Systematic Review of Salivary Versus Blood Concentrations of Antituberculosis Drugs and Their Potential for Salivary Therapeutic Drug Monitoring

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Systematic Review of Salivary Versus Blood Concentrations of Antituberculosis Drugs and Their Potential for Salivary Therapeutic Drug Monitoring

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Background: Therapeutic drug monitoring is useful in the treatment of tuberculosis to assure adequate exposure, minimize antibiotic resistance, and reduce toxicity. Salivary therapeutic drug monitoring could reduce the risks, burden, and costs of blood-based therapeutic drug monitoring. This systematic review compared human pharmacokinetics of antituberculosis drugs in saliva and blood to determine if salivary therapeutic drug monitoring could be a promising alternative.

Methods: On December 2, 2016, PubMed and the Institute for Scientific Information Web of Knowledge were searched for pharmacokinetic studies reporting human salivary and blood concentrations of antituberculosis drugs. Data on study population, study design, analytical method, salivary Cmax, salivary area under the time–concentration curve, plasma/serum Cmax, plasma/serum area under the time–concentration curve, and saliva–plasma or saliva–serum ratio were extracted. All included articles were assessed for risk of bias.

Results: In total, 42 studies were included in this systematic review. For the majority of antituberculosis drugs, including the first-line drugs ethambutol and pyrazinamide, no pharmacokinetic studies in saliva were found. For amikacin, pharmacokinetic studies without saliva–plasma or saliva–serum ratios were found.

Conclusions: For gatifloxacin and linezolid, salivary therapeutic drug monitoring is likely possible due to a narrow range of saliva–plasma and saliva–serum ratios. For isoniazid, rifampicin, moxifloxacin, ofloxacin, and clarithromycin, salivary therapeutic drug monitoring might be possible; however, a large variability in saliva–plasma and saliva–serum ratios was observed. Unfortunately, salivary therapeutic drug monitoring is probably not possible for doripenem and amoxicillin/clavulanate, as a result of very low salivary drug concentrations.

Key Words: tuberculosis, therapeutic drug monitoring, saliva, oral fluid

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INTRODUCTION

Tuberculosis (TB) is an infectious disease that is still a huge problem worldwide, although it is curable with antibiotics. In 2015, approximately 10.4 million people worldwide had TB for the first time, including 480,000 patients with multi–drug-resistant TB (MDR-TB).[1] MDR-TB is caused by strains of *Mycobacterium tuberculosis* resistant to at least the first-line drugs isoniazid and rifampicin. Drug-susceptible TB is treated with a standard combination of isoniazid, rifampicin, ethambutol, and pyrazinamide during 2 months followed by 4 months of only isoniazid and rifampicin.[2] The treatment of MDR-TB consists of a combination of at least 5 antibiotics that are likely to be effective.[3]

Therapeutic drug monitoring (TDM) can be used to assure adequate exposure, minimize antibiotic resistance, and reduce side effects.[4] TDM is, however, not a part of the standard TB treatment according to the World Health Organization (WHO) guidelines. Subtherapeutic drug concentrations cause decreased cure rates and can induce antibiotic resistance.[5,6] On the other hand, too high concentrations of some anti-TB drugs can lead to serious toxicity.[4,7] In addition, pharmacokinetics of anti-TB drugs show large interindividual variability.[8] Thus, applying TDM in TB therapy could be helpful to achieve therapeutic drug concentrations in an early stage of treatment.

Although blood samples have been routinely used for TDM, venipuncture is an invasive procedure with increased risks of infection, local hematoma, and pain at the puncture site.[9,10] In addition, pain-related fear plays a major role for patients.[9] In addition, venipuncture is rather expensive because it requires qualified staff and appropriate materials.[9,10] Blood sampling is undesirable for some patient groups because of limited blood supply (eg, neonates), less accessible veins (eg, elderly), or religious objections.[9] Because of these

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disadvantages, alternatives to regular blood sampling (eg, saliva) are being studied.

Oral fluid is a mixture of saliva secreted by all glands present in the oral cavity.[11] The terms saliva and oral fluid are used interchangeably in the literature.

Saliva sampling is less complicated compared with taking blood samples and reduces costs.[10,12] An economic study about saliva collection in children showed 58% savings with the saliva sampling procedure alone compared with blood sampling, caused by a shorter sampling time and less expensive materials.[13] If parents were collecting saliva samples instead of medical staff, the savings could increase up to 90%.[13] Collecting saliva samples is also experienced as more comfortable by patients.[9,12,14] For certain patient groups, such as children, elderly, and people with disabilities, saliva sampling is a preferred method.[10,12,14] Stimulated saliva samples can be taken by chewing on absorbent cotton rolls, paraffin, or after applying citric acid under the tongue. For nonstimulated saliva samples, the passive drooling technique is regularly used.

Dried blood spot (DBS) sampling is another less invasive method. However, DBS sampling can be painful, is more complicated, and has higher failure rates than saliva sampling.[15] The drug concentrations in DBS are influenced by the hematocrit value and spot volume.[16] In addition, free (unbound) drug concentrations are not determinable in DBS,[16] whereas salivary concentrations generally represent the free (unbound) drug concentrations.[14,17]

Distribution of drugs from blood to saliva generally occurs by passive diffusion. Protein binding, negative log of acid dissociation constant (pKa), molecular mass, lipid solubility, and chemical stability in saliva are physicochemical properties of drugs that influence the salivary drug concentration. Salivary pH value, salivary flow rate, and some diseases of the oral cavity are physiological properties that determine drug penetration into saliva.[12,18] Actively stimulating saliva flow will increase the excretion of bicarbonate and therefore can influence the drug distribution and concentration in saliva.[11,14] Generally, concentrations in saliva reflect the free (unbound) drug concentrations in plasma at a certain ratio.[14,17] The saliva–plasma ratio can be determined not only by calculating the mean saliva–plasma ratio of all chosen time points but also by using the area under the time–concentration curve (AUC) values of the time–concentration curves in saliva and plasma. For some anti-TB drugs, saliva–plasma or saliva–serum ratios are studied, but a clear overview of the comparison of salivary to blood-based TDM for anti-TB drugs is not available.

The aim of this systematic review was to investigate whether TDM of anti-TB drugs using saliva samples is feasible, and if so, for which of these drugs which bioanalytical assays for saliva-based TDM should be established and validated.

MATERIALS AND METHODS

A protocol of this systematic review was registered at PROSPERO with registration number CRD42017051749 and available through www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017051749. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for this review.[19]

For this review, the first-line and second-line anti-TB drugs were selected from the WHO guidelines.[2,3] Ertapenem, faropenem, doripenem, ofloxacin, and clarithromycin were added to this list.

PubMed and Institute for Scientific Information (ISI) Web of Knowledge searches were performed on the December 2, 2016. The keywords used for this systematic search were (isoniazid OR rifampicin OR pyrazinamide OR ethambutol OR levofloxacin OR moxifloxacin OR gatifloxacin OR amikacin OR capreomycin OR kanamycin OR streptomycin OR ethionamide OR prothionamide OR cycloserine OR terizidone OR linezolid OR clofazimine OR bedaquiline OR delamanid OR paraaminosalicylic acid OR imipenem/cilastatin OR imipenem OR cilastatin OR meropenem OR amoxicillin/clavulanate OR amoxicillin OR clavulanate OR thiacetazone OR ertapenem OR faropenem OR doripenem OR ofloxacin OR clarithromycin) AND saliva AND (pharmacokinetics OR saliva–plasma ratio OR saliva–serum ratio OR TDM OR penetration OR distribution OR drug concentration). No limitation of publication date was used. A second reviewer checked the reproducibility of the search using the stated keywords.

After duplicate articles were removed, titles and abstracts were screened for eligibility, and the selected manuscripts were read by 2 independent reviewers. Exclusion factors were as follows: no human study, no anti-TB drug concentration was measured in saliva or plasma/serum, and if the manuscript was a review article. Primary references of the excluded reviews were checked and included if the study was relevant and obtainable.

Data extraction of the included articles was performed by 1 person. A reviewer independently checked the data extraction afterward. Data on study population, study design, saliva sampling method, analytical method, peak concentration (Cmax) in saliva, AUC in saliva, Cmax in plasma or serum, AUC in plasma or serum, and saliva–plasma or saliva–serum ratio were extracted from the included articles. Authors of included articles were contacted if numerical Cmax values were missing, although a time–concentration curve was stated.

If the article contained a time–concentration curve of the drug, but no numerical Cmax value was available, the Cmax was estimated using the graph. If AUC values of both saliva and plasma or serum were given, the ratio was manually calculated by dividing the salivary AUC by the plasma or serum AUC. The saliva–plasma or saliva–serum ratio was calculated (1/plasma–saliva ratio or 1/serum–saliva ratio, respectively) if the article only mentioned the plasma–saliva or serum–saliva ratio. All calculated ratios and estimated Cmax values were marked in the table.

As no validated tool for risk of bias assessment of pharmacokinetic studies is available, we used the Risk Of Bias In Nonrandomized Studies—of Interventions (ROBINS-I) tool.[20] This tool was validated for nonrandomized intervention studies. Changes were made in the confounding section to make the tool more suitable for pharmacokinetic studies. The assessment was checked by a second reviewer.

