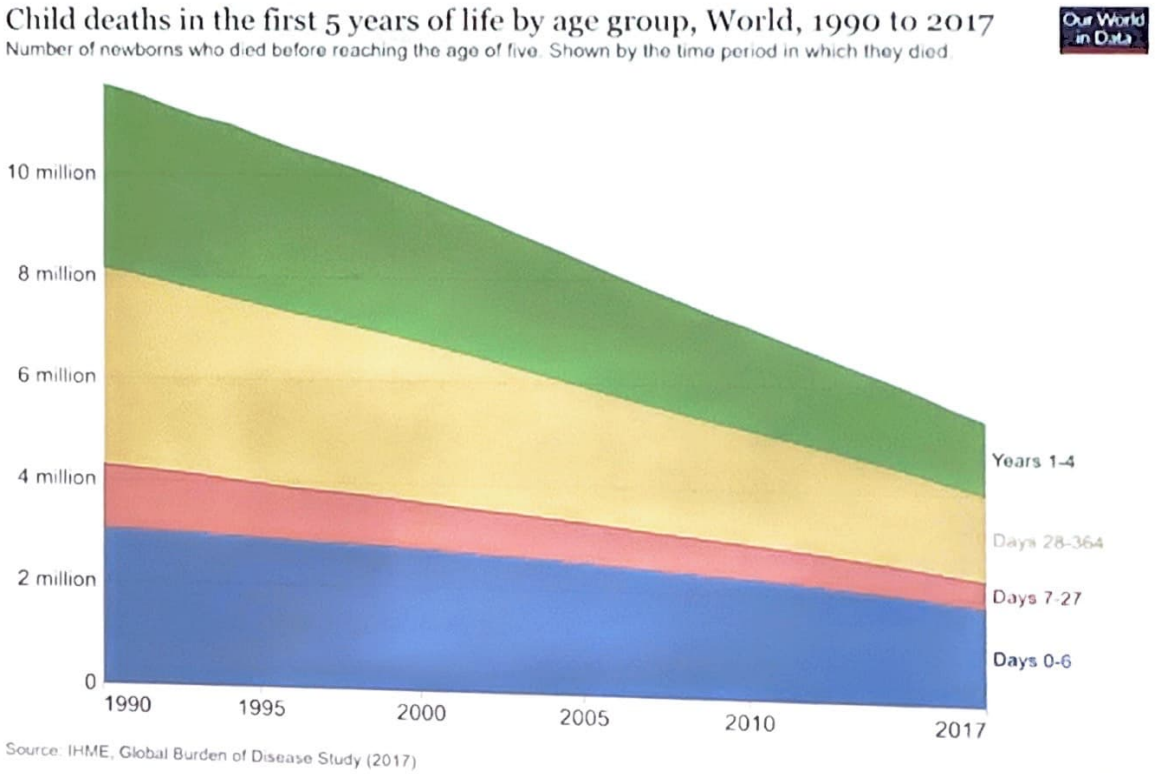
Overview

- Neonatal sepsis
- Optimising antimicrobial treatment of neonatal sepsis
- Microsampling to inform antimicrobial dosing
  - Facilitating PK
  - TDM
  - Personalised dosing

Towards the Sustainable Development Goals for neonatal mortality

- Five million deaths in children under 5 years of age/year
- Improvement since 1990
- Slower declines in neonatal mortality
- Half of all under 5 mortality occurs in the first month of life

- Major causes:
  - Preterm birth
  - Perinatal insult (hypoxia/infection)
  - Infections including sepsis



Neonatal sepsis

- 20-30 cases per 1000 live births
- Three million cases annually
- Mortality 11 to 19%

