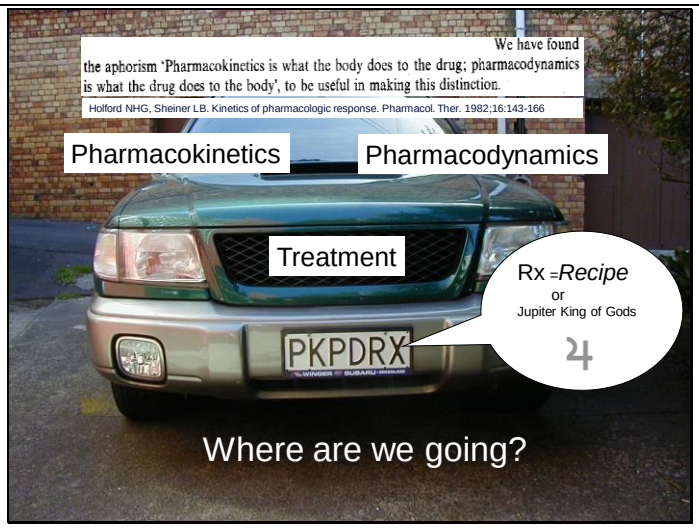
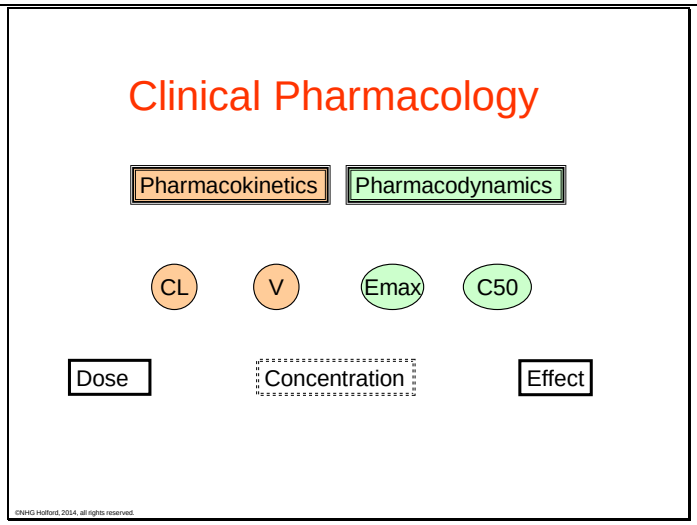
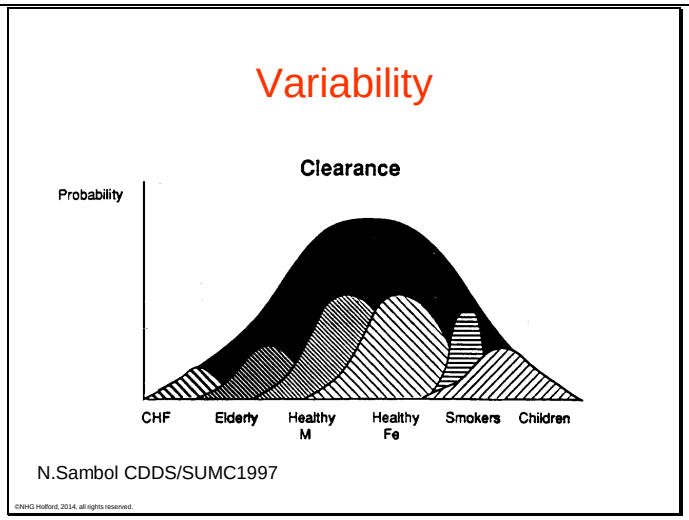
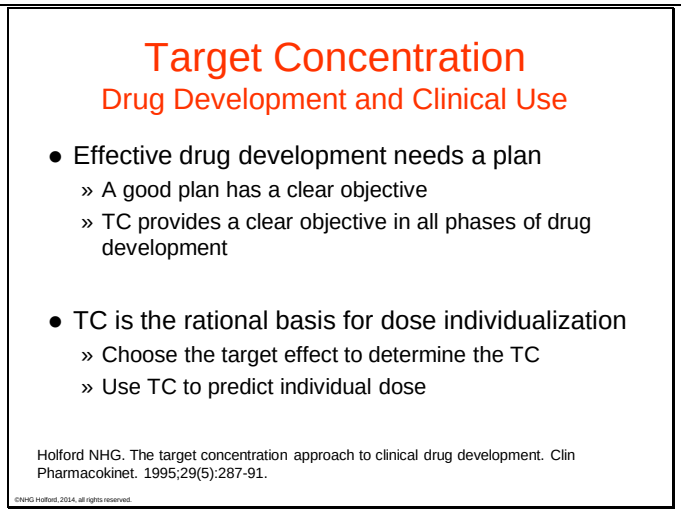
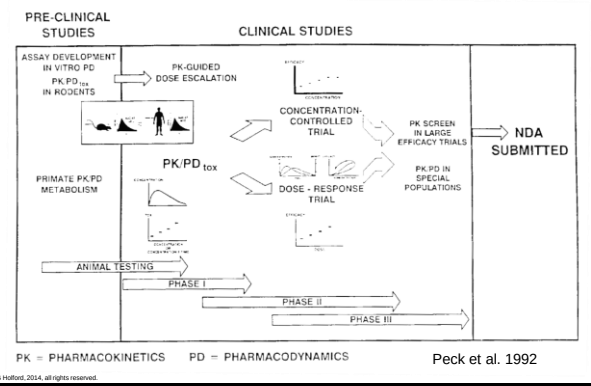
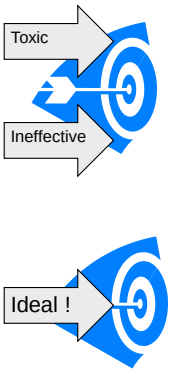
Slide 1	# PKPD Variability ## Quantifying Variability to aid Dose Individualization Nick Holford University of Auckland 	
Slide 2	# Objectives 1) Learn about the sources of variability in clinical pharmacology 2) Appreciate how a target concentration (TC) strategy is essential for rational drug development and clinical use 3) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM) 4) Understand how to make rational choices for dose individualization 	
Slide 3		PK = Pharmacokinetics: What the body does to the drug PD=Pharmacodynamics: What the drug does to the body Rx=Treatment: What the prescribed and patient need to know.

