

# New technologies to support dose optimisation

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Dr Timothy Miles Rawson, BSc (hons), MBBS, MRCP (UK), PDME, DTM&H, PhD  
Health Protection Research Unit for Healthcare Associated Infections and Antimicrobial Resistance

New technologies to  
support dose  
optimisation:  
where will we be in  
2024?

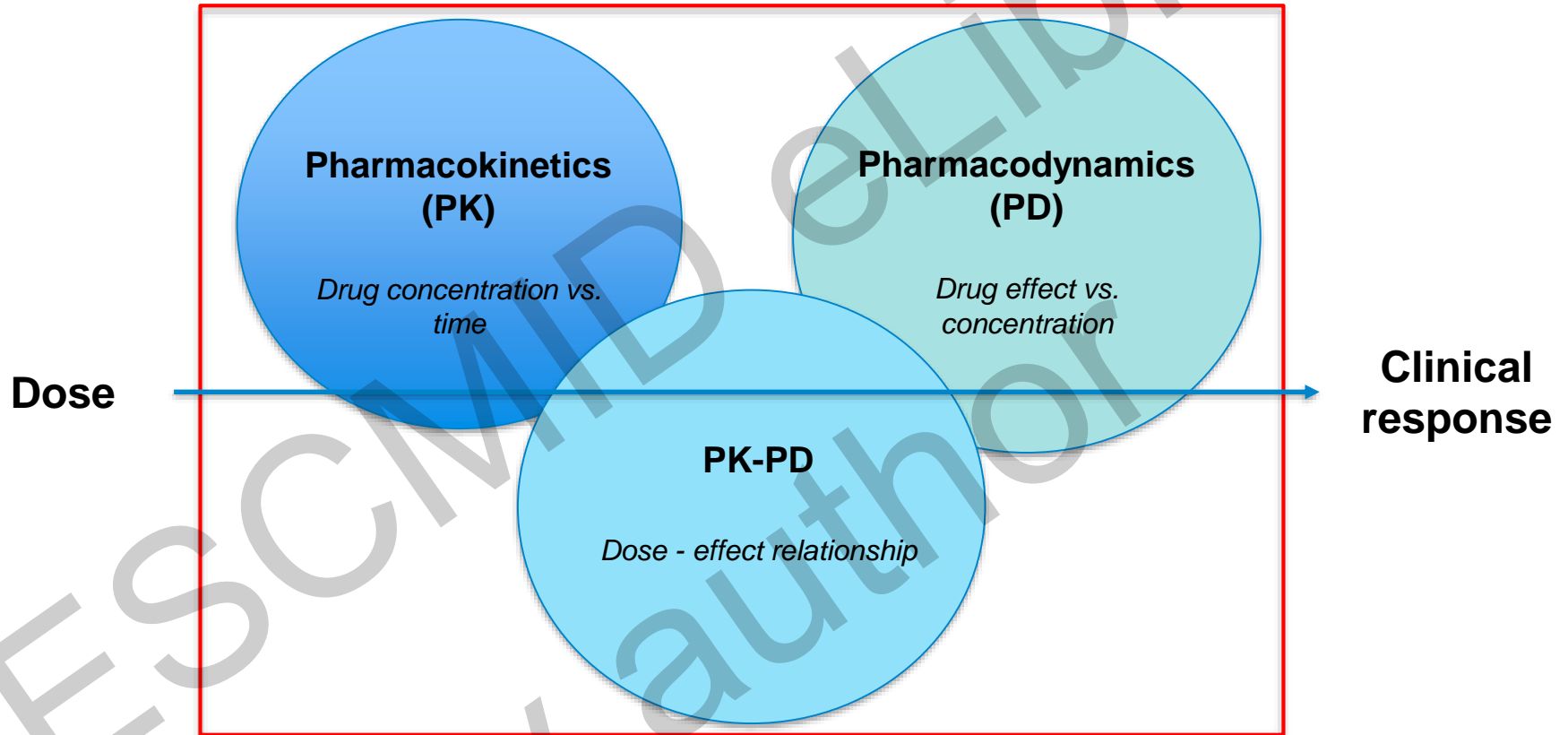
### Declaration

- No conflicts to declare

# Future technology for dose optimisation

- Current challenges
- Biosensor technology
- Future wearable technologies
- Linked PK-PD monitoring
- Integrated individualised dosing systems

# Antibiotic PK-PD



# Dosing is a dynamic process

Race

Weight

Age

Gender

Circulatory  
changes

Organ support



Renal failure



Hepatic  
dysfunction

Medications

Comorbidities

Clearance

Fluid balance

**Inter-individual variability**

**Intra-individual variability**

# Why explore individualised antibiotic dosing?

Improve treatment outcomes

Prevent toxicity

Minimize the impact on antimicrobial resistance

Utilisation of resources

Enhance our understanding of individual PK-PD

# Current approaches to individualise therapy

## Current examples

Therapeutic drug monitoring

Dose optimization software

Prolonged infusions

New PD indicators

### Imperial College London

#### A prospective study investigating the prediction of $\beta$ -lactam pharmacodynamics using AUC<sub>0-5</sub>

Dr Scott Wilson<sup>1</sup>, Andrew Walker<sup>1</sup>, Kevan Wang<sup>1</sup>, Timothy M. Rowson<sup>1</sup>, David Roberts<sup>1</sup>, Mark J. Gibberd<sup>1</sup>, Matthew Regier<sup>1</sup>, Alison H. Holmes<sup>1</sup>

