Is saliva-based therapeutic drug monitoring feasible? A systematic review (Part 2) Nguyen TA[1,2,3], Chen RH[1,4], Hawkins BA[1,5], Hibbs DE[1], Kim HY[1,3,6], Wheate NJ[1], Groundwater PW[1], Stocker SL[1,2,3,7], Alffenaar JWC[1,2,3,]; [1]Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; [2]Westmead Hospital, Sydney, NSW, Australia; [3]Sydney Institute for Infectious Diseases, The University of Sydney, Sydney, NSW, Australia; [4]Department of Pharmacy, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [5]Antimicrobial Discovery Center, Department of Biology, Northeastern University, Boston, MA, USA; [6]Department of Pharmacy, Westmead Hospital, Sydney, NSW, Australia; [7]Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW, Australia

Background and Objectives. Saliva is a patient-friendly matrix for therapeutic drug monitoring (TDM) but is infrequently used in routine care. This is due to the uncertainty of saliva-based TDM results to inform dosing. This study aimed to assess the suitability of commonly used drugs for saliva-based therapeutic drug monitoring (TDM).

Methods. Medline, Web of Science, and Embase (1974−2023) were searched for studies with at least 10 subjects and 5 paired saliva-plasma concentrations per subject were included. For each study, the ratio of the area under the concentration-time curve between saliva and plasma was determined to assess penetration into saliva. Correlation coefficients, describing the relationship between saliva and plasma drug exposure, were compared across studies. If not reported, they were computed from the concentration-time curves obtained in saliva and plasma. The variability of saliva-to-plasma ratios was assessed if available. Two criteria for suitability for saliva-based TDM were adequate saliva-plasma correlation ($R^2 > 0.6$) and relatively low variability (CV% < 20%) in saliva-to-plasma ratios. Drugs were classified: (i) likely suitable if they had both criteria, (ii) possibly suitable if they had either one of the two, (iii) unlikely if they did not meet either of the two criteria or were not detected in saliva, and (iv) unclear if there was a lack of pharmacokinetic data. Study quality was assessed by the Risk Of Bias In Non-randomised Studies–of Interventions tool.

Results. Overall, 42 studies including 40 drugs (antipsychotics, antimicrobials, immunosuppressants, antithrombotic, anticancer, and cardiac drugs) were included. Of the included drugs, 11 drugs (27.5%) were likely suitable for saliva TDM (piroxicam, metformin, lamotrigine, chloroquine, irinotecan, caffeine, disopyramide, phenytoin, moxifloxacin, voriconazole, and tacrolimus). Nineteen drugs (47.5%) were determined to be possibly suitable. Three drugs (7.5%) were determined to be unlikely to be suitable due to highly variable saliva-to-plasma ratios and it was unclear whether six drugs (15.0%) were suitable due to a lack of sufficient PK data to be evaluated. Amikacin was considered unlikely to be suitable because it was undetected in saliva. The studies had a low-to-moderate risk of bias.

Conclusion. Many commonly used drugs were considered likely or possibly suitable for saliva TDM due to high saliva-plasma correlations and/or relatively low variability in saliva-to-plasma ratios. Further research is required to better understand factors that may influence the saliva penetration of drugs and thereby develop a drug classification system for saliva TDM.

Keywords. Drug monitoring, suitability, saliva, oral fluid