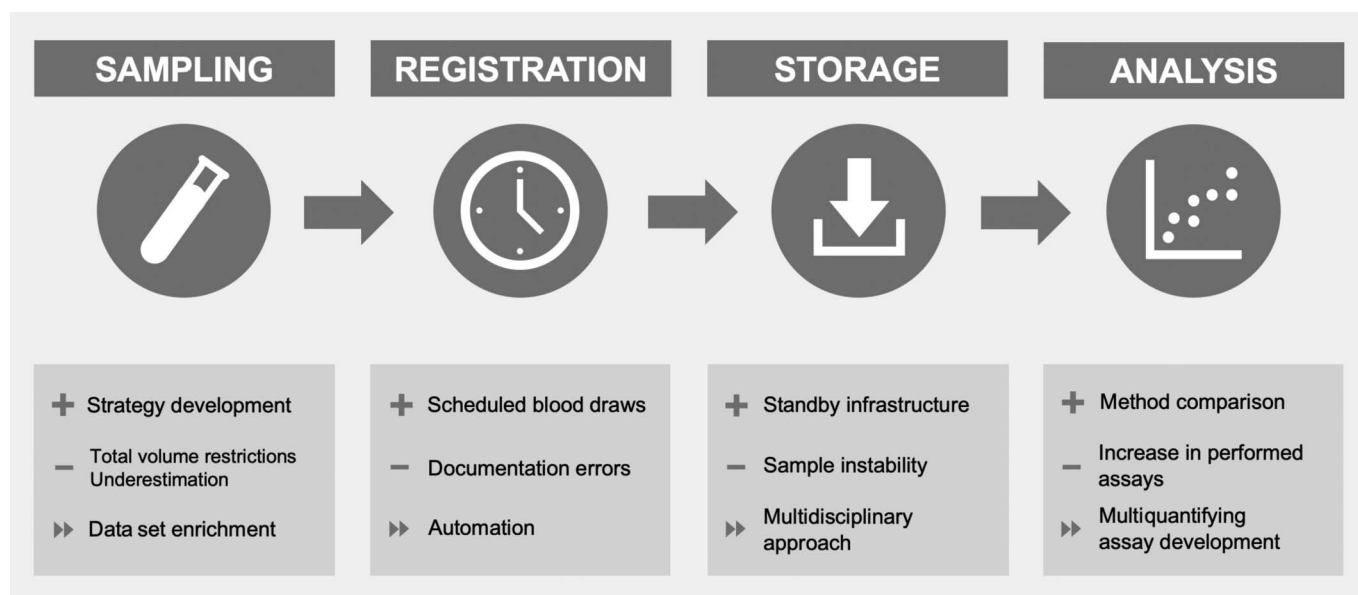


FIGURE 4. Infrastructural workflow for scavenged sampling with key benefits (+), pitfalls (-), and opportunities (>>) indicated at different steps.

sampling strategy. Second, the administrative and infrastructural procedures to record sampling times and ensure adequate sample handling need to be reliable; otherwise, the data cannot be used. Finally, drug stability plays a role when considering scavenging. Drug precipitation and degradation may occur if storage conditions are inadequate.

OUTLOOK

Scavenged sampling is a promising sustainable sampling strategy that may have considerable implications for routine TDM and PKPD research, as well as for monitoring other biomarkers. This strategy has the potential to broaden its scope further, bearing in mind that the technique can be used for all drug measurements using all types of residual material. In addition to scavenging blood samples to determine drug concentrations, alternative materials can be scavenged, including urine, saliva, mucous tissue, and liquor. This would enable the search for noninvasive or less-invasive sample collections for TDM by quantifying paired samples collected from different biological fluids from the same patient at the same time point. Interestingly, a recent study has explored the use of saliva for TDM by using popPK, which resulted in observations comparable with plasma TDM.⁴⁰ This might even enable continuous measurement of biomarkers or drugs with minimal burden. In principle, tissue biopsies can be used as a scavenged material to determine drug concentrations in tissues. However, this application is beyond the scope of scavenged sampling because these types of samples are unsuitable for routine drug monitoring.