<sup>1</sup>Imperial College London, National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, London

<sup>2</sup>UK Transmembrane Receptor Infection and Immunology Unit, York, London, UK

<sup>3</sup>Moore Law Trust Hospital, Department of Pharmacy, New Witham, UK

<sup>4</sup>Department of Medicine, Imperial College London, London, UK

<sup>5</sup>University of Sunderland, Centre for Clinical Research, Sunderland, UK

<sup>6</sup>Department of Microbiology and Clinical Pharmacology, Liverpool, UK

**Introduction**

Current intravenous prescribing regimens in outpatients are individualised. However, if steady state concentrations are desired it is also vital to reflect susceptibility of the microorganisms in a statistically evidenced,  $\beta$ -lactam protein (CRP) is a specific indicator of suboptimal efficacy but it is not viable drug exposure. The area under the concentration-time curve required to produce half a maximal response (AUC<sub>0-5</sub>) has been proposed as a novel pharmacodynamic (PD) index which reflects both pharmacokinetic (PK) and PD index which reflects both PK and PD. We investigated whether AUC<sub>0-5</sub> can be used to predict CRP response in a group of patients admitted to a tertiary infectious hospital in London.



**Results**

25 patients were enrolled on ceftriaxone (n=8), fosfomicin (n=9) and meropenem (n=7). 17 patients (68%) were male, the median age was 60 years (range 23-81), and the median Charlson-Diastolic clearance was 87 ml/min (range 10-133). Indications for ceftriaxone were skin and soft-tissue infections (n=4) and MSSA, bacteraemia (n=4). The predominant indication for fosfomicin and meropenem was sepsis (n=6 for each). Treatment was empiric in 93% cases. The median treatment duration was similar between groups. The median peak CRP<sub>max</sub> for ceftriaxone was lower than fosfomicin or meropenem. See table 1.

There was a strong association between AUC<sub>0-5</sub> and CRP at day 5 for meropenem (R<sup>2</sup> = 0.76). This was not observed for fosfomicin (R<sup>2</sup> = 0.08) or meropenem (R<sup>2</sup> = 0.18). See figure 1.

**Table 1. Patient characteristics**

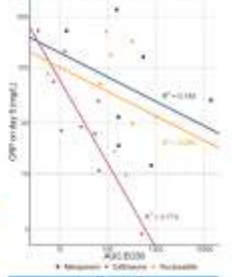
	Ceftriaxone	Fosfomicin	Meropenem
Number of patients	8	9	7
Age, years, median (range)	60 (20-76)	66 (28-81)	58 (24-76)
Male, %	88	78	86
Charlson-Diastolic clearance, ml/min, median (range)	122 (40-141)	88 (25-143)	80 (10-101)
Empirical treatment, %	94	89	86
Courses (duration, days), median (range)	8 (6-28)	8 (5-17)	12 (2-20)
Peak CRP <sub>max</sub> , mg/L, median (range)	62 (23-200)	103 (14-204)	160 (27-420)

**Conclusions**

AUC<sub>0-5</sub> predicts CRP response at day 5 in patients treated with meropenem but not fosfomicin or meropenem. Future work will explore factors driving this outcome. We will investigate other  $\beta$ -lactams, such as ampicillin and piperacillin, and AUC<sub>0-5</sub> endpoints which predict treatment success. Our findings will be especially important for multi-resistant populations where there is high PD variability associated with various treatment regimens.

### NiHR National Institute for Health Research

Figure 1. AUC<sub>0-5</sub> versus CRP at day 5, log-log plot.



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# To deliver truly individualised therapy