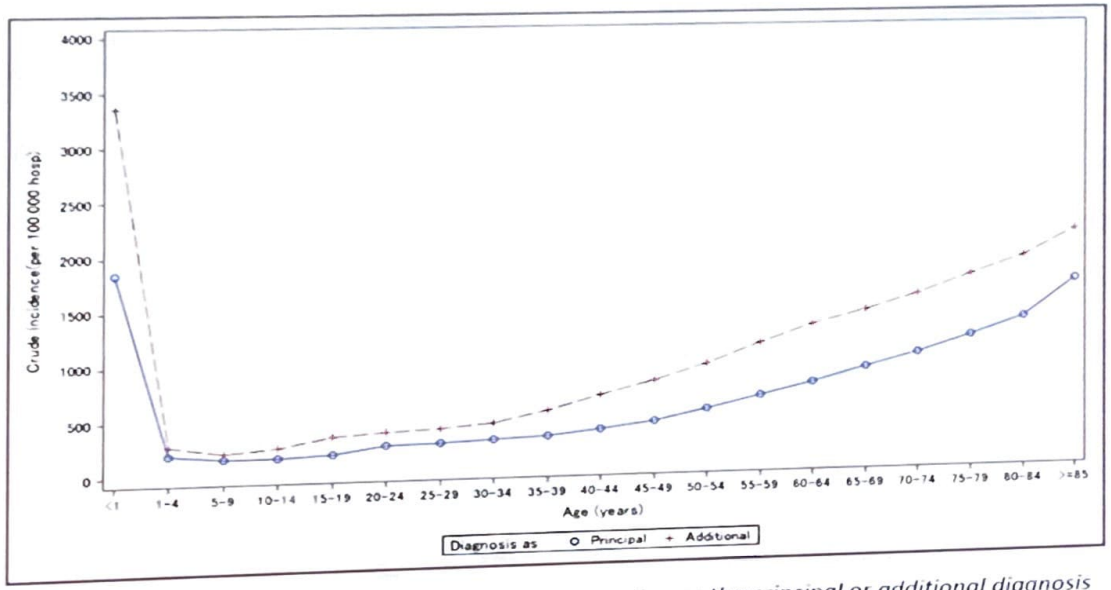


Figure 6: Age specific sepsis incidence by diagnosis recording as the principal or additional diagnosis

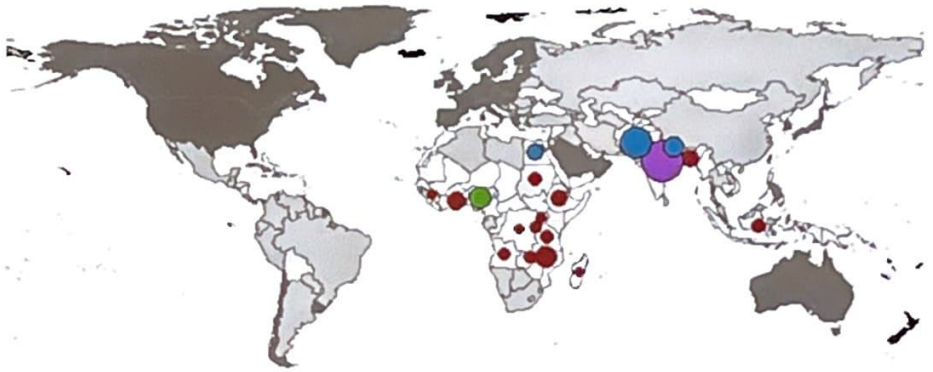
Li L, Sunderland N, Rathnayake K, Westbrook JI. Epidemiology of Sepsis in Australian Public Hospitals. Sydney: ACSQHC; 2020

Antimicrobial resistance in neonatal sepsis

- A global health priority
- New antimicrobials urgently needed for MDR Gram-negatives

- Substantial antimicrobial resistance:
  - Resistance to aminoglycosides: 42 to 69%
  - Resistance to 3GC: 59 to 84%

- WHO recommended regimens often inappropriate



Optimising antimicrobial use for neonatal sepsis

1. Need to ensure access
   - Understand the aetiology of neonatal sepsis and associated AMR
   - Implement appropriate regimens

2. Need to use optimally (steward)
   - Reduce unnecessary treatment
   - Right drug
   - Right dose
   - Right duration

- How can microsampling help?
  - Dosing recommendations based on neonatal PK
  - Therapeutic drug monitoring
  - Personalised dosing in critical illness