Slide 4		Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50).
Slide 5		
Slide 6		

Slide 7	**Target Concentration in Drug Development**  Peck et al. 1992 	The 1992 view was based on using PKPD for drug development but did not explicitly include how to use medicines in patients.
Slide 8	**Target Concentration in Clinical Use of Medicines** **Target Conc = Target Effect x C50 / (Emax-Target Effect)** | **Target Conc** | **Dose Model** | | Initial Peak | Loading Dose = **Target Conc** x **Volume of Distribution** | | Average Steady State | Maintenance Dose Rate = **Target Conc** x **Clearance** | Ideal dose prediction requires **individual** estimates of **Emax, C50, V and CL** 	The target concentration approach links PKPD to prediction of the right dose for a patient. If Emax and C50 and Target Effect are not known then the Target Conc may be estimated from: $\text{Target Conc} = \frac{\text{Typical Average Daily Dose}}{\text{Typical Clearance}}$
Slide 9	**TDM or TCI?** ● Therapeutic Drug Monitoring » TDM Therapeutic Range ☹ Imprecise » Sub-optimal at borders of the range ● Target Concentration Intervention » TCI Single Target ☺ Accurate » Optimal – do the best you can  	

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How to Find the Target?

Clin. Pharmacokinet. 25 (6): 495-505, 1993

Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L?
A Randomised Concentration-Controlled Trial

Nicholas Holford[1], *Peter Black*[1], *Ron Couch*[2], *Julia Kennedy*[3] and *Robin Briant*[1]

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- Randomized concentration controlled trials are the gold standard

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Why does PKPD vary?