RESULTS

A total of 162 records were found in the PubMed (n = 108) and ISI Web of Knowledge (n = 54) search (Figure 1). After duplicates were removed, a number of 129 articles remained, of which 58 were classified as not relevant based on title and abstract. After full-text assessment, 30 records were excluded. One article, Ichihara[21] was included after searching the references of the excluded review articles. Overall, 42 articles were included in this systematic review.

No articles concerning salivary pharmacokinetics of first-line anti-TB drugs ethambutol, pyrazinamide and second-line anti-TB drugs levofloxacin, capreomycin, kanamycin, streptomycin, ethionamide, prothionamide, cycloserine, terizidone, clofazimine, bedaquiline, delamanid, paraaminosalicylic acid, imipenem/cilastatin, meropenem, thiacetazone, ertapenem, or faropenem were found in the systematic search.

Study populations of the included articles were composed of healthy volunteers, patients with TB, children, neonates, or patients with numerous diseases and ranged from studies as few as 2 to as many as 80 participants. For each anti-TB drug, variable dosage regimens were administered, and multiple saliva sampling methods as well as several analytical methods were used (Table 1).

All included articles were assessed for risk of bias. Baglie et al,[22] Biasini et al,[23] Brown et al,[24] Fujita et al,[25] Goddard et al,[26] and Ohkubo et al[27] were considered at a serious risk of bias (Table 2). This means that the studies have some serious problems with bias for a nonrandomized study.[20] Baglie et al[22] and Brown et al[24] both used different

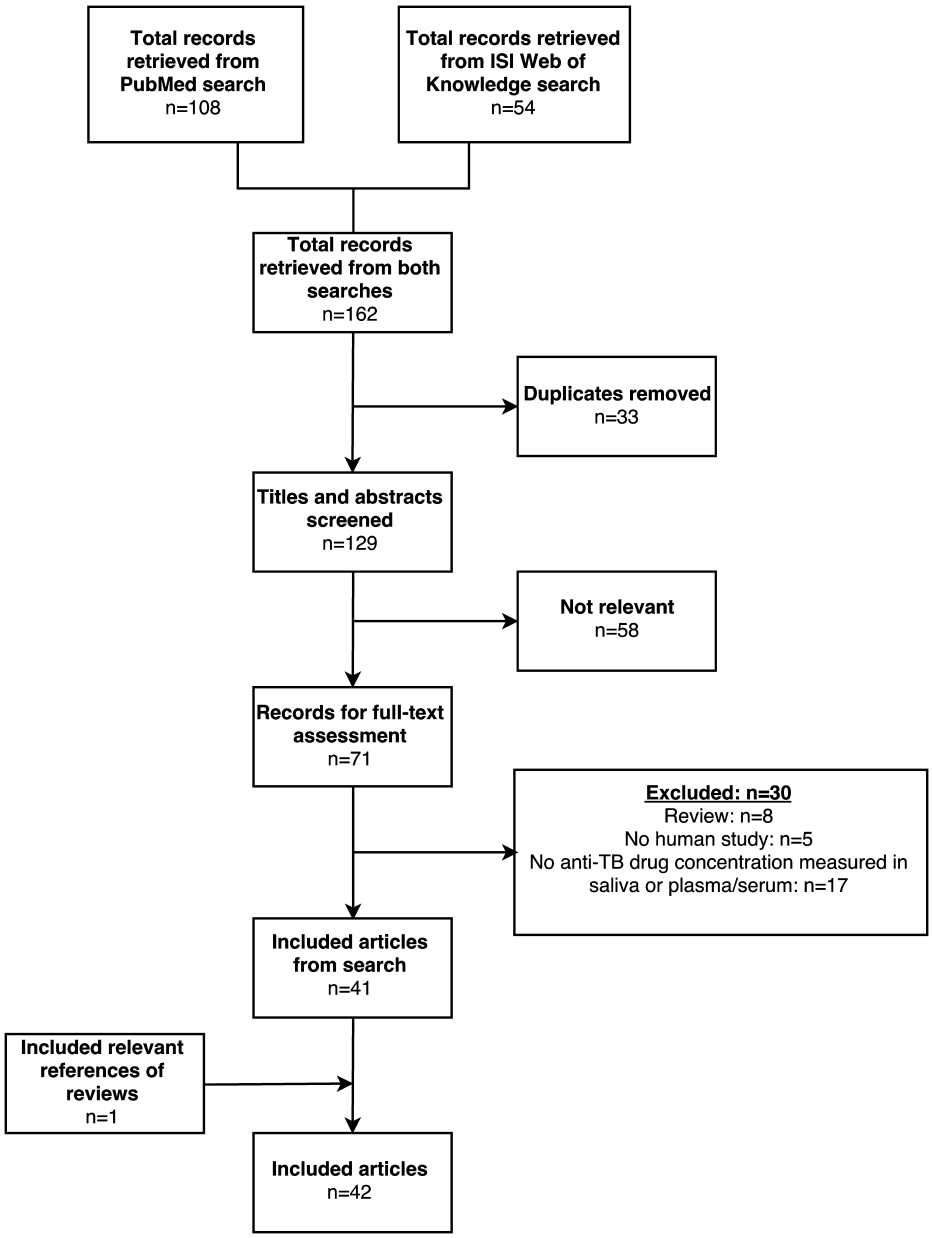

FIGURE 1. Results of searches and study selection. Using the search terms, 162 records were found, 71 of which were assessed as relevant. After full-text assessment, 30 articles were excluded. A total of 42 articles were included in this systematic review.

TABLE 1. Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Study	Study Population	Study Design	Dose	Saliva Sampling Method
Isoniazid	Brown et al[24]	HV; N = 5	Open-label cross-over	300 mg, single dose	S; unflavored chewing gum
	Gurumurthy et al[31]	PTB and ITB patients; N = 30	Open-label	300 mg, single dose	S; unflavored chewing gum
	Hutchings et al[79]	Patients with various diseases; N = 22	Open-label	200 mg, single dose	S; chewing teflon tape
	Suryawati et al[40]	HV; N = 8	Open-label	10 mg/kg, single dose	ND
Rifampicin	Gurumurthy et al[31]	PTB and ITB patients; N = 30	Open-label	10 mg/kg, single dose	S; unflavored chewing gum
	Orisakwe et al[32]	HV; N = 5	Open-label cross-over	600 mg, single dose	S; chewing gum
	Ezejiofor et al[30]	HV; N = 5	Open-label cross-over	600 mg, single dose	S; unflavored chewing gum
	Darouiche et al[29]	HV; N = 5	Open-label	600 mg, for 4 d	ND
	McCracken et al[80]	Children (6–58 mo old) with impetigo or cellulitis; N = 38	Open-label	10 mg/kg, single dose	Capillary pipettes
	Murthy et al[28]	PTB patients; N = 20	Open-label	450/600 mg, single dose	Wide, capped bottle
	Orisakwe et al[33]	Male HV; N = 6	Open-label	600 mg, single dose	ND
Moxifloxacin	Burkhardt et al[38]	Male, Caucasian HV; N = 12	Double-blind; randomized cross-over	400 mg, for 7 d	S; Salivette
	Müller et al[37]	Male HV; N = 13	Randomized; open-label cross-over	400 mg, single dose p.o and i.v. (during 60 min)	S; Salivette
	Stass et al[36]	Male, Caucasian HV; N = 39	Double-blind; randomized cross-over and group comparison	50–800 mg, single dose	S; chew on cotton roll
	Burkhardt et al[35]	Male patients with SCI and decubitus ulcer; N = 4	Open-label	400 mg, single dose	S; Salivette
	Kumar et al[34]	HV; N = 24	Open-label	400 mg, single dose	S; unflavored chewing gum
Ofloxacin	Kozjek et al[44]	Male HV; N = 6	Randomized parallel group	400 mg, single dose	NS
	Koizumi et al[41]	Patients with chronic respiratory tract infections; N = 18	Open-label	300 mg, single dose	Sterile glass dishes
	Warlich et al[45]	HV; N = 6	Open-label	200 mg b.i.d., for 3 d	S; chewing parafilm
	Leigh et al[46]	HV; N = 11	Open-label	200 mg b.i.d., for 3.5 d	NS
	Immanuel et al	Male HV; N = 7	Open-label	600/800 mg, single dose	S; unflavored chewing gum
	Miya et al[81]	PTB or NSCLC patients; N = 12	Open-label	200 mg t.i.d., for at least 7 d	ND
	Ohkubo et al[27]	Male HV; N = 4	Open-label	100/200 mg, single dose	S; chewing parafilm
	Fujita et al[25]	Patients with infections or antibiotic prophylaxis and HV; N = 80	Open-label	100 mg alt. d.–200 mg t.i.d., (depending on renal function), for 5 d	ND
	Edlund et al[48]	Gastric surgery patients; N = 20	Open-label	400 mg, single dose	Sterile glass tubes
	Ichihara et al[21]	Male HV; N = 19	Open-label	100/300/600 mg, single dose	ND

TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Study	Study Population	Study Design	Dose	Saliva Sampling Method
	Tsubakihara et al[49]	Patients with renal failure; N = 12 (6 HD, 6 non-HD)	Open-label	100 mg, single dose	ND
Gatifloxacin	Nakashima et al[53]	Male, Asian HV; N = 30	Open-label	100/200/400/600 mg, single dose 300 mg b.i.d., for 6.5 d	NS
	Mignot et al*[54]	Male, Caucasian HV; N = 36	Double-blind, randomized, placebo controlled	400/600 mg, single dose and for 10 d	NS
Amikacin	Masumi et al[39]	Neonates (2- and 12-day old); N = 2	Open-label	3.0–6.0 mg/kg i.v.	ND
	Biasini et al[23]	Children with CF and pneumonia; N = ND	Open-label	10 mg/kg i.v. injection	ND
Linezolid	Bolhuis et al[51]	MDR-TB patients (5 African, 1 Caucasian, 1 Asian); N = 7	Open-label	300 mg b.i.d. at steady state	S; Salivette
	Hara et al[82]	HV; N = 4	Open-label	600 mg, single dose	S; Salivette
Amoxicillin/clavulanate	Goddard et al[26]	Male HV; N = 8	Double-blind, randomized, placebo-controlled cross-over	750 mg (amoxicillin), for 5 d	ND
	Ortiz et al[62]	HV; N = 26	Open-label, randomized, cross-over	500 mg (amoxicillin), single dose	ND
	Ginsburg et al[61]	Children (4–54-month old) with AOM; N = 24	Open-label, cross-over	15 and 25 mg/kg (amoxicillin), single dose	Capillary pipettes
	Baglie et al[22]	HV; N = 20	Open-label; randomized cross-over	875 mg (amoxicillin), single dose	NS, Sterile glass tubes
	Wüst et al[60]	HV; N = 10	Open-label	750 mg (amoxicillin); single dose	ND
Doripenem	Burian et al[59]	Male HV; N = 6	Open-label	500 mg i.v. in 1 h, single dose	ND
Clarithromycin	Fassbender et al[83]	HV; N = 10	Randomized, cross-over	500 mg b.i.d., for 3 d	S; chewing on cotton roll
	Kees et al[50]	Male HV; N = 12	Open-label, randomized, cross-over	500 mg q.d./250 mg b.i.d., for 5 d	NS; dental tampon
	Burkhardt et al[38]	Male, Caucasian HV; N = 12	Double-blind, randomized, cross-over	500 mg b.i.d., for 7 d	S; Salivette
	Bolhuis et al[51]	MDR-TB patients (5 African, 1 Caucasian, 1 Asian); N = 7	Open-label	250 mg at steady state	S; Salivette
	Goddard et al[26]	Male HV; N = 8	Double-blind, randomized, placebo-controlled, cross-over	500 mg, for 5 d	ND
	Edlund et al[52]	HV; N = 10	Double-blind, randomized	500 mg b.i.d., for 10 d	NS; Glass tubes
	Wüst et al[60]	HV; N = 10	Open-label	500 mg, single dose	ND
	Morihana et al[84]	Male HV; N = 3	Open-label	300 mg, single dose	NS

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
Isoniazid	UV (saliva), Ehrlich reagent and UV (plasma)	Cmax: 1.70 ± 0.10	Plasma Cmax: 4.50 ± 0.20	0.14	Conc
		$AUC_{0–24\ h}$: 8.96 ± 0.37	Plasma $AUC_{0–24\ h}$: 65.50 ± 6.82	0.14‡	$AUC_{0–24\ h}$
		$AUC_{0–inf}$: 10.06 ± 0.43	Plasma $AUC_{0–inf}$: 65.90 ± 6.67	0.15‡	$AUC_{0–inf}$
	UV	Cmax: Slow acetylators: 7.6 (5.4–13.2)	Serum Cmax: Slow acetylators: 7.8 (4.8–15.0)	Slow acetylators: 0.95‡; Rapid acetylators: 0.94‡	AUC

(*continued on next page*)

TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
		Rapid acetylators: 6.0 (4.8–7.4)	Rapid acetylators: 5.9 (4.6–8.7)		
		AUC: Slow acetylators: 37 (20–58);	Serum AUC: Slow acetylators: 39 (21–62)		
		Rapid acetylators: 17 (12–22)	Rapid acetylators: 18 (11–27)		
	HPLC-UV	Cmax: Slow acetylators: 2.5†; Rapid acetylators: 2.3†	Plasma Cmax: Slow acetylators: 2.0†; Rapid acetylators: 1.7†	—	—
		AUC: ND	Plasma AUC: ND		
	UV	Cmax: ND	Serum Cmax: ND	0.80 ± 0.05; Elimination: 0.81 ± 0.05; Absorption: 1.09 ± 0.29	$AUC_{0–inf}$ Conc
		$AUC_{0–inf}$: 31.88 ± 9.57	Serum $AUC_{0–inf}$: 38.66 ± 10.53		
Rifampicin	Plate diffusion assay with *Staphylococcus aureus*	Cmax: 0.9	Serum Cmax: 8.5	0.07–0.13	Conc
		AUC: ND	Serum AUC: ND		
	UV	Cmax: 12.8 ± 0.33	Plasma Cmax: 17.8 ± 1.04	0.67‡	$AUC_{0–24\ h}$
		$AUC_{0–24\ h}$: 63.6 ± 1.4	Plasma $AUC_{0–24\ h}$: 95.5 ± 2.2	0.66‡	$AUC_{0–inf}$
		$AUC_{0–inf}$: 68.1 ± 1.8	Plasma $AUC_{0–inf}$: 103.6 ± 3.6		
	UV	Cmax: 9.00 ± 0.70	Plasma Cmax: 16.00 ± 2.12	0.15	Conc
		$AUC_{0–24\ h}$: 68.85 ± 5.48	Plasma $AUC_{0–24\ h}$: 485.60 ± 62.57	0.14‡	$AUC_{0–24\ h}$
		$AUC_{0–inf}$: 72.18 ± 8.18	Plasma $AUC_{0–inf}$: 505.60 ± 77.13	0.14‡	$AUC_{0–inf}$
	HPLC-UV	Cmax: ND	Serum Cmax: ND	—	—
		Highest measured conc at 2 h: 0.42 ± 0.12	Highest measured serum conc at 5 h: 10.65 ± 4.55		
		AUC: ND	Serum AUC: ND		
	Agar disk diffusion micro-method with *Sarcina lutea*	Cmax: ND	Serum Cmax: ND	—	—
		Median conc at t = 2 h	Highest measured serum conc at 1 h:		
		Suspension: 1.7 (0.54–7.2)	Suspension: 10.7 ± 0.81		
		Suspension in apple sauce: 1.6 (0.48–4.0)	Suspension in applesauce: 8.9 ± 1.29		
		Powder in applesauce: 2.4 (0.85–3.8)	Powder in applesauce: 11.5 ± 2.3		
		AUC: ND	Serum AUC: Suspension: 56		
			Suspension in applesauce: 38		
			Powder in applesauce: 57		
	RP-HPLC-EC	Cmax: 450 mg: 0.84 ± 0.21, 600 mg: 1.23 ± 0.17	Serum Cmax: ND; Highest measured serum conc at t = 3 h: 450 mg: 7.99 ± 1.98, 600 mg: 12.18 ± 1.92	600 mg: 0.1, 450 mg: 0.11–0.31	Conc
		AUC: 450 mg: 10.59 ± 4.36, 600 mg: 15.13 ± 2.81	Serum AUC: ND		

TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
	UV	Cmax: 11.6 ± 4.9	Plasma Cmax: 17.8 ± 5.1	0.53‡	$AUC_{0–24h}$
		$AUC_{0–24\ h}$: 49.68 ± 9	Plasma $AUC_{0–24\ h}$: 94.15 ± 18	0.52‡	$AUC_{0–inf}$
		$AUC_{0–inf}$: 50.01 ± 11	Plasma $AUC_{0–inf}$: 96.76 ± 12		
Moxifloxacin	HPLC-Fluor	Cmax: day 1: 3.6†, day 7: 4.8†	Serum Cmax: day 1: 3.10 ± 0.60, day 7: 3.98 ± 1.10	t >2 h: 0.8	Conc
		AUC: ND	Serum $AUC_{0–12\ h}$: day 1: 28.2 ± 4.1, day 7: 39.5 ± 6.6		
			Serum $AUC_{0–inf}$: day 1: 35.6 ± 6.5		
	HPLC-Fluor	Cmax	Plasma Cmax	0.83 ± 0.20	$AUC_{0–12\ h}$
		p.o.: 3.6 ± 1.0	p.o.: 3.2 ± 0.6	p.o.: 0.88‡	$AUC_{0–12\ h}$
		i.v.: 5.1 ± 1.4	i.v.: 3.7 ± 0.7	i.v.: 0.93‡	
		$AUC_{0–12\ h}$	Plasma $AUC_{0–12\ h}$		
		p.o.: 17.6 ± 2.7	p.o.: 19.8 ± 1.5		
		i.v.: 21.4 ± 5.0	i.v.: 22.9 ± 11.1		
	HPLC-Fluor	Cmax	Plasma Cmax	50 mg: 0.72‡	$AUC_{0–inf}$
		50 mg: 0.31 ± 1.55	50 mg: 0.29 ± 1.25	100 mg: 0.97‡	
		100 mg: 0.84 ± 1.74	100 mg: 0.59 ± 1.21	200 mg: 0.91‡	
		200 mg: 1.62 ± 1.44	200 mg: 1.16 ± 1.35		
			400 mg: 2.50 ± 1.31		
			600 mg: 3.19 ± 1.19		
			800 mg: 4.73 ± 1.16		
		$AUC_{0–inf}$	Plasma $AUC_{0–inf}$		
		50 mg: 2.81 ± 1.40	50 mg: 3.88 ± 1.13		
		100 mg: 8.27 ± 1.54	100 mg: 8.51 ± 1.21		
		200 mg: 14.0 ± 1.29	200 mg: 15.4 ± 1.20		
			400 mg: 26.9 ± 1.18		
			600 mg: 39.9 ± 1.11		
			800 mg: 59.9 ± 1.24		
	HPLC-Fluor	Cmax: 1.4 ± 0.4	Serum Cmax: 4.4 ± 2.7	0.45	Conc
		$AUC_{0–8\ h}$: 4.7 ± 3.0	Serum $AUC_{0–8\ h}$: 15.0 ± 9.7	0.31‡	$AUC_{0–8\ h}$
	RP-HPLC-Fluor	Cmax: ND	Plasma Cmax: ND	0.54	Conc
		AUC: ND	Plasma AUC: ND		
Ofloxacin	RP-HPLC-Fluor	Cmax: 1.71 ± 0.44	Plasma Cmax: 3.66 ± 0.72	0.43 ± 0.02	Conc
		AUC: 6.41 ± 1.08	Plasma AUC: 18.22 ± 2.52	0.36 ± 0.07	AUC
				0.455	Corr
	RP-HPLC-Fluor	Cmax: 4.53 ± 0.75	Serum Cmax: 4.25 ± 0.41	T = 0–4 h: <1	Conc
		AUC: 63.0 ± 8.9	Serum AUC: 51.5 ± 5.7	T = 4–8 h: increases from <1 to >1	AUC