## Ideally....

Real-time pharmacokinetics

In-vivo pharmacodynamic indices

- Organism
- Host

Individualised, automated methods for dose adjustment



# Barriers to wider implementation of TDM

**Risk of exposure  
to HCW's**

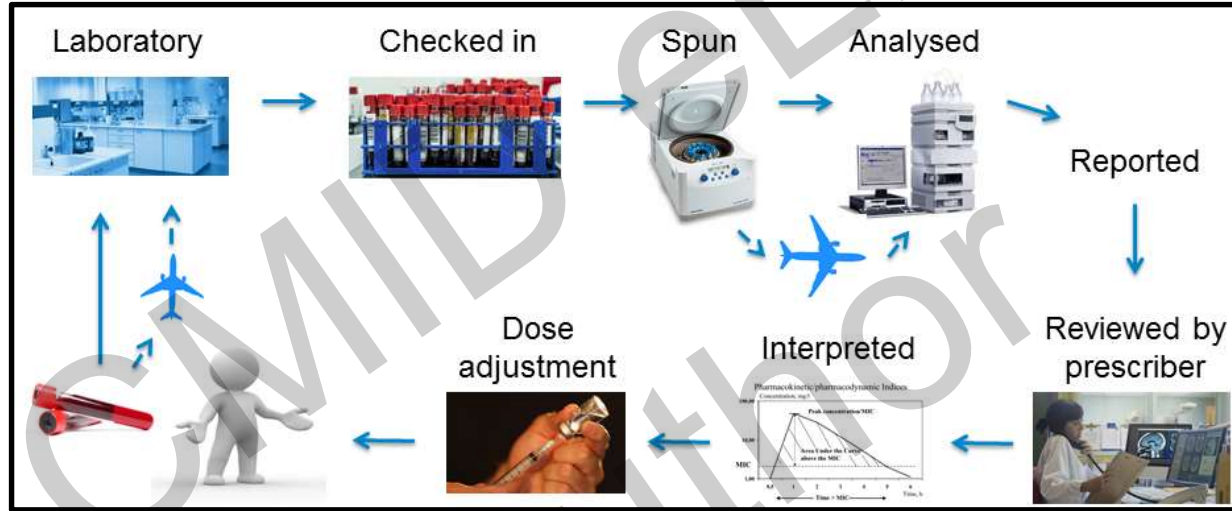
**Valid assay**

**Stability of  
drug**