In addition to TDM testing, scavenged sampling could be used for other bioanalytical methods. For example, pharmacogenomic information for patient characteristic identification is valuable for personalized treatment regimens, particularly in oncology. However, the routine use of pharmacogenomic biomarkers in clinical practice in other therapeutic areas is currently sparse.⁴¹ For example, the influence of genetic variation (OCT1 ontogeny) on morphine clearance has been investigated using scavenging strategies.²⁵ Both drug level measurement and genetic testing were estimated in scavenged samples to avoid the additional patient burden.

The broad collection of residual material might contribute to the evolution of “real-time” monitoring of small molecules in clinical practice. Molecular measurements can provide a perspective of the patients’ current health status (eg, liver/kidney function) and aid in TDM.⁴² Through scavenged sampling in patient populations that require multiple blood withdrawals per day, delayed real-time monitoring is possible through swift analysis of samples, thus providing 24/7 continuous monitoring of drug exposure. Moreover, this approach with enriched data enables a more detailed description of each biomarker pattern in relation to disease progression, age, circadian rhythm, and organ function. Consequently, this enhances the search for improved predictive biomarkers for patient conditions. In infectious diseases, biomarker monitoring is preferred because it provides information on the onset of infection, and it may enable the evaluation of response to treatment using advanced prediction

222

models.⁴³ Based on the timing and progression, procalcitonin-guided antibiotic therapy could be used to de-escalate antibiotic treatment in patients with sepsis and those at high risk for severe bacterial sepsis or septic shock.⁴⁴ Recently, Santa Cruz et al (2021) established a model in which interleukin-6 was a greater predictor for developing fatal acute respiratory syndrome coronavirus 2 pneumonia than age and C-reactive protein.⁴⁵ In addition, Kurul et al reported that serum interleukin-6 and procalcitonin levels at the time point of suspected late-onset neonatal sepsis offer valuable information regarding sepsis severity and mortality risk in infants born below 32 weeks of gestation, and these were superior to C-reactive protein.⁴⁶ Biomarkers have the potential to more precisely and rationally guide individual dose adjustments when included in the model-informed precision dosing framework.⁴⁷

To stimulate samples that allow multidisciplinary interchange, the centralization of biochemical laboratories in hospitals would be the next rational step. Assays should be developed to simultaneously quantify predefined combinations of different compounds (drugs, biomarkers, and metabolites) during the same run. Automation of sample registration and processing that connects diagnostic specialties improves efficiency, organization, standardization, quality, and safety of laboratory testing.⁴⁸ However, higher costs, space requirements, and procedural hurdles warrant precise assessment before transition.

Finally, scavenged sampling reportedly reduces the total obtained blood volume and the number of scheduled sample draws from patients. Although scavenged sampling is only applied in pediatric patients, multiple subpopulations may benefit from this strategy. The included studies demonstrated that scavenged sampling is a suitable and unique strategy for TDM while considering infrastructural requirements. Given the burden and wasteful consequences of the presently used TDM process and PKPD research, sustainable sampling strategies are a promising approach to introduce a green mindset in research and clinical practice. Sample scavenging can be introduced in countless settings to do more with less.

ACKNOWLEDGMENTS

The authors wish to thank Dr Wichor M. Bramer from the Erasmus MC Medical Library for the help in developing the search strategies.

REFERENCES

- Balevic SJ, Cohen-Wolkowicz M. Innovative study designs optimizing clinical pharmacology research in infants and children. *J Clin Pharmacol*. 2018;58:S58–S72.
- O’Hara K, Martin JH, Schneider JJ. *Barriers and Challenges in Performing Pharmacokinetic Studies to Inform Dosing in the Neonatal Population*. Basel: Pharmacy; 2020;8.
- Le J, Bradley JS. Optimizing antibiotic drug therapy in pediatrics: current state and future needs. *J Clin Pharmacol*. 2018;58(suppl 10):S108–S122.
- Hensher M, McGain F. Health care sustainability metrics: building a safer, low-carbon health system. *Health Aff (Millwood)*. 2020;39:2080–2087.
- Kleber J, Cohen B. Reducing waste and increasing sustainability in health care settings. *Am J Nurs*. 2020;120:45–48.