(*continued on next page*)

TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
				T = 8–16 h: >1	
				T = 16 h: 1.14 ± 0.11	
				1.22‡	
	RP-HPLC-Fluor	Cmax: 2.07 ± 0.38	Serum Cmax: 2.96 ± 0.30	0.61 ± 0.03	Conc
		$AUC_{0–12\ h}$: 10.8 ± 0.8	Serum $AUC_{0–12\ h}$: 17.8 ± 0.5	0.606	$AUC_{0–12\ h}$
	Micro-biological assay with *Bacillus subtilis*	Cmax	Serum Cmax	0.78	Corr
		1st dose: 1.9 ± 0.7	1st dose: 2.7 ± 0.7	1st dose: 0.64‡	$AUC_{0–8\ h}$
		7th dose: 2.6 ± 0.7	7th dose: 3.4 ± 0.5	7th dose: 0.74‡	$AUC_{0–inf}$
		$AUC_{0–8\ h}$	Serum $AUC_{0–8\ h}$	1st dose: 0.64‡	
		1st dose: 8.9 ± 3.1	1st dose: 13.9 ± 3	7th dose: 0.73‡	
		7th dose: 12.9 ± 4.5	7th dose: 17.5 ± 3.6		
		$AUC_{0–inf}$	Serum $AUC_{0–inf}$		
		1st dose: 14.8 ± 5.0	1st dose: 23.0 ± 5.3		
		7th dose: 20.7 ± 8.5	7th dose: 28.2 ± 7.4		
	RP-HPLC-Fluor	Cmax	Plasma Cmax	600 mg: 0.40–0.57	Conc
		600 mg: 4.1	600 mg: 8.0 (7.4–8.6)	800 mg: 0.40–0.56	$AUC_{0–24\ h}$
		800 mg: 4.2	800 mg: 9.8 (8.2–11.4)	600 mg: 0.49‡	
		$AUC_{0–24\ h}$	Plasma $AUC_{0–24\ h}$	800 mg: 0.47‡	
		600 mg: 29.7	600 mg: 60.8 (54.2–67.4)		
		800 mg: 40.2	800 mg: 85.3 (69.4–101.2)		
			Plasma $AUC_{0–inf}$:		
			600 mg: 67.9 (60.9–74.9)		
			800 mg: 93.1 (79.7–106.5)		
	HPLC-Fluor	Cmax: ND	Serum Cmax: ND	—	—
		Conc at day 3, t = 2 h: 3.36 ± 2.23	Serum conc at day 3, t = 2 h: 3.15 ± 1.52		
		AUC: ND	Serum AUC: ND		
	HPLC-UV	Cmax	Serum Cmax	0.508	Corr
		100 mg: 0.5133–0.7333	100 mg: 0.7682–1.1785	100 mg: 0.42–0.71	$AUC_{0–6\ h}$
		200 mg: 0.9442–2.0530	200 mg: 1.8792–3.0890	200 mg: 0.40–0.63	
		$AUC_{0–6\ h}$	Serum $AUC_{0–6\ h}$		
		100 mg: 1.7368–2.4653	100 mg: 2.8755–4.6179		
		200 mg: 3.8850–6.5199	200 mg: 7.0148–10.0860		
	Paper disk method with *Bacillus subtilis* and *Escherichia coli*	Cmax: ND	Serum Cmax: ND	0.9969	Corr
		AUC: ND	Serum AUC: ND		
	Agar-well diffusion method with *Escherichia coli*	No Cmax detected in 40% of samples of day 2	Serum Cmax: 3.6 ± 1.7	—	—
		Conc: 0.1–0.7			
		AUC: ND	Serum $AUC_{0–inf}$: 47.3 ± 28.3		

TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
	RP-HPLC-UV (serum), paper disk-plate method with *Bacillus subtilis* or *Escherichia coli* (serum and saliva)	Cmax: ND	Serum Cmax of single doses	0.655	Corr
		Highest measured conc of single doses	100 mg: 0.95 ± 0.17		
		100 mg: 0.77 ± 0.17 at 2 h	300 mg: 2.65 ± 0.41		
		300 mg: 2.51 ± 0.24 at 2 h	300 mg fasting: 3.86 ± 0.85		
		300 mg fasting: 3.02 ± 1.20 at 1 h	600 mg: 6.64 ± 0.76		
		600 mg: 4.44 ± 0.79 at 3 h			
		AUC: ND	Serum $AUC_{0-24\ h}$ of single doses		
			100 mg: 6.02 ± 1.05		
			300 mg: 21.70 ± 2.63		
			300 mg fasting: 29.38 ± 4.74		
			600 mg: 68.40 ± 7.61		
	Paper disk method with *Bacillus subtilis* and *Escherichia coli*	Cmax	Serum Cmax	Non-HD: 0.75	Corr
		Non-HD: 1.32	Non-HD: 1.68	HD: 1.07	
		HD: ND	HD: ND	Non-HD: 0.61‡	AUC
		AUC	Serum AUC		
		Non-HD: 64.29	Non-HD: 105.23		
		HD: ND	HD: ND		
Gatifloxacin	RP-HPLC-Fluor	Cmax	Serum Cmax	0.81	Corr
		200 mg: 1.55 ± 0.51	100 mg: 0.873 ± 0.187		
		400 mg: 3.05 ± 0.74	200 mg: 1.71 ± 0.35		
			400 mg: 3.35 ± 0.55		
			600 mg: 5.41 ± 1.13		
			Serum 300 mg b.i.d.:		
			Day 1: 2.77 ± 0.54		
			Day 4: 3.45 ± 0.63		
			Day 7: 3.36 ± 0.46		
		AUC: ND	Serum AUC_{0-inf}		
			100 mg: 7.00 ± 1.36		
			200 mg: 14.5 ± 2.6		
			400 mg: 32.4 ± 4.1		
			600 mg: 53.5 ± 2.6		
	HPLC-Fluor	Cmax	Plasma Cmax	About 1	Conc
		400 mg: day 1: 3.2†	400 mg: day 1: 3.682 ± 0.75, day 15: 4.226 ± 1.283		

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TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
		600 mg: day 1: 7.0†	600 mg: day 1: 5.266 ± 1.237, day 15: 5.811 ± 1.043		
		AUC: ND	Plasma AUC_{0-inf}		
			400 mg: day 1: 30.871 ± 4.390		
			600 mg: day 1: 51.728 ± 7.625		
			Plasma $AUC_{0-24\ h}$:		
			400 mg: day 15: 34.409 ± 5.740		
			600 mg: day 15: 61.763 ± 10.198		
Amikacin	Paper disk method with *Bacillus subtilis*	Cmax: ND	Serum Cmax: ND	—	—
		AUC: ND	Serum AUC: ND		
	ND	Cmax: ND	Serum Cmax: ND	—	—
		AUC: ND	Serum AUC: ND		
Linezolid	HPLC-MS/MS	Cmax: 10.1 (8.2–10.7)	Serum Cmax: 10.9 (6.8–11.5)	0.97	Conc serum-saliva
		$AUC_{0-12\ h}$: 62.1 (50.5–89.2)	Serum $AUC_{0-12\ h}$: 63.9 (47.8–83.8)	1.03‡	Conc saliva-serum
				0.97‡	$AUC_{0-12\ h}$
				1.05	Corr serum-saliva
				0.95‡	Corr saliva-serum
	HPLC-UV	Cmax: ND	Plasma Cmax: ND	—	—
		Highest measured mean conc at t = 3 h: 7.1–17.0	Highest measured mean plasma conc at t = 3 h: 10.4–14.1		
		AUC: ND	Plasma AUC: ND		
Amoxicillin/clavulanate	Bioassay with *Sarcina lutea*	Not detected	Plasma Cmax: 14.56 (11.03–18.1)	—	—
		AUC: ND	Plasma AUC_{0-4h}: 24.4 (21.1–27.6)		
			Plasma AUC_{0-inf}: 25.9 (21.8–30.1)		
	RP-HPLC-UV	Not detected	Plasma Cmax	—	—
			H. Pylori−: 51.9 (29.0–74.8)		
			H. Pylori+: 41.7 (23.3–60.0)		
		AUC: ND	Plasma $AUC_{0-2\ h}$		
			H. Pylori−: 1587.7 (1208.2–1967.2), H. Pylori+: 1203.3 (989.3–1417.3)		
			Plasma AUC_{0-inf}		
			H. Pylori−: 1755.1 (1394.0–2116.2), H. Pylori+: 1358.4 (1135.4–1581.4)		
	Micro-method with *Sarcina lutea*	Cmax: ND	Serum Cmax: ND	—	—
		Highest measured conc at t = 2 h	Highest measured serum conc at t = 1 h		

TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
		15 mg/kg: 0.3 (0–0.36); Detected in 50% of samples	15 mg/kg: Fasting: 5.4 ± 0.76; Fed: 3.2 ± 0.48		
		25 mg/kg: 0.17 (0–0.4); Detected in 70% of samples	25 mg/kg: Fasting: 8.9 ± 1.4; Fed: 7.9 ± 1.7		
		AUC: ND	Serum AUC		
			15 mg/kg: fasting: 16; 15 mg/kg, fed: 14		
			25 mg/kg: fasting: 24; 25 mg/kg, fed: 24		
	RP-LC-ESI-MS (plasma), RP-HPLC-UV (saliva)	Cmax	Plasma Cmax	Amoxil: 0.47‡	$AUC_{0–8\ h}$
		Amoxil: 6.37 ± 3.63	Amoxil: 14.37 ± 6.01	Amoxicillin EMS: 0.34‡	
		Amoxicillin EMS: 6.23 ± 4.89	Amoxicillin EMS: 16.94 ± 6.39	Amoxil: 0.55‡	
		$AUC_{0–8\ h}$	Plasma $AUC_{0–8\ h}$	Amoxicillin EMS: 0.34‡	$AUC_{0–inf}$
		Amoxil: 22.83 ± 13.92	Amoxil: 48.28 ± 20.00		
		Amoxicillin EMS: 18.78 ± 14.62	Amoxicillin EMS: 55.10 ± 14.25		
		$AUC_{0–inf}$	Plasma $AUC_{0–inf}$		
		Amoxil: 26.29 ± 14.27	Amoxil: 47.62 ± 18.42		
		Amoxicillin EMS: 18.50 ± 15.06	Amoxicillin EMS: 54.14 ± 12.38		
	Agar diffusion method with *Bacillus subtilis*	Cmax: ND	Serum Cmax: ND	—	—
		Conc at est Tmax (2 h): 0.03 ± 0.01	Serum conc at est Tmax (2 h): 7.16 ± 2.53		
		AUC: ND	Serum AUC: ND		
Doripenem	UHPLC-MS/MS	Cmax: 0.5 ± 0.2	Plasma Cmax: 15.3 ± 6.0	0.04 ± 0.03	$AUC_{0–inf}$
		$AUC_{0–8\ h}$: 0.9 ± 0.5	Plasma $AUC_{0–8\ h}$: 26.0 ± 9.9	0.03‡	$AUC_{0–8\ h}$
		$AUC_{0–inf}$: 1.0 ± 0.5	Plasma $AUC_{0–inf}$: 26.3 ± 10.1		
Clarithromycin	RP-HPLC-coulometric detection	Cmax at steady state	Serum Cmax	—	—
		Day 3: 1.9†	Day 1: 2.1 ± 0.7		
		Highest measured conc	Day 3: 2.3 ± 1.0		
		Day 1 at 4 h: 1.06 ± 0.7			
		Day 3 at 4 h: 1.87 ± 1.3			
		AUC: ND	Serum $AUC_{0–inf}$		
			Day 1: 15.3 ± 4.8		
			Day 3: 27.9 ± 12.4		
	HPLC-EC	Cmax: 500 mg q.d.	Serum Cmax: 500 mg q.d.:	0.25–0.40	Conc

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TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
		Day 1: 0.89 ± 0.32, day 5: 1.06 ± 0.38 250 mg b.i.d. Day 1: 0.31 ± 0.15, day 5: 0.29 ± 0.07 AUC: ND	Day 1: 2.10 ± 0.49, day 5: 2.33 ± 0.58 250 mg b.i.d. Day 1: 0.94 ± 0.33, day 5: 1.23 ± 0.37 Serum $AUC_{0–12\ h}$ 250 mg b.i.d., day 1: 5.21 ± 1.31 Serum $AUC_{0–inf}$ 500 mg q.d., day 1: 15.63 ± 4.46 250 mg b.i.d., day 1: 5.80 ± 1.31 Serum AUC_{ss} 500 mg q.d., day 5: 18.32 ± 4.77 250 mg b.i.d., day 5: 7.85 ± 2.00		
	HPLC-EC	Cmax Day 1: 0.9† Day 7: 1.6† AUC: ND	Serum Cmax Day 1: 1.76 ± 0.51 Day 7: 2.41 ± 0.81 Serum $AUC_{0–12\ h}$ Day 1: 10.6 ± 2.51 Day 7: 18.0 ± 5.0 $AUC_{0–inf}$ Day 1: 12.6 ± 3.34	Around 0.5	Conc
	HPLC-MS/MS	Cmax: 2.8 (2.0–3.4) $AUC_{0–12\ h}$: 10.7 (9.4–12.1)	Serum Cmax: 1.7 (1.3–2.7) Serum $AUC_{0–12\ h}$: 8.2 (6.2–12.2)	3.07 0.33‡ 1.30‡ 2.67 0.37‡	Conc serum-saliva Conc saliva-serum $AUC_{0–12\ h}$ Corr serum-saliva Corr saliva-serum
	Bioassay with *Sarcina lutea*	Cmax: 3.87 (3.03–4.72) $AUC_{0–4\ h}$: 9.48 (7.56–11.41)	Plasma Cmax: 5.39 (4.54–6.23) Plasma $AUC_{0–4\ h}$: 12.7 (11.5–13.9) Plasma $AUC_{0–inf}$: 29.5 (20.2–38.8)	0.75‡	$AUC_{0–4\ h}$
	Agar plate diffusion method with *Bacillus subtilis*	Cmax Day 1: 2.38 (0.78–4.58) Day 10: 4.29 (2.67–7.39) $AUC_{0–10\ h}$ Day 1: 13.3 (5.2–28.4) Day 10: 27.4 (20.2–35.9)	Plasma Cmax Day 1: 2.98 (1.74–4.94) Day 10: 3.87 (2.23–7.41) Plasma $AUC_{0–10\ h}$ Day 1: 18.1 (9.8–27.8) Day 10: 27.8 (18.8–42.8)	Day 1: 0.73‡ Day 10: 0.99‡	$AUC_{0–10\ h}$

TABLE 1. (*Continued*) Data of Included Pharmacokinetic Studies Comparing Salivary and Blood Anti-TB Drug Peak Concentrations, Values of AUC, and the Saliva-Plasma or Saliva-Serum Ratio in Humans

Drug	Analytical Method	Saliva Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Plasma or Serum Cmax (mcg/mL) and AUC (mcg·h·mL^{-1})	Saliva-Plasma or Saliva-Serum Ratio	Characteristics of Ratio
	Agar diffusion method with *Micrococcus luteus*	Cmax: ND	Serum Cmax: ND	—	—
		Conc at estimated Tmax (2 h): 2.72 ± 0.87	Serum conc at estimated Tmax (2 h): 4.04 ± 1.14		
		AUC: ND	Serum AUC: ND		
	Paper disk method with *Micrococcus luteus*	Cmax: 1.93457	Serum Cmax: 1.48624	0.95‡	AUC
		AUC: 17.7031	Serum AUC: 18.584		

*The legend of the graph in the article referred to the upper curve as a result of a 400-mg dose. We assumed this was a mistake; therefore, the Cmax values of 400 and 600 mg are exchanged. Authors of the article were contacted but did not respond.
†Estimated value.
‡Calculated value.
alt. d., every other day; AOM, acute otitis media; AUC, area under the time-concentration curve; b.i.d., twice a day; Cmax, peak concentration; conc, concentration; corr, slope of correlation of saliva and plasma or serum; EC, electro-chemical; fluor, fluorescence; HD, hemodialysis; HPLC, high-performance liquid chromatography; HV, healthy volunteers; ITB, intestinal TB; i.v., intravenous; ND, not defined; NS, non-stimulated; NSCLC, non-small cell lung cancer; p.o., per oral; PTB, pulmonary TB; q.d., once a day; RP, reversed phase; S, stimulated; SCI, spinal cord injury; SP, spectrophotometry; t.i.d., three times a day; Tmax, time of peak concentration; UV, ultraviolet-visible spectrophotometry.

analytical methods for saliva and plasma. This could have introduced bias in the measurement of outcomes. Fujita et al[25] and Biasini et al[23] were judged at a serious risk of bias because important information, for instance, the sampling or analytical procedure, was scarcely described. Fujita et al[25] did not mention any validation of the analytical method, whereas Biasini et al[23] provided too little information about the analytical procedures to estimate the risk of bias. Goddard et al[26] did not use paired sampling for all time points. Ohkubo et al[27] sampled saliva after tooth brushing. This could have contaminated the samples with blood. All other studies were estimated at a moderate risk of bias, meaning the study provides evidence for a nonrandomized study but is not comparable with a well-performed randomized trial.[20]

In general, a large variability in saliva–plasma and saliva–serum was observed for isoniazid, rifampicin, moxifloxacin, ofloxacin, and clarithromycin (Figures 2 and 3). The saliva–plasma and saliva–serum ratios of rifampicin were clustered in 2 groups: Murthy and Kumar,[28] Darouiche et al,[29] Ezejiofor et al,[30] and Gurumurthy et al,[31] with ratios of 0.1–0.2, in contrast to Orisakwe et al,[32] and Orisakwe and Ofoefule[33] with ratios around 0.6. A similar clustering effect was seen with moxifloxacin. Kumar et al[34] and Burkhardt et al[35] reported saliva–plasma and saliva–serum ratios of 0.4–0.6, whereas Stass et al,[36] Müller et al,[37] and Burkhardt et al[38] found ratios of 0.8–0.9. Isoniazid, ofloxacin, and clarithromycin showed an overall large diversity of reported saliva–plasma and saliva–serum ratios. For gatifloxacin, linezolid, and doripenem, relatively small ranges of saliva–plasma and saliva–serum ratios were found.