- Systematic (predictable)
  - » Body size
  - » Disease state (liver, kidney)
  - » Genotype
  - » etc...
- Random (not predictable)
  - » Between Subject Variability
  - » Within Subject Variability

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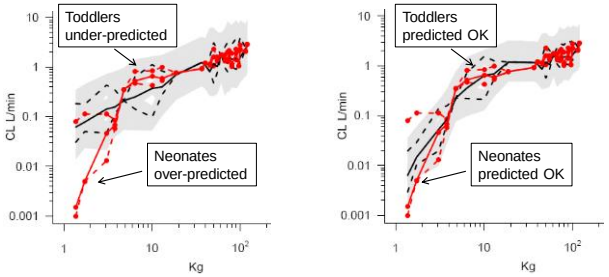
Predictable Variability Size and Maturation

¾ Allometry Alone
explains 67% of CL variability

¾ Allometry + Maturation
explains 80% of CL variability



Original data from Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010 Apr 1;49(4):269-75.

Slide 13	**Unexplained Clearance Variability** **Drug** / **BSV_U %** / **WSV_U %** / **Source** Metoprolol 53 35 Lunn (1997) Fenoterol 12 16 Bouillon (1996) Riluzole 51 28 Bruno (1997) Felodipine 34 33 Wade (1995) Drug A 57 29 Karlsson (1993) Drug B 35 19 Karlsson (1993) Drug B 33 19 Jonsson (1996) Moxonidine 22 15 Karlsson (1998) Artemisinin 48 53 Sidhu (1998) **Average** **41** **30** **BSV_U=Between Subject** **WSV_U=Within Subject** 	BSVu=Between Subject Variability unexplained by predictable factors such as weight, etc. WSVu=Within Subject Variability unexplained by predictable factors such as weight, etc. % expresses an apparent co-efficient of variation
Slide 14	**Safe and Effective Variability** ● CLINICAL JUDGMENT Suppose medicine use is safe and effective if: 1. Individual Css is on average at the Target Conc – Aim for the optimum target 2. 90% of the time Css is within 80%-125% of Target Conc – 'therapeutic range' with optimum target ● STATISTICS Assume log-normal distribution for Css 90% of Css must lie within ± 1.64 x SD – Therefore SD must be 0.136 The Safe and Effective Variability (SEV) is 13.6% 	Css = Average steady state concentration SD = Standard Deviation SEV=Safe and Effect Variability around target concentration
Slide 15	**Three Ways to Dose** ● Population » Same dose for everyone – The dream dosing method! ● Group (Covariate guided) » Same dose for similar group – e.g. same weight, CLcr, genotype ● Individual » Dose determined by individual response – e.g. BP, INR, blood conc 	CLcr = Creatinine clearance, BP = Blood Pressure, INR=International Normalized Ratio

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Identifying Variablility

- PPVtotal = Population Parameter Variability total of predictable and unexplained sources
- PPVu=Population Parameter Variability that is unexplained
- BSVp=Between Subject Variability that is predictable
- BSVu=Between Subject Variability that is unpredictable
- WSVu=Within Subject Variability that is unpredictable
- SEV=Safe and Effect Variability around target concentration

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Dosing Individualization Method Depends on SEV

Suppose PPV_{total}=0.7, BSV_u=0.4, WSV_u=0.3

$PPV_U=sqrt(BSV_u^2 + WSV_u^2)=0.5$ $BSV_P=sqrt(PPV_{total}^2 - BSV_u^2)=0.57$

SEV	Method Criteria	Example	Dosing Strategy
0.9	SEV>PPV_{total}	**0.9>0.7**	Population dosing
0.55	PPV_{total} > SEV SEV>PPV_u	0.7>0.55 **0.55>0.5**	Group dosing (WT, CLcr, etc) (BSV_P ⇨ 0)
0.35	PPV_u > SEV SEV>WSV_u	0.5>0.35 **0.35>0.3**	Individual response dosing (TCI) (BSV_U ⇨ 0)