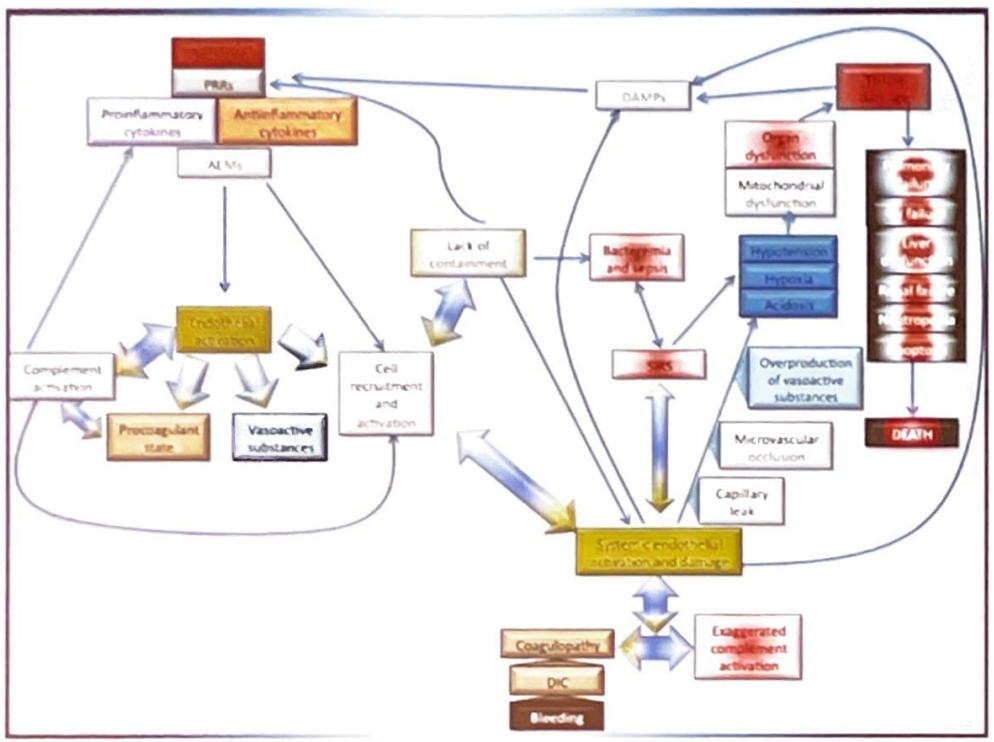
Antimicrobial pharmacokinetics in neonates

- Significant progress in last decade, but:
  - Still relatively few studies
  - Small, sparse samples
  - Largely opportunistic

- Need for high-quality PK studies
  - Well-designed
  - Transparently reported
  - New and repurposed drugs

Challenges in neonatal PK studies
Patient heterogeneity
Physiological maturation
Critical illness
Drug-drug interactions
Appropriate sampling
Frequency
Method
Volume
Type/Matrix

Physiological variation in neonatal sepsis



- Significant haemodynamic compromise and fluid shifts
- Decreased or increased renal excretion
- Reduced protein binding
- Overlay maturational effects

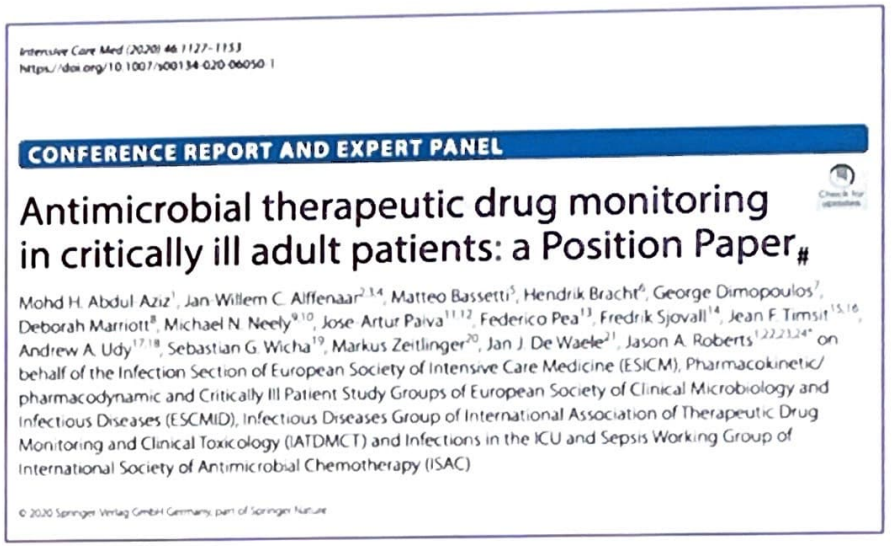
Existing antimicrobial TDM in neonates

- Gentamicin
- Commonly used in empirical regimens
- Aminoglycoside
  - C_{max}:MIC target
- TDM
  - Trough used to ensure clearance