All included studies of amoxicillin/clavulanate administered only amoxicillin instead of the combination with clavulanate that is used in TB treatment. The small range of saliva–plasma ratios for amoxicillin is distorted. In fact, all studies, except Baglie et al,[22] reported a very low or even no detectable salivary concentration of amoxicillin, indicating a saliva–plasma or saliva–serum ratio of close to 0. By contrast, Baglie et al[22] reported amoxicillin quantifiable salivary Cmax and AUC values as well as a saliva–plasma ratio of 0.34–0.55. The 2 included studies of amikacin, Masumi et al[39] and Biasini et al[23] did not report any saliva–plasma or saliva–serum ratios.

Several studies reported a time-dependent saliva–plasma or saliva–serum ratio. Suryawati and Santoso[40] reported a rifampicin saliva–serum ratio of 1.09 ± 0.29 during the absorption phase and 0.81 ± 0.05 during the elimination phase. For moxifloxacin, Burkhardt et al[38] and Müller et al[37] observed a saliva–plasma or saliva–serum ratio higher than 1 during the first 2 hours after administration. Thereafter, the ratio declined to below 1. A time-dependent saliva–serum ratio was also found for ofloxacin by Koizumi et al.[41] During the first 4 hours after administration, the saliva–serum ratio was below 1, and during the following 4 hours, the ratio increased to above 1 and remained above 1 during 8–16 hours after administration. After 16 hours, a mean saliva–serum ratio of 1.14 was measured.

DISCUSSION

In this systematic review, we aimed to investigate whether TDM of anti-TB drugs using saliva samples is

TABLE 2. Results of Risk of Bias Assessment of Included Articles Using Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) Tool

Study	Confounding	Selection of Participants	Classification of Interventions	Deviations From Interventions	Missing Data	Measurement of Outcomes	Selection of Reported Result	Overall
Baglie et al	+	+	+	+	+	−	+/−	−
Biasini et al	−	+	+	+	−	?	+/−	−
Bolhuis et al	+	+	+	+	+	+	+/−	+/−
Brown et al	+	+	+	+	+	−	+/−	−
Burian et al	+	+	+	+	+	+	+/−	+/−
Burkhardt et al, 2006	+	+	+	+	+	+	+/−	+/−
Burkhardt et al, 2002	+	+	+	+	+	+	+/−	+/−
Darouiche et al	+	+	+	+	+	+	+/−	+/−
Edlund et al, 2000	+	+	+	+	+	+	+/−	+/−
Edlund et al, 1998	+	+	+	+	+	+	+/−	+/−
Ezejiofor et al	+	+	+	+	+	+	+/−	+/−
Fassbender et al	+	+	+	+	+	+	+/−	+/−
Fujita et al	−	+	+	+	+	+	+/−	−
Ginsburg et al	+	+	+	+	+	+	+/−	+/−
Goddard et al	−	+	+	+	+	+	+/−	−
Gurumurthy et al	+	+	+	+	+	+	+/−	+/−
Hara et al	+	+	+	+	+	+	+/−	+/−
Hutchings et al	+	+	+	+	+	+	+/−	+/−
Ichihara et al	+	+	+	+	+/−	+	+/−	+/−
Immanuel et al	+	+	+	+	+	+	+/−	+/−
Kees et al	+	+	+	+	+	+	+/−	+/−
Koizumi et al	+	+	+	+	+	+	+/−	+/−
Kozjek et al	+	+	+	+	+	+	+/−	+/−
Kumar et al	+	+	+	+	+	+	+/−	+/−
Leigh et al	+	+	+	+	+	+	+/−	+/−
Masumi et al	+	+	+	+	+	+	+/−	+/−
McCracken et al	+	+	+	+	+	+	+/−	+/−
Mignot et al	+	+	+	+	+	+	+/−	+/−
Miya et al	+	+	+	+	+	+	+/−	+/−
Morihana et al	+	+	+	+	+	+	+/−	+/−
Müller et al	+	+	+	+	+	+	+/−	+/−
Murthy et al	+	+	+	+	+	+	+/−	+/−
Nakashima et al	+	+	+	+	+	+	+/−	+/−
Ohkubo et al	−	+	+	+	+	+	+/−	−
Orisakwe et al, 2004	+	+	+	+	+	+	+/−	+/−
Orisakwe et al, 1996	+	+	+	+	+	+	+/−	+/−
Ortiz et al	+	+	+	+	+	+	+/−	+/−
Stass et al	+	+	+	+	+	+	+/−	+/−
Suryawati et al	+	+	+	+	+	+	+/−	+/−
Tsubakihara et al	+	+	+	+	+	+	+/−	+/−
Warlich et al	+	+	+	+	+	+	+/−	+/−
Wüst et al	+	+	+	+	+	+	+/−	+/−

Low risk of bias (+), moderate risk of bias (+/−), serious risk of bias (−), and no information (?).

feasible. We found this to be likely possible for linezolid and gatifloxacin, whereas possible for isoniazid, rifampicin, ofloxacin, moxifloxacin, and clarithromycin. For other anti-TB drugs, either too few data were available, or the drugs seemed unlikely to be feasible for salivary TDM.

The review was strengthened by the inclusion of all WHO-approved anti-TB drugs as well as ertapenem,

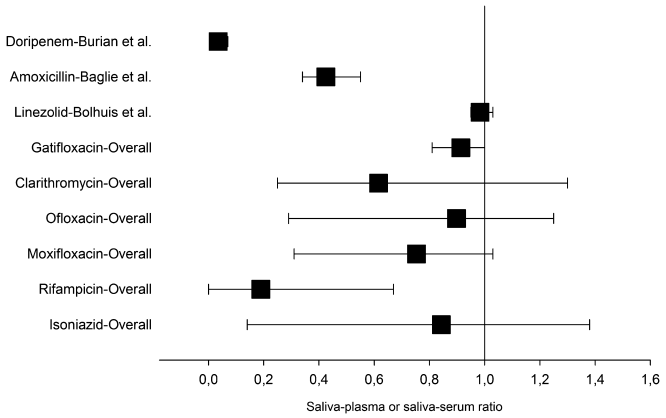

FIGURE 2. Saliva–plasma or saliva–serum ratio of anti-TB drugs. The weighted mean () and range of saliva–plasma or saliva–serum ratio are displayed per drug. Mean (range) of doripenem: 0.04 (0.01–0.07); amoxicillin: 0.43 (0.34–0.55); linezolid: 0.98 (0.95–1.03); gatifloxacin: 0.91 (0.81–1.00); clarithromycin: 0.62 (0.25–1.30); ofloxacin: 0.90 (0.29–1.25); moxifloxacin: 0.75 (0.31–1.03); rifampicin: 0.19 (0.00–0.67); and isoniazid: 0.84 (0.14–1.38). For doripenem, amoxicillin, and linezolid, only 1 study with a saliva–plasma or saliva–serum ratio was included. For the other drugs, the numbers of included studies were as follows: gatifloxacin (n = 2), clarithromycin (n = 6), ofloxacin (n = 9), moxifloxacin (n = 5), rifampicin (n = 6), and isoniazid (n = 3).

faropenem, and doripenem because interest in using these other carbapenems as part of anti-TB treatment has increased.[42] Ofloxacin and clarithromycin were still included, despite the WHO recommendation to not use these drugs.[3] In specific situations, ofloxacin and clarithromycin might be useful to treat difficult cases.[43] The information gained from this systematic review could also be applied to other infectious diseases.

Isoniazid,[24,31,40] moxifloxacin,[34–38] ofloxacin,[21,25,27,41,44–49] and clarithromycin[26,38,50–52] showed varying saliva–plasma and saliva–serum ratios. The same issue applied to rifampicin, although rifampicin showed some low saliva–plasma and saliva–serum ratios that could complicate the detection of the drug in saliva for low-dosage regimes. A wide range of saliva–plasma and saliva–serum ratios is especially caused by highly varying mean ratios across studies, not by wide ranges of study-specific ratios. A wide range of saliva–plasma and saliva–serum ratios could be caused by differences in study population, dose, saliva sampling method, and analytical method between the studies. The influences of these factors on the saliva–plasma and saliva–serum ratio are hard to determine because of the great variation of these factors among the included studies. Salivary TDM of these 5 anti-TB drugs may be possible; however, 1 workable saliva–plasma or saliva–serum ratio is required (Table 3). For instance, if the saliva–plasma ratio of isoniazid of 0.14 as found by Brown et al[24] is applied to predict AUC values in blood using salivary AUC, the calculated AUC in blood will be almost 7 times higher than if the ratio of Gurumurthy et al[31] (0.95) or of Suryawati and Santoso[40] (0.90) is used. These substantial differences could have an effect on dosing recommendations based on such TDM results. However, the quality of Brown et al[24] was unclear, as said study was classified as at a serious risk of bias.