Note: If SEV<WSV_u then medicine cannot be used safely

Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68

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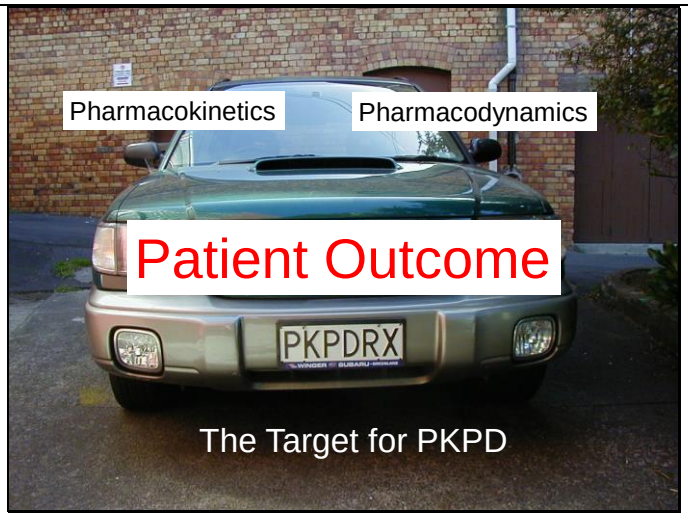
Safe and Effective Variability (SEV) Aminoglycosides

PPV_U	BSV_U	WSV_U
0.33	0.30	0.13

- Suggested Therapeutic Success Criterion
  90% of Concs Within 80%-125% of Target Css
  ∴ SEV is 0.136 (log normal SD)
- Unpredictable PPV_U is 0.33 and is > SEV
  ∴ Covariate (WT, CLcr) prediction alone will be inadequate
- Unpredictable WSV_U is 0.13 and is < SEV (just!)
  ∴ TCI can achieve safe and effective target

Matthews I, Kirkpatrick C, Holford NHG. Quantitative justification for target concentration intervention - Parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. British Journal of Clinical Pharmacology 2004;58(1):8-19

Slide 19	**Which Way to Aim?** ● Phase 2 Drug Development » PK and PKPD relationships (Target Effect ⟶ Target Conc) » Predictable and Unpredictable variability (PPV_T) » Between (BSV_U) and within subject (WSV_U) ● Phase 3 Drug Development » Safe and effective variability (SEV) » The BIG difficulty is deciding on SEV ! ● Clinical Use of Medicines » Use quantitative criteria to decide on dosing method » Covariate Dosing if PPV_T>SEV>PPV_U » TCI Dosing if PPV_U>SEV>WSV_U 	
Slide 20		The target for PKPD is improving patient outcome by developing medicines which can achieve the target effect
Slide 21	**Why TCI?** Clin. Pharmacokinet. 25 (6): 495-505, 1993 Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L? A Randomised Concentration-Controlled Trial *Nicholas Holford[1], Peter Black[1], Ron Couch[2], Julia Kennedy[3] and Robin Briant[1]* 1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand 2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand 3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand ● How can a target concentration of 10 mg/L be achieved and maintained? 	

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Which Drugs for TCI?

1. Effect is hard to measure (drug is working when the response is not observable)
   - » Anti-arrhythmics e.g. lignocaine
   - » Anti-convulsants e.g. phenytoin
   - » Anti-coagulants e.g. warfarin
2. Big unpredictable variability (using weight, renal function,etc) and small within subject variability
   - » Too much variability means either inadequate beneficial effect or too much adverse effect
   - » Observing patient response can predict future dose needs

The first reason for using TCI uses a response, such as BP, as a substitute for being able to measure the clinical disease state that is being treated. When the medicine is working well or it is not working at all the clinical disease state may appear to be the same. It is assumed that trying to reach a typical response that is usually associated with benefit is better than giving everyone the same dose.

The second reason for using TCI is when group based dosing (e.g. using weight) is not enough to reduce the between subject variability so that the medicine can be used safely and effectively. TCI can only work however if the within subject variability (that cannot be influenced by TCI) is small enough so that dose individualization is really predictive for future use of the medicine in the same patient.