6. Evans D, McMeekin A, Southerton D. Sustainable consumption, behaviour change policies and theories of practice. *COLLeGIUM: Stud Across Disciplines Humanities Soc Sci.* 2012;12:12.
7. Parker SL, Dorofaeff T, Lipman J, et al. Is there a role for microsampling in antibiotic pharmacokinetic studies? *Rev Expert Opin Drug Metab Toxicol.* 2016;12:601–614.
8. Autmizguine J, Benjamin DK, Smith PB, et al. Pharmacokinetic studies in infants using minimal-risk study designs. *Curr Clin Pharmacol.* 2014; 9:350–358.
9. Cohen-Wolkowicz M, Ouellet D, Smith PB, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. *Antimicrob Agents Chemother.* 2012;56:1828–1837.
10. Bramer WM, Milic J, Mast F. Reviewing retrieved references for inclusion in systematic reviews using EndNote. *J Med Libr Assoc.* 2017;105: 84–87.
11. Kipper K, Barker CIS, Standing JF, et al. Development of a novel multi-penicillin assay and assessment of the impact of analyte degradation: lessons for scavenged sampling in antimicrobial pharmacokinetic study design. *Antimicrob Agents Chemother.* 2018;62:e01540–17.
12. Saito J, Tanzawa A, Kojo Y, et al. A sensitive method for analyzing fluconazole in extremely small volumes of neonatal serum. *J Pharm Health Care Sci.* 2020;6:14.
13. Laughon MM, Benjamin DK Jr, Capparelli EV, et al. Innovative clinical trial design for pediatric therapeutics. *Expert Rev Clin Pharmacol.* 2011; 4:643–652.
14. Wade KC, Wu D, Kaufman DA, et al. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother.* 2008;52: 4043–4049.
15. Cohen-Wolkowicz M, Benjamin DK Jr, Ross A, et al. Population pharmacokinetics of piperacillin using scavenged samples from preterm infants. *Ther Drug Monit.* 2012;34:312–319.
16. Zhao W, Hill H, Le Guellec C, et al. Population pharmacokinetics of ciprofloxacin in neonates and young infants less than three months of age. *Antimicrob Agents Chemother.* 2014;58:6572–6580.
17. Leroux S, Turner MA, Guellec CB, et al. Pharmacokinetic studies in neonates: the utility of an opportunistic sampling design. *Clin Pharmacokinet.* 2015;54:1273–1285.
18. Zhao W, Zhang D, Storme T, et al. Population pharmacokinetics and dosing optimization of teicoplanin in children with malignant haematological disease. *Br J Clin Pharmacol.* 2015;80:1197–1207.
19. Leroux S, Roué JM, Gouyon JB, et al. A population and developmental pharmacokinetic analysis to evaluate and optimize cefotaxime dosing regimen in neonates and young infants. *Antimicrob Agents Chemother.* 2016;60:6626–6634.
20. Momper JD, Capparelli EV, Wade KC, et al. Population pharmacokinetics of fluconazole in premature infants with birth weights less than 750 grams. *Antimicrob Agents Chemother.* 2016;60:5539–5545.
21. Germovsek E, Kent A, Metsvaht T, et al. Development and evaluation of a gentamicin pharmacokinetic model that facilitates opportunistic gentamicin therapeutic drug monitoring in neonates and infants. *Antimicrob Agents Chemother.* 2016;60:4869–4877.
22. Dallefeld SH, Atz AM, Yogeve R, et al. A pharmacokinetic model for amiodarone in infants developed from an opportunistic sampling trial and published literature data. *J Pharmacokinet Pharmacodyn.* 2018;45:419–430.
23. Chen XK, Shi HY, Leroux S, et al. Penetration of cefotaxime into cerebrospinal fluid in neonates and young infants. *Antimicrob Agents Chemother.* 2018;62:e02448–17.
24. Dong Q, Leroux S, Shi HY, et al. Pilot study of model-based dosage individualization of ganciclovir in neonates and young infants with congenital cytomegalovirus infection. *Antimicrob Agents Chemother.* 2018; 62:e00075–18.
25. Hahn D, Emoto C, Euteneuer JC, et al. Influence of OCT1 ontogeny and genetic variation on morphine disposition in critically ill neonates: lessons from PBPK modeling and clinical study. *Clin Pharmacol Ther.* 2019;105:761–768.
26. Tang BH, Wu YE, Kou C, et al. Population pharmacokinetics and dosing optimization of amoxicillin in neonates and young infants. *Antimicrob Agents Chemother.* 2019;63:e02336–18.