For gatifloxacin and linezolid, salivary TDM is likely possible because of the narrow range of saliva–serum and saliva–plasma ratios.[51,53,54] An additional study of gatifloxacin, preferably in patients with TB, should be performed to confirm the reported findings because pharmacokinetic parameters could significantly differ in patients with TB using several anti-TB drugs compared with healthy volunteers. However, in 2006, the US Food and Drug Administration (FDA) officially warned that gatifloxacin is associated with an elevated risk of dysglycemia.[55,56] So, gatifloxacin might be replaced in TB treatment by other fluoroquinolones, such as moxifloxacin or levofloxacin, in the future. Additional studies of linezolid using other dosages are necessary to rule out any dose dependency of the saliva–serum ratio and to complete the salivary pharmacokinetic profile of linezolid.

For doripenem and amoxicillin/clavulanate, salivary TDM is probably not possible because of very low salivary drug concentrations (Table 3). Both doripenem and amoxicillin are hydrophilic drugs and this complicates passage through membranes.[57,58] This problem could also apply to the other carbapenems. More studies comparing doripenem concentrations in blood and saliva are needed to confirm the results of Burian et al[59] and to rule out any dose dependency. Nearly all studies regarding amoxicillin/clavulanate reported undetectable amoxicillin concentrations in saliva.[26,60–62] Only Baglie et al[22] reported a substantial salivary concentration of amoxicillin and a saliva–plasma ratio. A possible reason is that this study administered the highest dose of all included studies. Besides, the variant results of Baglie et al[22] could also be explained by the serious risk of bias.

More information is needed about the salivary pharmacokinetics of amikacin because no saliva–plasma or saliva–serum ratios or salivary AUC values are reported in the analyzed articles.[23,39]

For many anti-TB drugs, salivary pharmacokinetic information is lacking, even for the first-line drugs pyrazinamide and ethambutol (Table 3). As the incidence of drug-susceptible TB is significantly greater than the incidence of MDR-TB, the first-line drugs have to be prioritized in future studies of salivary TDM. Especially, for pyrazinamide, more information about the pharmacokinetic parameters in saliva versus blood is important, as it is part of the MDR-TB regimen.[3] Besides, pyrazinamide is one of the few anti-TB drugs for which low serum concentrations are associated with poor treatment outcomes.[63,64] The priority of second-line drugs should be ranked according to the grouping system of WHO as shown in Table 3. Anti-TB drugs in group A are considered the most beneficial in MDR-TB treatment and will be often used, whereas groups D2 and D3 contain add-on anti-TB drugs that will be less frequently prescribed.

Obviously, more pharmacokinetic studies comparing anti-TB drug concentrations in saliva and plasma or serum are needed before salivary TDM could be implemented in the treatment of TB. To overcome the observed variability in saliva–plasma and saliva–serum ratios, large study populations and comparable study designs, study populations, dosage regimes, saliva sampling methods (stimulated versus

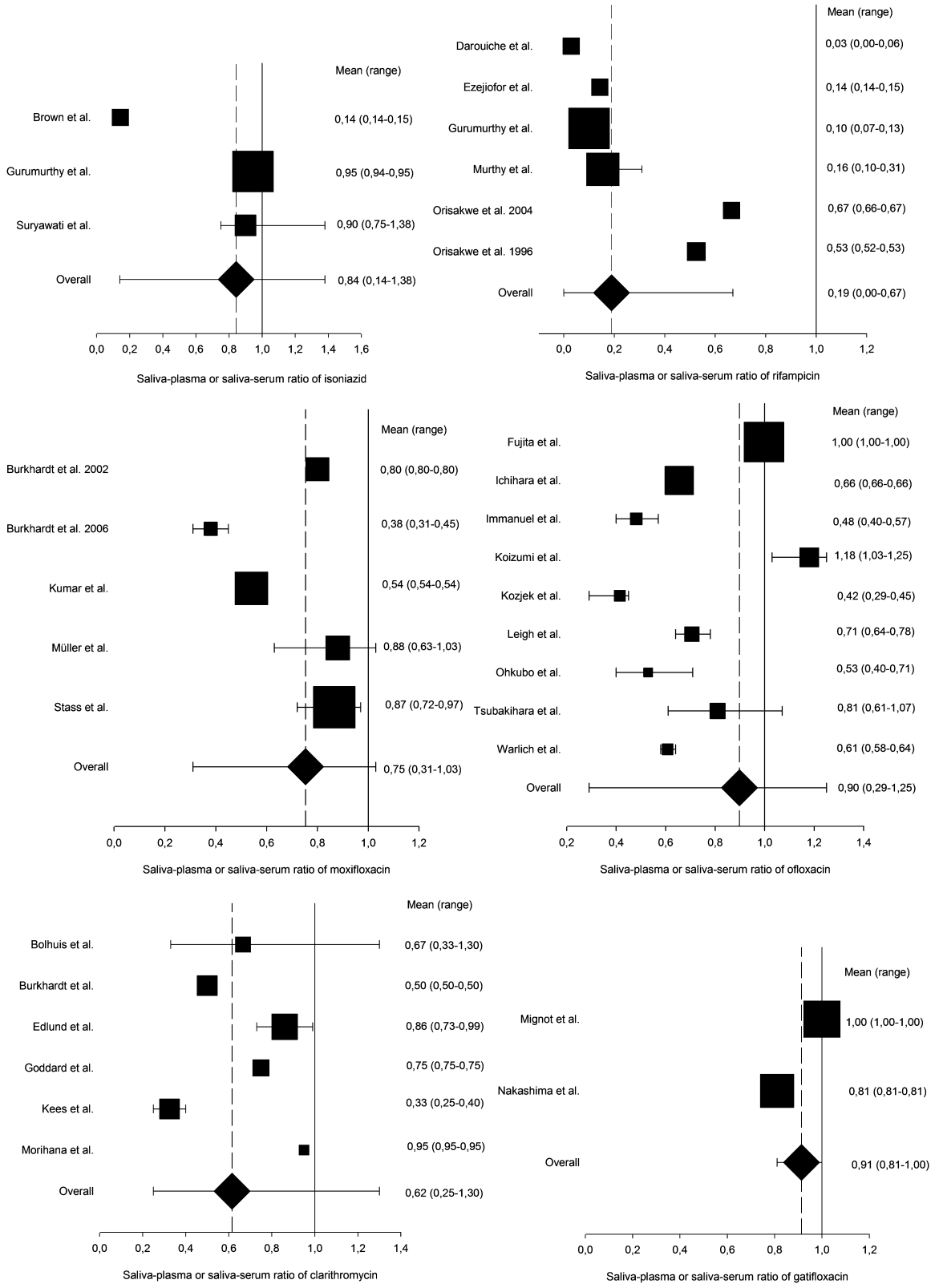

FIGURE 3. Saliva–plasma or saliva–serum ratios of anti-TB drugs. Top left: isoniazid; top right: rifampicin; middle left: moxifloxacin; middle right: ofloxacin; bottom left: clarithromycin; and bottom right: gatifloxacin. As per drug, the saliva–plasma or saliva–serum ratios of the included articles are displayed as weighted mean () with range. In addition, the overall mean (♦) and range were determined for each drug. All numerical values of mean and range are presented to the right of the graphs.

TABLE 3. Summary of Salivary TDM Potentials of all Anti-TB Drugs

Group	Anti-TB Drug	Conclusion	Comments
First-line drugs	Isoniazid	Maybe possible	Wide range of saliva–plasma and saliva–serum ratios.
	Rifampicin	Maybe possible	Wide range of saliva–plasma and saliva–serum ratios. Some low ratios reported.
	Ethambutol	No data	Studies needed.
	Pyrazinamide	No data	Studies needed.
Group A: fluoroquinolones	Levofloxacin	No data	Studies needed.
	Moxifloxacin	Maybe possible	Wide range of saliva–plasma and saliva–serum ratios.
	Gatifloxacin	Likely possible	Promising saliva–plasma and saliva–serum ratios. Additional study in patients with TB needed.
Group B: second-line injectable agents	Amikacin	No data	Studies needed. Included studies did measure salivary concentrations, but no Cmax, AUC, or saliva–plasma or saliva–serum ratio was reported.
	Capreomycin	No data	Studies needed.
	Kanamycin	No data	Studies needed.
	Streptomycin	No data	Studies needed.
Group C: other core second-line agents	Ethionamide	No data	Studies needed.
	Prothionamide	No data	Studies needed.
	Cycloserine	No data	Studies needed.
	Terizidone	No data	Studies needed.
	Linezolid	Likely possible	Promising saliva–serum ratios. More studies with other dosage regimes needed.
	Clofazimine	No data	Studies needed.
Group D1: add-on agents	Pyrazinamide	See first-line drugs	See first-line drugs.
	Ethambutol		
	High-dose isoniazid		
Group D2: add-on agents	Bedaquiline	No data	Studies needed.
	Delamanid	No data	Studies needed.
Group D3: add-on agents	p-aminosalicylic acid	No data	Studies needed.
	Imipenem/cilastatin	No data	Studies needed.
	Meropenem	No data	Studies needed.
	Amoxicillin/clavulanate	Probably not possible	Low or undetectable drug concentrations in saliva, probably due to low lipophilicity.
	Thioacetazone	No data	Studies needed.
Other	Ofloxacin	Maybe possible	Wide range of saliva–plasma and saliva–serum ratios.
	Clarithromycin	Maybe possible	Wide range of saliva–plasma and saliva–serum ratios.
	Ertapenem	No data	Studies needed.
	Doripenem	Probably not possible	Low saliva–plasma ratio, probably due to low lipophilicity. More studies with other dosage regimes needed.
	Faropenem	No data	Studies needed.