**Equipment /  
staff costs**

**Timing  
samples**

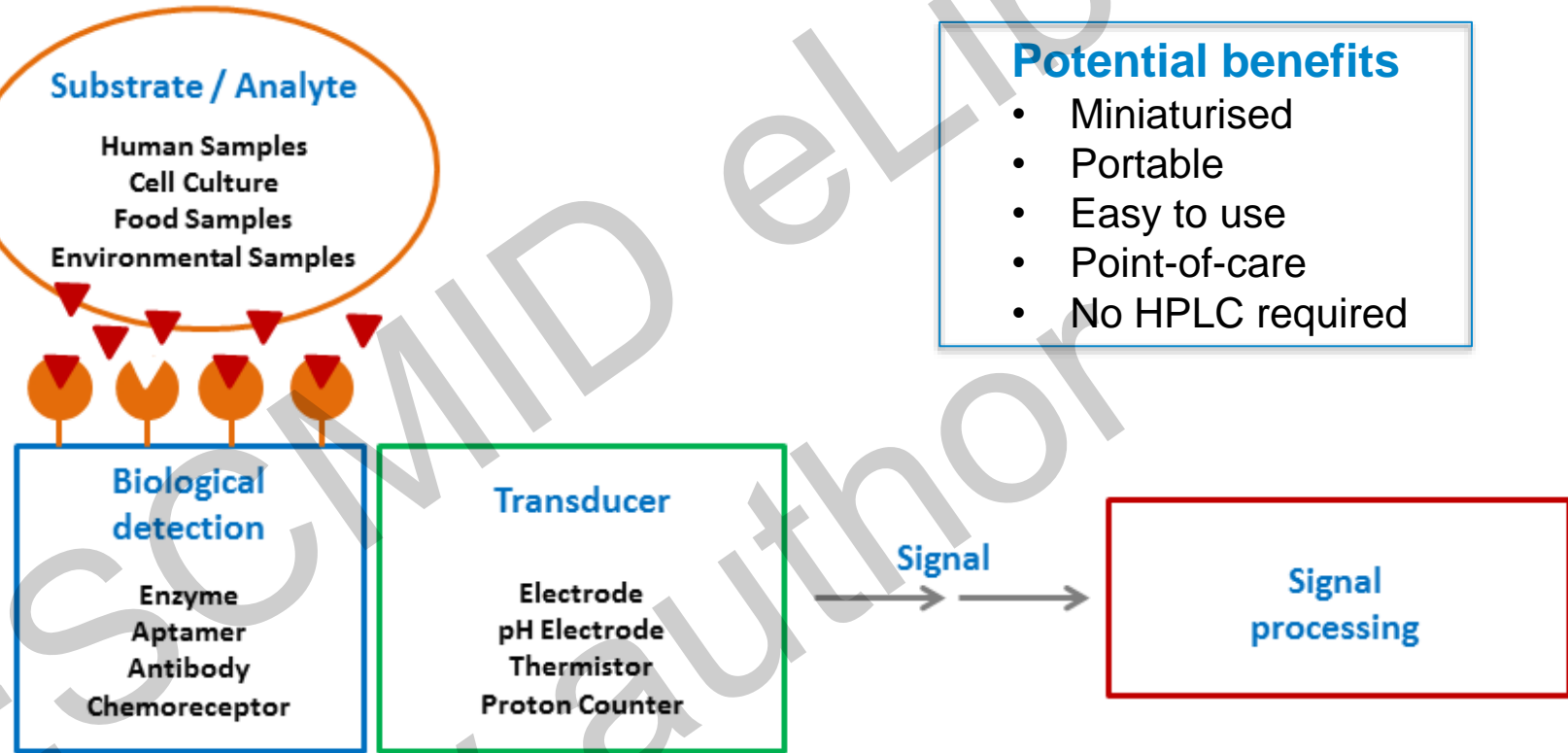
**Delays in  
reporting**



**Population level  
estimates**

**Expertise to  
interpret**

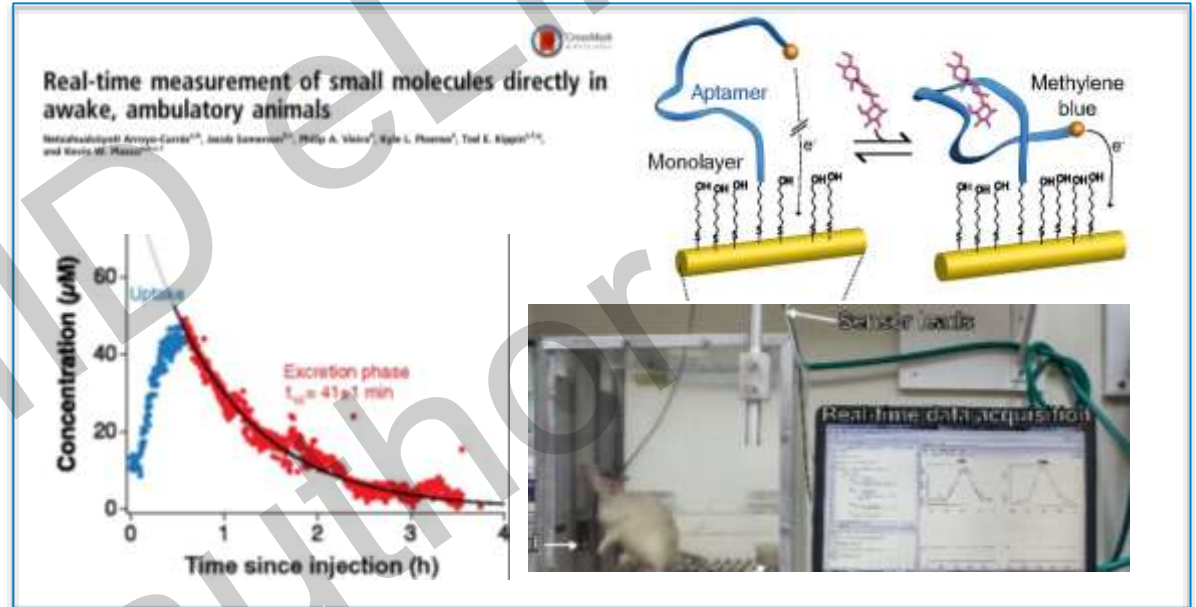
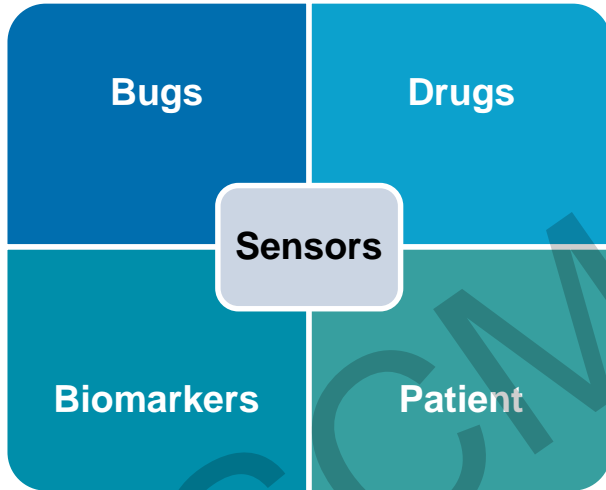
# Electrochemical Biosensors