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How?
Target Concentration Strategy

1. Choose Target Concentration
2. Determine V and CL using WT etc.
3. Calculate LD and MDR
4. Measure Response (e.g. INR)
   Revise Target Conc
5. Measure Concs
   Revise V and CL
6. Goto Step 3

The target concentration strategy is an algorithm for reaching the best individual dose. It starts with choosing a target concentration based on pharmacodynamic studies. A group value for volume (V) and or clearance (CL) can be determined before the medicine is given. These PK parameters are then used to calculate the initial loading dose (LD) and maintenance dose rate (MDR). A response is measured reflecting how the individual is different from the group of patients who are otherwise similar in weight, genotype, etc. If the response is a measure of drug effect e.g. INR, then it can be used to revise the target conc. If the response is a concentration then it can be used to revise V and CL. Most commonly the focus will be on CL so that a new individualized maintenance dose rate can be calculated.

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Target Concentrations

Target Concentrations and Pharmacokinetic Parameters for Selected Medicines (70 kg standard individual). Css is the average steady state concentration.

Drug	Target Conc	Clearance	Volume of distribution
Aminoglycosides	Peak 20 mg/L* Css 3 mg/L	6 L/h	18 L
Ciclosporin**	150 ng/mL	17 L/h	245 L
Phenytoin	10 mg/L	Vmax=415 mg/d, Km= 4mg/L	45 L
Digoxin	2 ng/mL	9 L/h	500 L
Theophylline	10 mg/L	3 L/h	35 L

* 24 hour dosing ** whole blood

Target concentrations and PK parameters are known for most medicines which are helped by TCI.

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Target Effects

Target Effects and Pharmacodynamic Parameters for Selected Medicines. Emax is the maximum effect due to the drug, EC50 is the concentration producing 50% of Emax. PEFR is peak expiratory flow rate.

Drug	Target Effect	Emax	EC50
Aminoglycosides	"cure"	?	?
Cyclosporine	"prevention of rejection"	?	?
Phenytoin	"prevention of seizures"	?	?
Digoxin	"control of atrial fibrillation"	?	?
Theophylline	"normal PEFR"	344 L/min	11 mg/L
Warfarin	INR 2-3	100% *	1.5 mg/L

- Inhibition of prothrombin complex synthesis

The pharmacodynamic parameters for medicines that use TCI are typically not well known. This is a reflection of the difficulty of measuring a clinical response that can be related to concentration.

Holford NHG, Black P, Briant R, Couch R, Kennedy J. Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? A randomised concentration-controlled trial. *Clinical Pharmacokinetics* 1993; 25:495-505

Holford NHG, Hashimoto Y, Sheiner LB. Time and theophylline concentration help explain the recovery of peak flow following acute airways obstruction. Population analysis of a randomised concentration controlled trial. *Clinical Pharmacokinetics* 1993; 25:506-515

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Determine Group V and CL

- Volume of Distribution
  - » size $V = V_{pop} \times WT/WT_{std}$
  - » body composition
- Clearance
  - » size $CL = Cl_{pop} \times (WT/WT_{std})^{3/4}$
  - » renal function
  - » hepatic function
  - » concomitant drugs

WT=patient weight
WTstd=standard weight e.g. 70 kg
Vpop, CLpop=population volume and clearance in a standard subject e.g. 70 kg.