- Vancomycin
- Active against Gram-positives, particular value in MRSA
- Glycopeptide
  - AUC:MIC target
- TDM
  - Trough level used to infer AUC:MIC

Microsampling to facilitate TDM

- Reduced blood volumes
- Simplification of obtaining sample
  - Sample can be collected from syringe discard
  - Heel-prick sampling is in routine use in neonatology
- Simplification of sample processing
  - Concentrations can be measured directly in whole blood
  - Requires an understanding of blood-plasma drug partitioning



Intensive Care Med (2020) 46:1127–1153
https://doi.org/10.1007/s00134-020-06050-1

CONFERENCE REPORT AND EXPERT PANEL

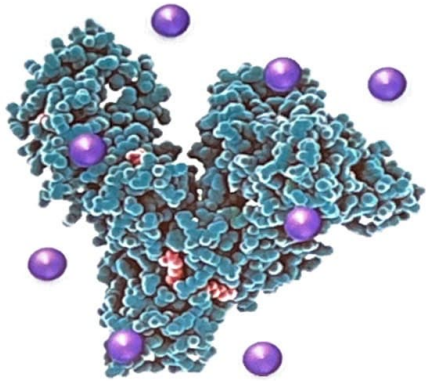
Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper#

Mohd H. Abdul Aziz[1], Jan-Willem C. Alffenaar[2,3,4], Matteo Bassetti[5], Hendrik Bracht[6], George Dimopoulos[7], Deborah Marriott[8], Michael N. Neely[9,10], Jose-Artur Paiva[11,12], Federico Pea[13], Fredrik Sjovall[14], Jean F. Timsit[15,16], Andrew A. Udy[17,18], Sebastian G. Wicha[19], Markus Zeitlinger[20], Jan J. De Waele[21], Jason A. Roberts[1,22,23,24]* on behalf of the Infection Section of European Society of Intensive Care Medicine (ESICM), Pharmacokinetic/pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Group of International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and Infections in the ICU and Sepsis Working Group of International Society of Antimicrobial Chemotherapy (ISAC)

"Although concentration measurements are usually performed in blood matrices (e.g. plasma or serum), several alternative sampling strategies (e.g. dried blood spots and volumetric absorptive microsamples), which are minimally or non-invasive approaches, need to be further investigated and validated for routine TDM in critically ill patients. Importantly, these "patient-friendly" strategies may play an important role in the establishment of TDM centres in remote and resource-limited settings."

Challenges for microsampling in neonates

- Highly sensitive instrumentation across a large dynamic range
- Highly specific methodology
  - Withstand matrix effects from hemolytic, lipemic, icteric samples
- Limitation with protein binding
  - Total concentrations available only
  - Unbound available for biological activity
  - Understand relationship between albumin and total drug concentration



APPLICATION OF MICROSAMPLING IN NEONATES

Bioanalysis

DBS–LC–MS/MS assay for caffeine: validation and neonatal application

- 44 pre-term neonates
- Loading dose: 20 mg/kg
- Maintenance daily dose: 5-10 mg/kg
- 101 plasma samples
- 136 DBS samples