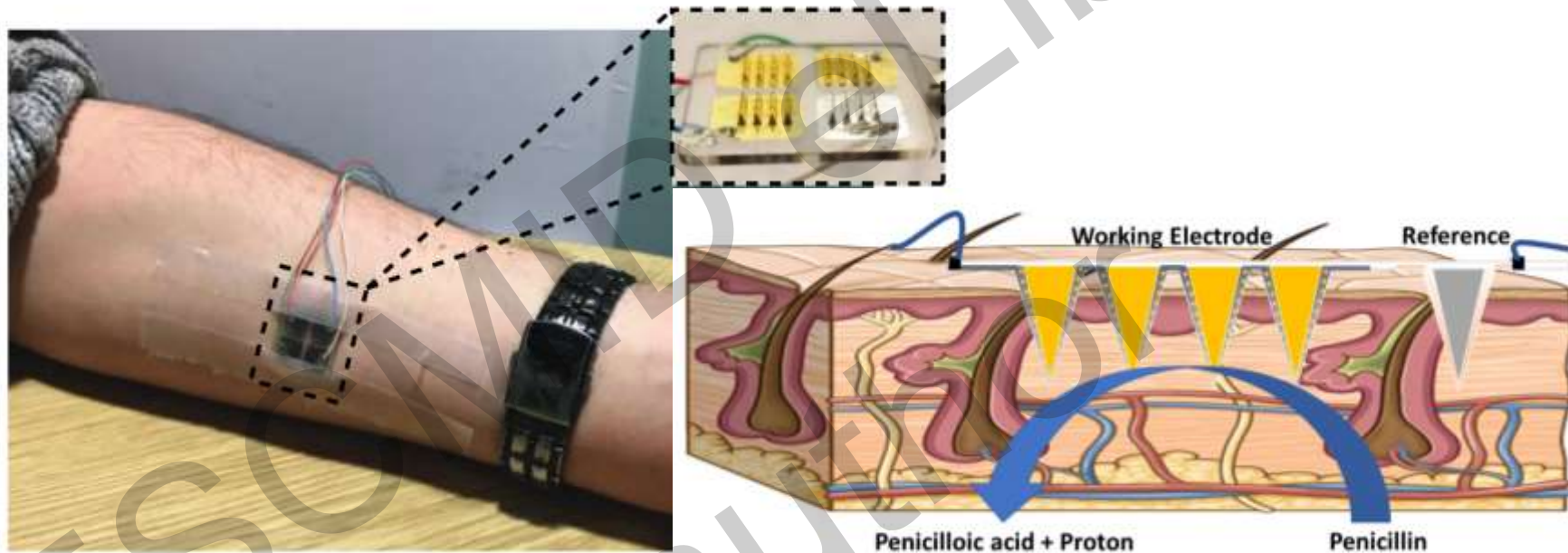
## Potential benefits

- Miniaturised
- Portable
- Easy to use
- Point-of-care
- No HPLC required

# Biosensors in infection management

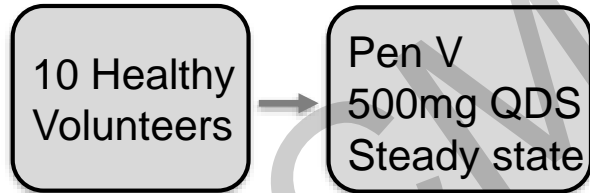


# Wearable technology for dose optimisation

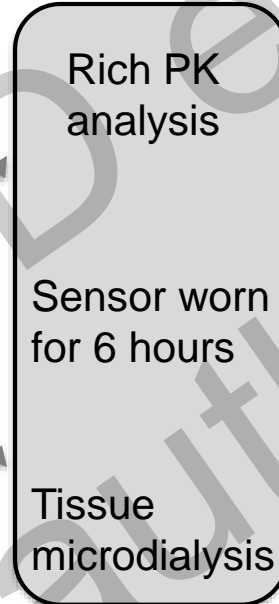


# MISBLA study – Penicillin monitoring

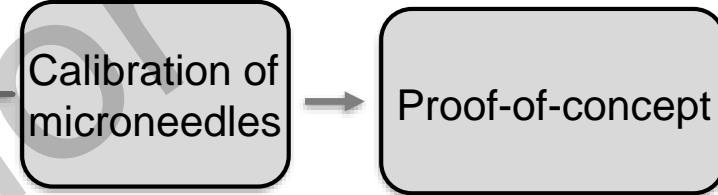
## Recruitment & preparation



## Study day

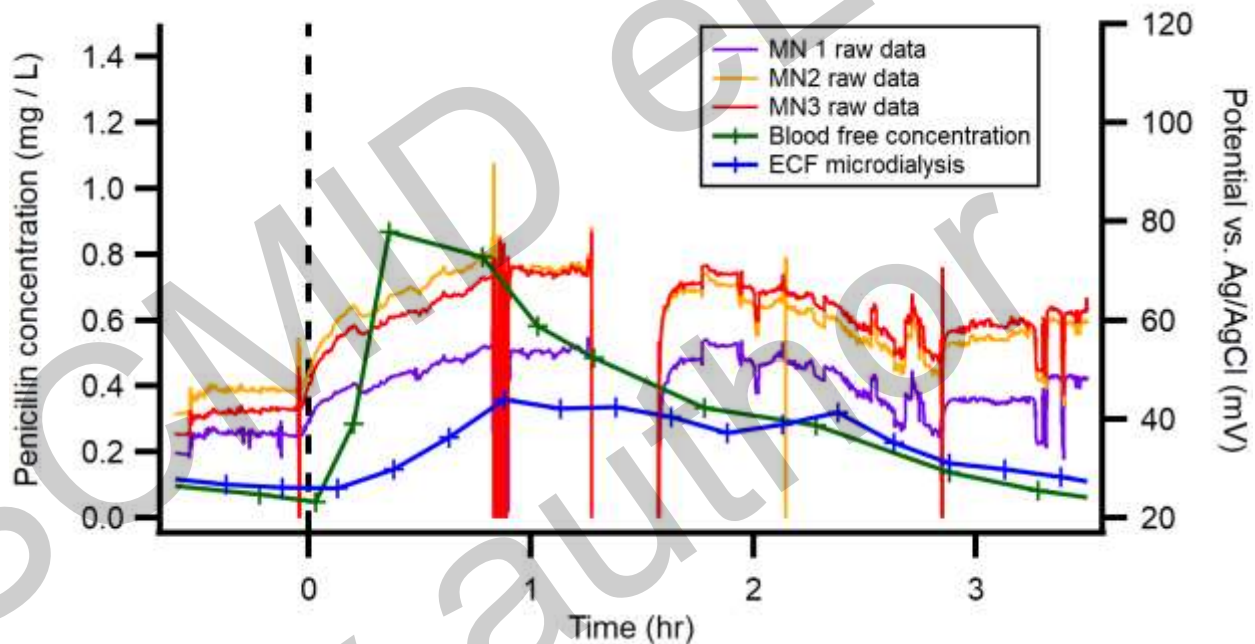


## Outcomes and analysis



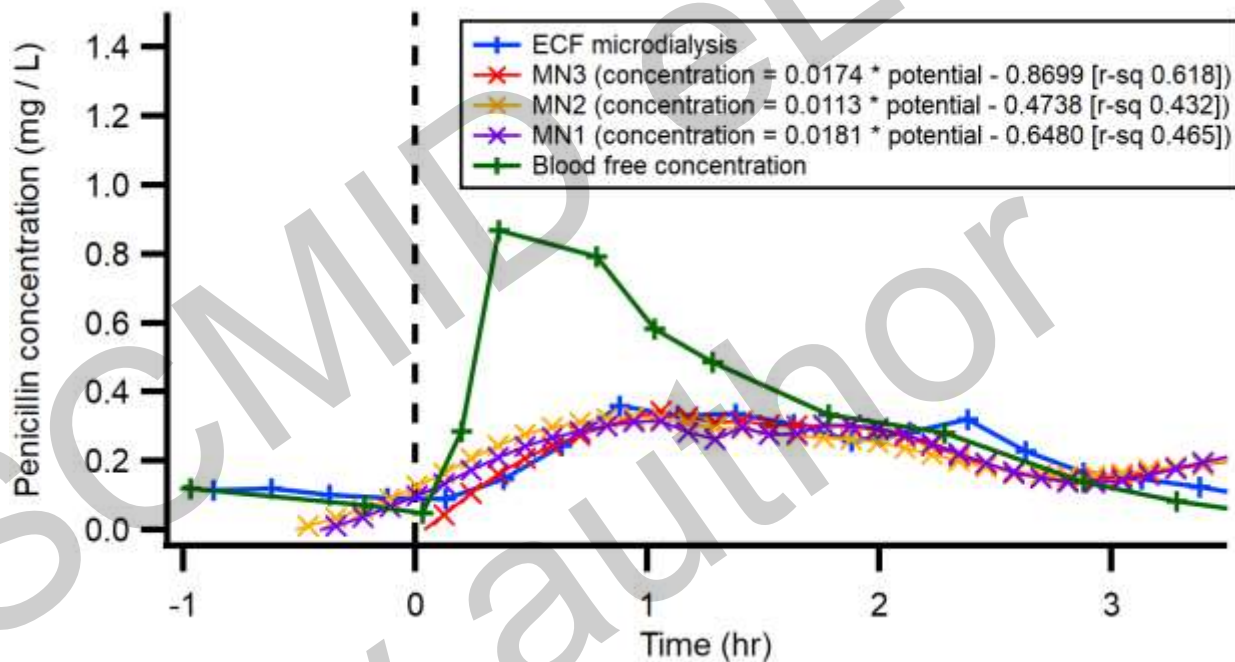