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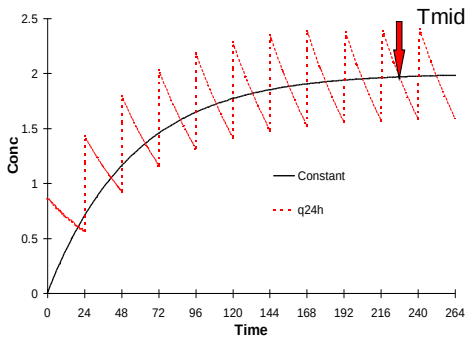
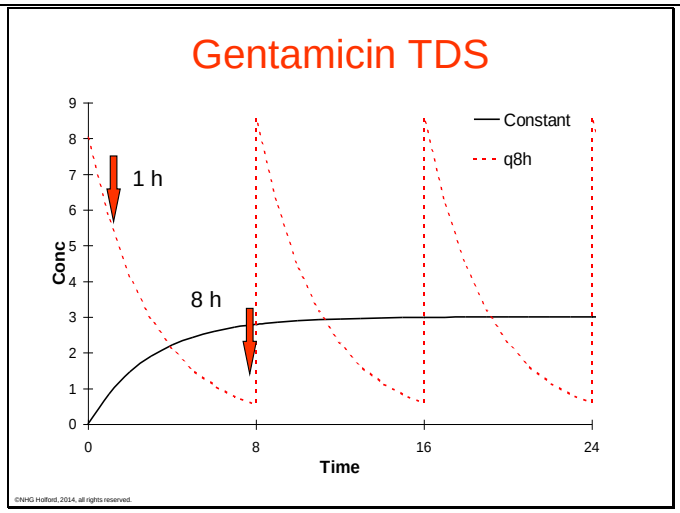
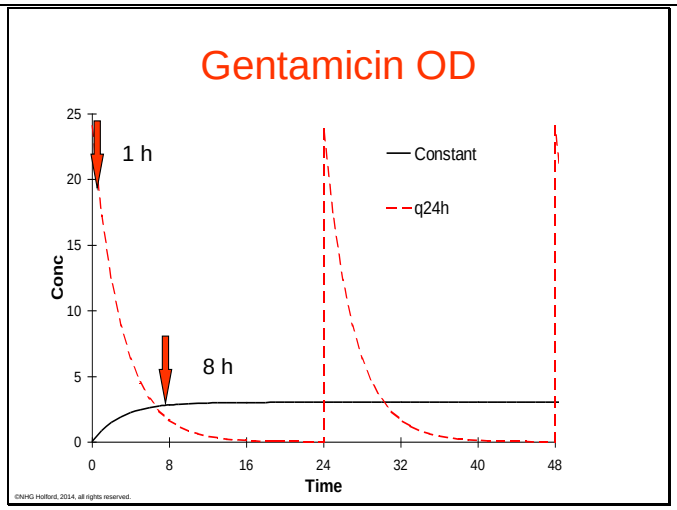
Calculate LD and MDR e.g. gentamicin

- LD = TC x V
  = 20 mg/L x 20 L = 400 mg
- MDR = TC x CL
  = 3 mg/L x 6 L/h= 18 mg/h

Slide 28	**When to Measure Concs?** Goal is to estimate PK e.g. CL ● Number of Samples » Most medicines 1 » Gentamicin 2 ● Timing of Sample » Most medicines Middle of dosing interval » Gentamicin "peak" and "trough" 	A rational approach to measuring drug concentrations is based on using the measurement to predict pharmacokinetic parameters – most commonly clearance. The least informative time to measure concentrations is just before the next dose (the 'trough' concentration) unless this is paired with another 'peak' concentration. This is because clearance determines the average concentration. So measuring a concentration in the middle of the dosing interval will be closer to the average and therefore more useful for predicting clearance. Gentamicin concentrations vary widely in a dosing interval so two concentrations are needed to reliably estimate clearance.
Slide 29	**When to Measure Concs?** Goal is to estimate PK e.g. CL ● Number of Samples » Most medicines 1 » Gentamicin 2 ● Timing of Sample » Most medicines Middle of dosing interval » Gentamicin "peak" and "trough" 	A rational approach to measuring drug concentrations is based on using the measurement to predict pharmacokinetic parameters – most commonly clearance. The least informative time to measure concentrations is just before the next dose (the 'trough' concentration) unless this is paired with another 'peak' concentration. This is because clearance determines the average concentration. So measuring a concentration in the middle of the dosing interval will be closer to the average and therefore more useful for predicting clearance. Gentamicin concentrations vary widely in a dosing interval so two concentrations are needed to reliably estimate clearance.
Slide 30	**Digoxin**  Tmid = middle of dosing interval 	A concentration in the middle of the dosing interval (Ctmid) will be closer to the average steady state concentration (Css) then either a peak or trough concentration. Clearance is easily calculated from CL=DoseRate/Css which can be approximated by CL=DoseRate/Ctmid.

Slide 31		
Slide 32		Gentamicin concentrations with once a day dosing vary considerably. The trough concentration at 24 h is often unmeasurable because it is below the limit of quantitation. Concentrations are best measured 1h and 8 h after the dose.
Slide 33