27. Wu YE, Wang YK, Tang BH, et al. Population pharmacokinetics and dosing optimization of amoxicillin in chinese infants. *J Clin Pharmacol.* 2020;61(S1):S141–S151.
28. Zhao Y, Yao BF, Kou C, et al. Developmental population pharmacokinetics and dosing optimization of cefepime in neonates and young infants. *Front Pharmacol.* 2020;11:14.
29. Tang Girdwood SC, Tang PH, Murphy ME, et al. Demonstrating feasibility of an opportunistic sampling approach for pharmacokinetic studies of β -lactam antibiotics in critically ill children. *J Clin Pharmacol.* 2021; 61:538–546.
30. Shi HY, Wang K, Wang RH, et al. Developmental population pharmacokinetics-pharmacodynamics and dosing optimization of cefoperazone in children. *J Antimicrob Chemother.* 2020;75:1917–1924.
31. Wang YK, Wu YE, Li X, et al. Optimal dosing of ceftriaxone in infants based on a developmental population pharmacokinetic-pharmacodynamic analysis. *Antimicrob Agents Chemother.* 2020;64: e01412–20.
32. ICH Harmonised Guideline. Bioanalytical method validation M10. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-m10-bioanalytical-method-validation-step-2b_en.pdf. Accessed June 15, 2021.
33. Reed MD, Goldfarb J, Yamashita TS, et al. Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother.* 1994;38:2817–2826.
34. Kacet N, Roussel-Delvallez M, Gremillet C, et al. Pharmacokinetic study of piperacillin in newborns relating to gestational and postnatal age. *Pediatr Infect Dis J.* 1992;11:365–369.
35. Irie K, Nakagawa A, Fujita H, et al. Population pharmacokinetics of favipiravir in patients with COVID-19. *CPT pharmacometrics syst pharmacol.* 2021;10:1161–1170.
36. Aulin LBS, de Lange DW, Saleh MAA, et al. Biomarker-guided individualization of antibiotic therapy. *Clin Pharmacol Ther.* 2021;110:346–360.
37. Kozikowski BA, Burt TM, Tirey DA, et al. The effect of freeze/thaw cycles on the stability of compounds in DMSO. *J Biomol Screen.* 2003;8: 210–215.
38. Hobson P, Badrick T. The impact on costs and efficiency of reducing the number of collected tubes. *Clin Chem Lab Med.* 2013;51:e53–4.
39. Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-medical-products-term-preterm-neonate-first-version_en.pdf. Accessed June 10, 2021.
40. Kruizinga MD, Stuurman FE, Driessen GJA, et al. Theoretical performance of nonlinear mixed-effect models incorporating saliva as an alternative sampling matrix for therapeutic drug monitoring in pediatrics: a simulation study. *Ther Drug Monit.* 2021;43:546–554.
41. Lauschke VM, Milani L, Ingelman-Sundberg M. Pharmacogenomic biomarkers for improved drug therapy—recent progress and future developments. *AAPS J.* 2017;20:4.
42. Arroyo-Currás N, Somerson J, Vieira PA, et al. Real-time measurement of small molecules directly in awake, ambulatory animals. *Proc Natl Acad Sci U S A.* 2017;114:645–650.
43. Thorsted A, Nielsen EI, Friberg LE. Pharmacodynamics of immune response biomarkers of interest for evaluation of treatment effects in bacterial infections. *Int J Antimicrob Agents.* 2020;106059:56.
44. Samsudin I, Vasikaran SD. Clinical utility and measurement of procalcitonin. *Clin Biochem Rev.* 2017;38:59–68.
45. Santa Cruz A, Mendes-Frias A, Oliveira AI, et al. Interleukin-6 is a biomarker for the development of fatal severe acute respiratory syndrome coronavirus 2 pneumonia. *Front Immunol.* 2021;12:613422.
46. Kurul Ş, Simons SHP, Ramakers CRB, et al. Association of inflammatory biomarkers with subsequent clinical course in suspected late onset sepsis in preterm neonates. *Crit Care.* 2021;25:12.
47. Wicha SG, Mårtson AG, Nielsen EI, et al. From therapeutic drug monitoring to model-informed precision dosing for antibiotics. *Clin Pharmacol Ther.* 2021;109:928–941.
48. Giuseppe L, Giorgio Da R. Advantages and limitations of total laboratory automation: a personal overview. *Clin Chem Lab Med.* 2019;57:802–811.