# In-vivo penicillin monitoring

## Microneedle raw data output

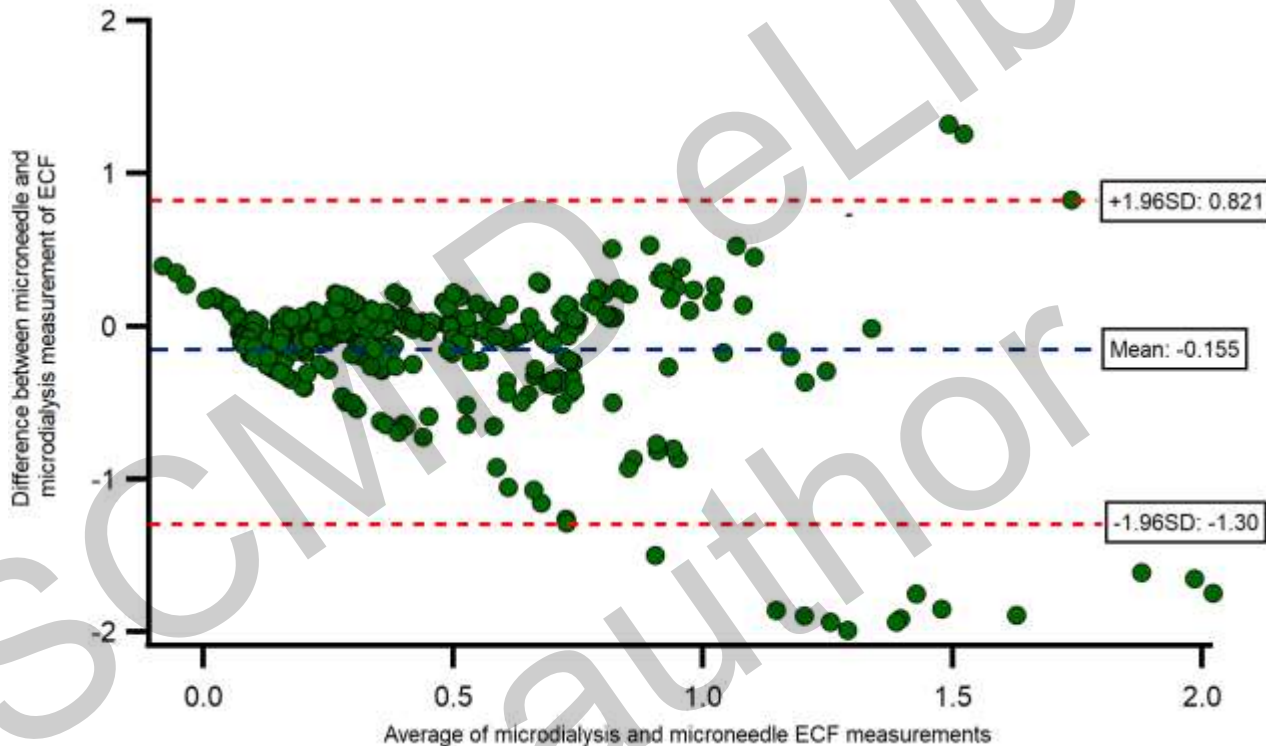


# In-vivo penicillin monitoring

## Microneedle calibrated to concentration



# In-vivo penicillin monitoring





# A role for microneedle technology

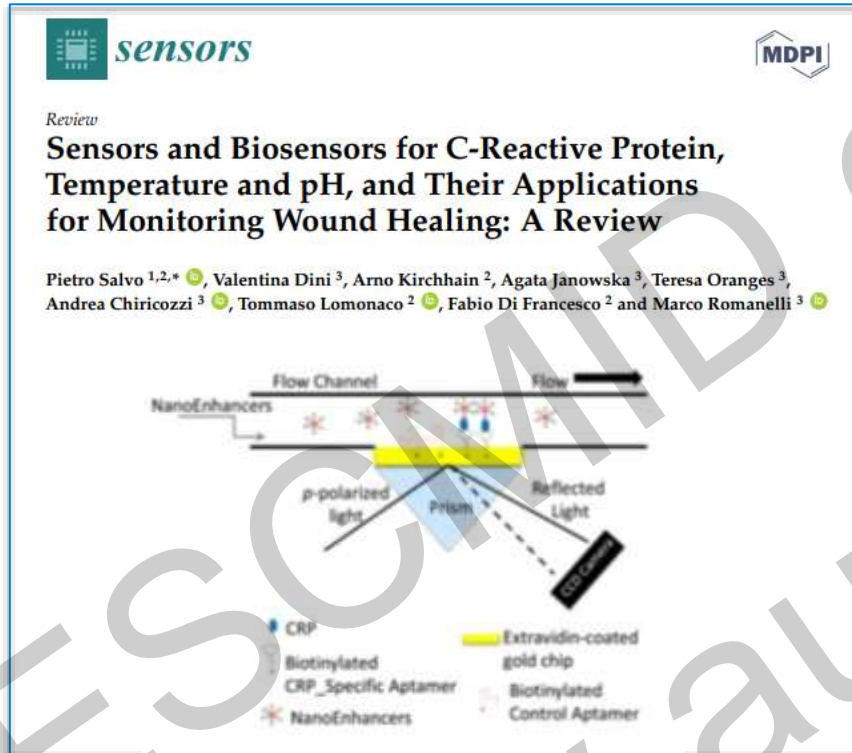
## Benefits

- Direct in-vivo monitoring
- No need for HPLC / internal standard
- Application to wide range of settings
- Multiple agent sensing
- Potential to optimise multiple compartments

## Ongoing challenges

- PK variation in critical illness
- Presence of inhibitors