The conclusion of this systematic review is displayed as per anti-TB drug using "No data," "Probably not possible," "Maybe possible," and "Likely possible." Besides, comments are added to clarify these conclusions.

nonstimulated), and analytical methods should be used in future studies.

An ideal design for this kind of study is proposed in Figure 4 to assist and advice all future researchers. Most important factors are inclusion of patients with TB, paired sampling, validation, salivary flow, salivary pH, and saliva–plasma or saliva–serum ratios calculated using AUC values.

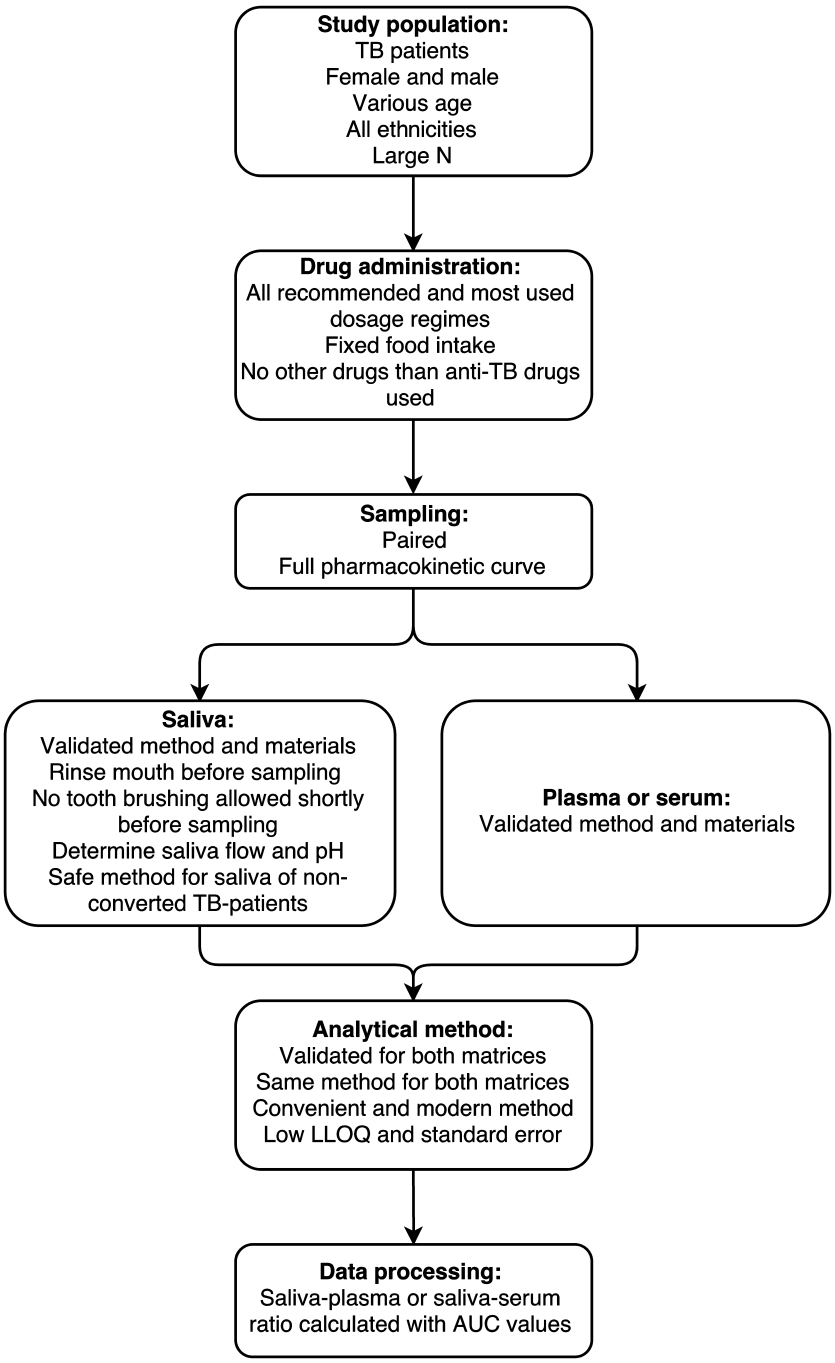

FIGURE 4. Ideal study design for pharmacokinetic studies comparing anti-TB drug concentrations in saliva and plasma or serum. LLOQ, lower limit of quantification; N, number.

A limitation of this systematic review is that many studies included healthy volunteers instead of patients with TB. It is hard to extrapolate the findings of these studies to the clinic because the effect of TB on the salivary pharmacokinetics is unknown. Furthermore, almost none of the included studies reported the saliva flow and pH, although both can influence the salivary drug concentration.[12,18] The salivary flow and pH values were not included in this review because of a lack of information. In future studies of salivary pharmacokinetics, salivary flow and pH should be measured to provide a complete profile. Besides, risk of bias assessment of the included articles was problematic because no tool is validated for pharmacokinetic studies. The ROBINS-I tool was not used in its validated structure as a result of changes in the confounding section. A validated and appropriate tool for the risk of bias assessment of pharmacokinetic studies is needed to assess the quality of these studies. Overall, our review found predictable saliva–plasma or saliva–serum ratios of less than 1. However, 3 studies of isoniazid and moxifloxacin reported saliva–plasma or saliva–serum ratios with values of above 1 during the absorption phase.[37,38,41] A high ratio during the absorption phase could be explained by drug

adhesion to the oral mucosa.[38] Normally, this effect is averted by rinsing the mouth with water before sampling, but this precaution was not reported in the 2 moxifloxacin studies.[37,38] An active transport system across the salivary epithelium can also cause a high concentration in saliva.[37] However, this seems unlikely because not all studies of isoniazid and moxifloxacin reported this high saliva–plasma or saliva–serum ratios.

In the future, many TB endemic settings may benefit from TDM with saliva samples, particularly if the saliva sample collection is standardized and sample analysis is optimized. For instance, salivary TDM would allow patients the option to sample themselves at any location and afterward bring their saliva samples to a local health post. Importantly, for the first-line drugs isoniazid and rifampicin, several analytical methods using ultraviolet-visible (UV-VIS) spectrophotometry have been used in several studies.[65–67] In addition, for ethambutol,[68] moxifloxacin,[69] levofloxacin,[70] ofloxacin,[71] paraaminosalicylic acid,[72] amoxicillin/clavulanate,[73] and imipenem/cilastatin,[74] UV-VIS spectrophotometry methods were described in literature. Remarkably, 1 analytical method that determines isoniazid, rifampicin, and pyrazinamide simultaneously with a UV-VIS spectrophotometer was published.[75] After validation in both blood and saliva, these UV-VIS methods could easily be implemented in referral laboratories of more resource-limited settings because of their relative simplicity and lower costs. Of caution, however, before implementing salivary TDM, the chemical stability of anti-TB drugs in saliva should be thoroughly studied to determine the necessity for rapid sample analysis. Isoniazid, for instance, is known to be unstable in both saliva and blood.[76,77] Furthermore, the eventuality of *M. tuberculosis* being culturable from the saliva of nonconverted patients with TB is an extra factor that must be taken into account. The sampling method should be thoroughly designed and tested in advance to create a safe technique for the investigators working with the saliva samples and all other people involved. A recent study showed that membrane filtration (pore size 0.22 mcg) is suitable for decontamination of saliva samples containing *M. tuberculosis*.[78] However, before membrane filtration can be implemented in salivary TDM, recovery testing should rule out any adhesion of the drug to membranes.

CONCLUSION

In this systematic review, we summarized the current knowledge about the salivary and blood concentrations of anti-TB drugs and their saliva–plasma or saliva–serum ratio in humans and determined for which anti-TB drugs salivary TDM should be further investigated either in basic pharmacokinetic studies or in larger validation cohorts.

Unfortunately, for most anti-TB drugs, salivary pharmacokinetic information is entirely lacking. For these drugs, such as pyrazinamide, pharmacokinetic studies comparing drug concentrations in saliva and blood are needed. For amikacin, pharmacokinetic studies using saliva samples were found but without saliva–plasma or saliva–serum ratios. Salivary TDM is likely possible for gatifloxacin and linezolid because of their promising, narrow-ranged saliva–plasma and saliva–serum ratios. It may be possible for isoniazid, rifampicin, moxifloxacin, ofloxacin, and clarithromycin, but because of the wide range of saliva–plasma and saliva–serum ratios, further well-designed pharmacokinetic studies in patients with TB would be recommended. TDM with salivary samples is probably not feasible for doripenem and amoxicillin/clavulanate because of very low salivary concentrations. Overall, it seems worthwhile to further explore saliva as potential matrix for TDM of anti-TB drugs, especially for children.

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