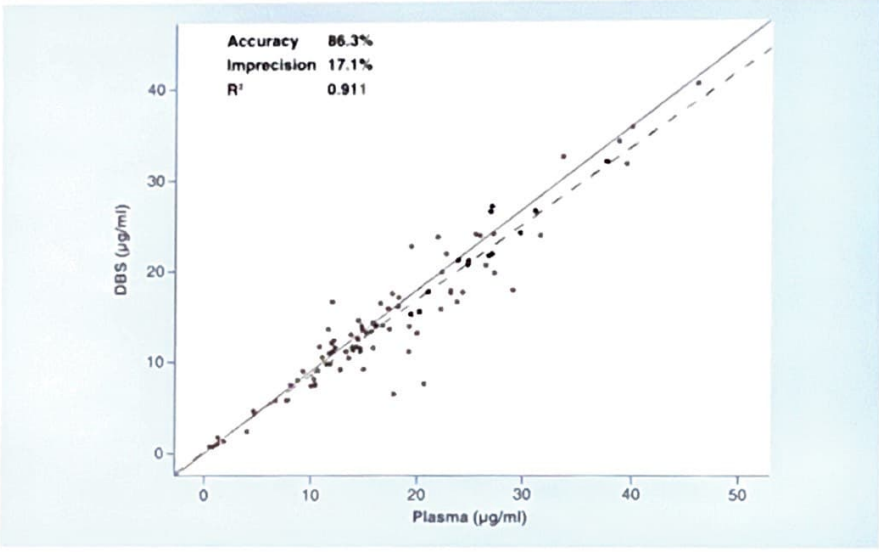


Figure 1. Correlation plot between plasma and DBS caffeine concentration.

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APPLICATION OF MICROSAMPLING IN NEONATES

Antimicrobial Agents and Chemotherapy

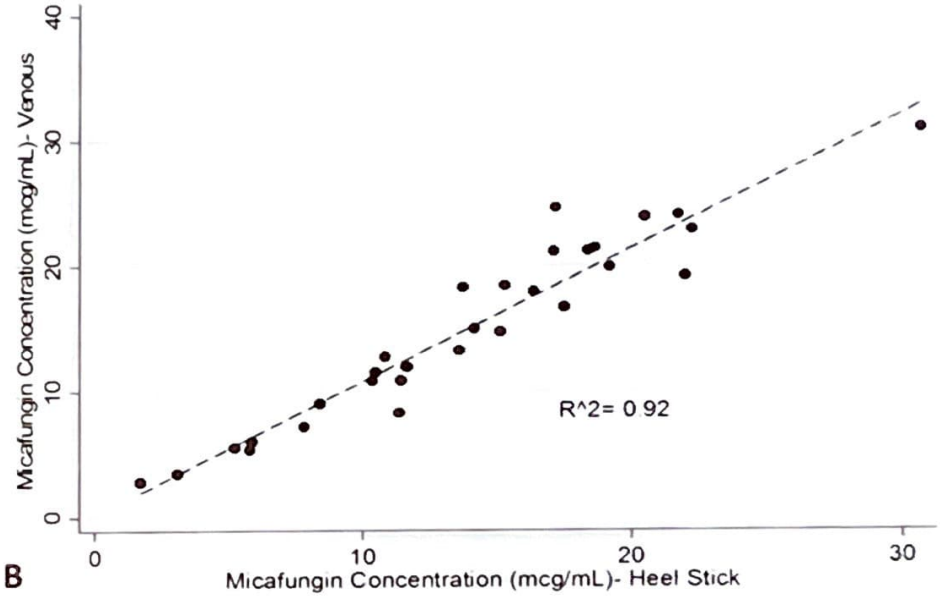
24 September 2018

Validation of Heel Stick Microsampling To Optimize Micafungin Doses in Neonates and Young Infants

Authors: Cinzia Auriti, Bianca Maria Goffredo, Maria Paola Ronchetti, Fiammetta Piersigilli, Sara Cairoli, Iliana Bersani, Andrea Dotta, and Manjunath P. Pai AUTHORS INFO & AFFILIATIONS

DOI: https://doi.org/10.1128/AAC.01199-18 • Check for updates

- 8 pre-term neonates
- 8 mg/kg daily dose of micafungin
- 8 samples per patient (2 dosing intervals)



B

OPTIONS microsampling correlative study

POPULATION

24 neonates at risk of sepsis

LOCATION

Grantley Stable Neonatal Unit RBWH

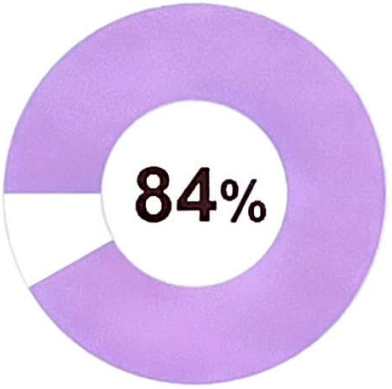
INTERVENTION

- Gentamicin TDM
- Blood collection using volumetric absorptive microsampling (VAMS) via heel-prick or syringe