- Paucity of data for agents
- Paucity of data for biomarker sensing

# Is real-time measurement of in-vivo PD indices possible?



## C-Reactive Protein

- Acute Phase Response protein
- Kinetics well understood
- Rationale for predicting response to infection
- ISF Indistinguishable in terms of protein diversity compared with plasma
- Over 60 types of CRP sensor reported

# Predicting antibiotic PD using CRP

## Antibiotic PK

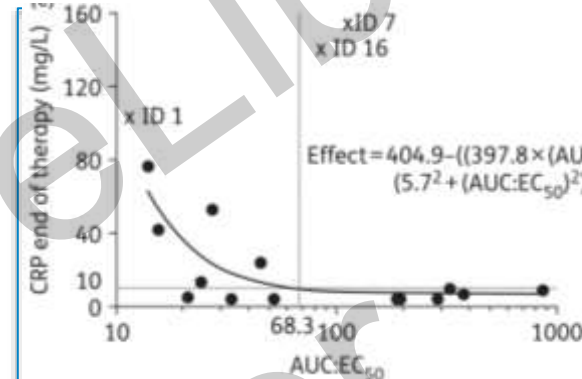
$$\frac{dX(1)}{dt} = R(1) + X(2) \cdot K_{pc} - X(1) \cdot \left(\frac{SCL}{V}\right) - X(1) \cdot K_{cp}$$

$$\frac{dX(2)}{dt} = X(1) \cdot K_{cp} - X(2) \cdot K_{pc}$$

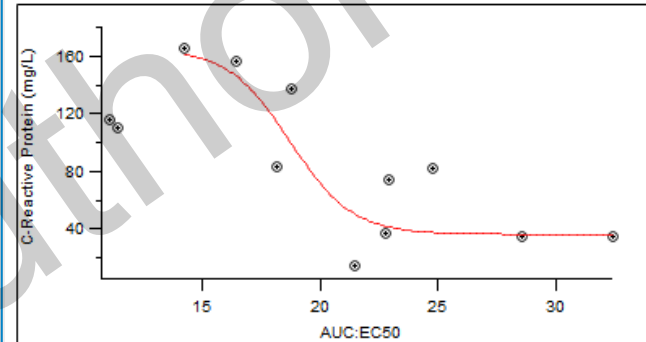
## C-reactive protein

$$\frac{dX(3)}{dt} = \left( K_{CRPp} \cdot X(3) \cdot \left[ 1 - \frac{X(3)}{POP_{max}} \right] - \frac{K_{CRPi} \cdot X(3) \cdot \left[ \frac{X(1)}{V} \right]^H}{EC50^H \cdot \left[ \frac{X(1)}{V} \right]^H} \right)$$

Individual  
 $AUC:EC_{50}$



Antibiotic  
PD  
**Teicoplanin**  
Paediatrics



Antibiotic  
PD

**Vancomycin**  
Adults

# Evidence for in-vivo biomarker monitoring

Lactate important marker for sepsis

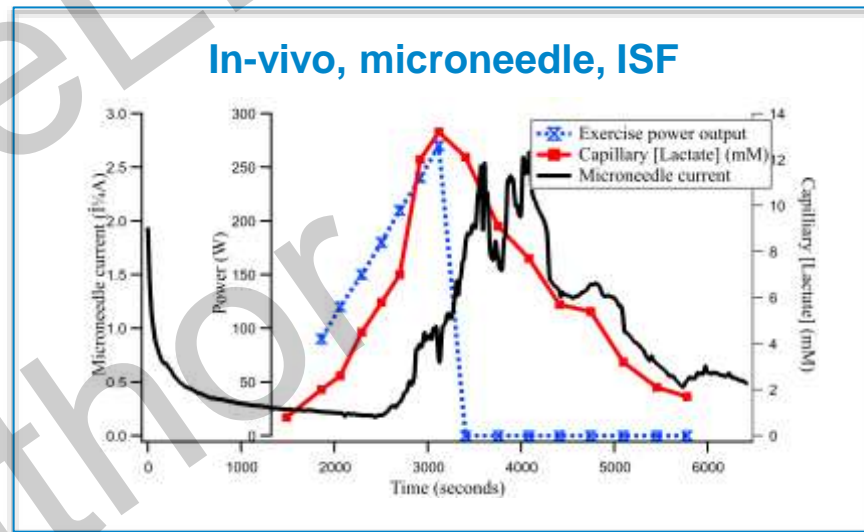
Ex-vivo validation on plasma

In-vivo monitoring with exercise bike challenge

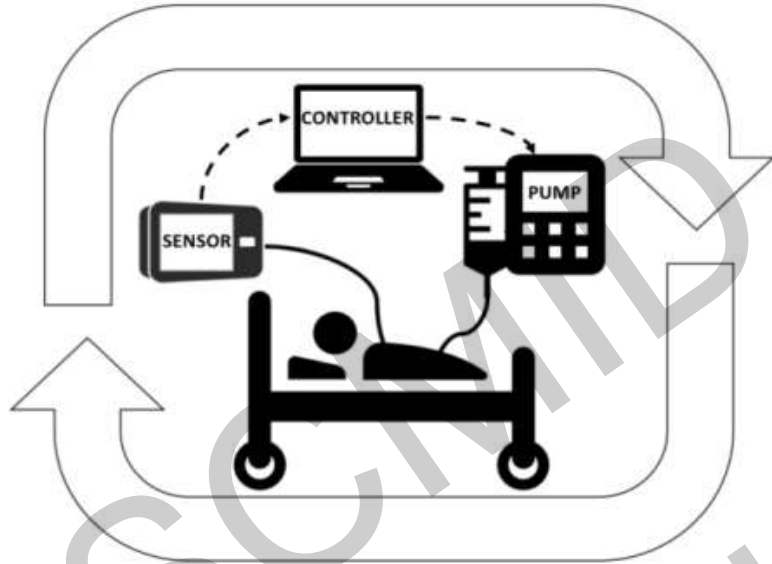
Proof-of-concept



caura



## Next steps



Closed-loop control of penicillin delivery in healthy volunteers

Antibiotic / biomarker sensing in patients

Validation of new PK-PD indices

# Where will we be in 2024?

- Microneedle based technology offers new frontier in individualised antimicrobial therapy
- New array of wearable technologies to support in-vivo PK-PD evaluation
- Greater understanding of antimicrobial PK-PD
- Automated dose optimisation



# Acknowledgements



Imperial Biomedical Research Centre