FINDINGS

27 of 32 paired samples within 20% of the mean concentration for VAMS and plasma

Bias +3.4%



OPTIONS our proof-of-concept study

POPULATION

2 neonates at risk of sepsis

LOCATION

Grantley Stable Neonatal Unit RBWH

INTERVENTION

- Gentamicin TDM using wet VAMS
- Timing to report: from collection to bedside result

FINDINGS

Wet VAMS paired samples within 20% of the mean concentration for VAMS and plasma

Bias -18.0, -0.4%

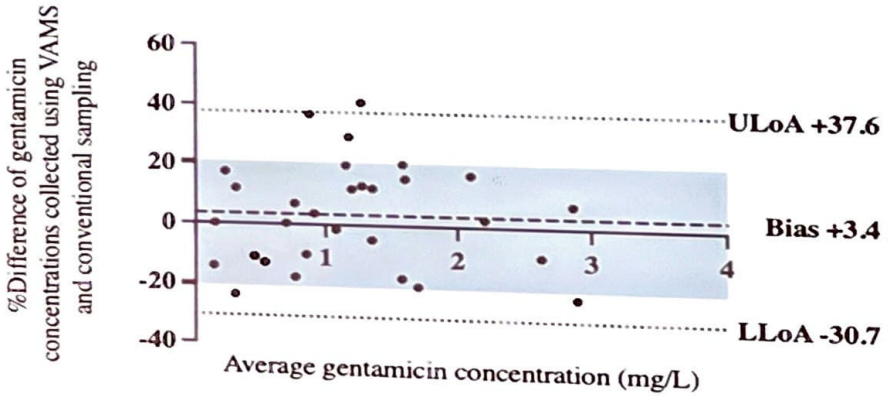
TIMINGS

	Pathology Lab	Research Lab
Patient 1	2 h 55 min	1 h 0 min
Patient 2	2 h 33 min	2 h 8 min

> Int J Antimicrob Agents. 2022 Feb;59(2):106513. doi: 10.1016/j.ijantimicag.2021.106513. Epub 2022 Jan 6.

Innovation in microsampling for therapeutic drug monitoring of gentamicin in neonates: a proof-of-concept study

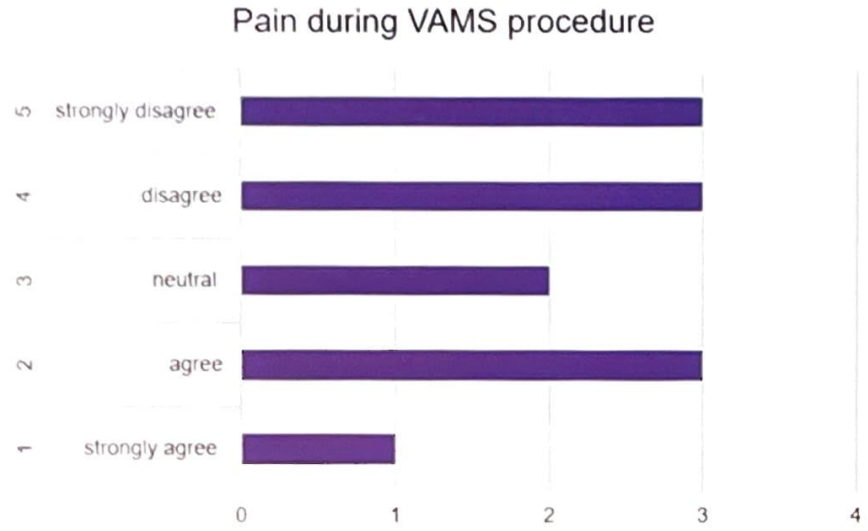
OPTIONS microsampling correlative study



Quality Controls	Accuracy (%)		
Conc (mg/L)	0.6	2.0	16
VAMS	95.7	94.0	96.9
Plasma	108	107	99.3

Quality Control	Imprecision (%)		
Conc (mg/L)	0.6	2.0	16
VAMS	5.2	9.0	7.7
Plasma	8.6	9.3	5.8

OPTIONS: Bedside nurse survey



N = 12 nurses

50% nurses perceived microsampling to be 'less invasive and less painful'

100% nurses agreed they would 'recommend microsampling to support clinical studies in neonatal patients'