

## Accepted Manuscript

Title: The implications of model-informed drug discovery and development for tuberculosis

Author: Morris Muliaditan Geraint R. Davies Ulrika S.H. Simonsson Stephen H. Gillespie Oscar Della Pasqua



PII: S1359-6446(16)30324-5  
DOI: <http://dx.doi.org/doi:10.1016/j.drudis.2016.09.004>  
Reference: DRUDIS 1887

To appear in:

Received date: 5-6-2016  
Revised date: 5-8-2016  
Accepted date: 6-9-2016

Please cite this article as: Muliaditan, M., Davies, G.R., Simonsson, U.S.H., Gillespie, S.H., Pasqua, O.D., The implications of model-informed drug discovery and development for tuberculosis, *Drug Discovery Today* (2016), <http://dx.doi.org/10.1016/j.drudis.2016.09.004>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

## HIGHLIGHTS

- Dose selection for new combination therapy in tuberculosis has remained empirical.
- Novel tools are needed for effective translation of preclinical models to humans.
- A model-based approach is needed to support dose rationale and better trial designs.

Accepted Manuscript

# The implications of model-informed drug discovery and development for tuberculosis

Morris Muliaditan<sup>1</sup>, Geraint R. Davies<sup>2</sup>, Ulrika S.H. Simonsson<sup>3</sup>, Stephen H. Gillespie,<sup>4</sup> and Oscar Della Pasqua<sup>1,5</sup>

<sup>1</sup>UCL School of Life and Medical Sciences, London, UK

<sup>2</sup>Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK

<sup>3</sup>Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

<sup>4</sup>School of Medicine, University of St Andrews, St Andrews, UK

<sup>5</sup>GlaxoSmithKline, London, UK

Corresponding author: Della Pasqua, O. (o.dellapasqua@ucl.ac.uk)

Keywords: PKPD; tuberculosis; drug development; modelling and simulation.

Teaser: Trial and error have prevailed in the development of drugs for tuberculosis (TB). Understanding of the pharmacokinetics/pharmacodynamics (PKPD) relation is crucial for the selection of doses of antibacterial drugs in humans. Here, we propose an integrated approach to guide efficient development of anti-TB drug combinations.

**Despite promising advances in the field and highly effective first-line treatment, an estimated 9.6 million people are still infected with tuberculosis (TB). Innovative methods are required to effectively transition the growing number of compounds into novel combination regimens. However, progression of compounds into patients occurs despite the lack of clear understanding of the pharmacokinetic-pharmacodynamic (PK/PD) relations. The PreDiCT-TB consortium was established in response to the existing gaps in TB drug development. The aim of the consortium is to develop new preclinical tools in concert with an *in silico* model-based approach, grounded in PKPD principles. Here, we highlight the potential impact of such an integrated framework on various stages in TB drug development and on the dose rationale for drug combinations.**

## Introduction

The development of new combination therapies for TB is lengthy and costly [1]. Despite promising advances in the field, innovative methods are still needed to effectively transition the growing number of compounds into novel combination regimens. Among other things, it is essential to shorten current treatment regimens and tackle multidrug-resistant TB.

### Shift in the TB drug development paradigm: reality or fiction?

The disappointing results from all recent Phase III trials of TB drugs [2–5] clearly demonstrate that a shift in paradigm is needed in TB drug development. Insufficient efficacy is the main cause for failures in clinical drug development [6,7]. Achieving efficacious drug exposure at the site of action is imperative for producing the desired response (i.e., reducing or preventing relapses). Nevertheless, the decision-making process in Phase II or III trials has remained empirical and recent development programs have progressed with limited PKPD knowledge to support the dose selection and study design. Clearly, dose selection must be based on evaluation of the PK properties and concentration effect (PKPD) relation of each drug, rather than by trial and error. Such concerns are also applicable to the most common approach to dose selection (i.e., the use of currently approved doses for the background standard of care treatment).

The challenges above are compounded by another major bottleneck in the development pathway in that current regulatory guidelines support the need for a long and often poorly informative range of studies. The rationale for testing different doses, regimens, and sequence of add-on drugs of each potential combination is clearly inefficient [8]. At least 6 years (an estimated 1 year for Phase I, 2 years for Phase II, and 3 years for Phase III) are required to develop one new antibiotic [1], whereas more than two decades (4×6 years) would be needed for the development and approval of a completely novel regimen comprising four new antibiotics through successive trials [1]. Here, we focus on how an integrated PKPD–disease modelling and simulation framework, also known as model-informed drug discovery and development (MID3), could accelerate the development of novel combination therapies and highlight the potential impact of such framework to inform more robust decision making in TB drug development.

Historically, the approval of current first short-course therapy for TB was preceded by sequential testing of promising candidates in preclinical experiments, which were then followed by clinical studies under the sponsorship of the British Medical Research Council (BMRC) during the 1970s and 1980s [9]. These drugs were approved based on the traditional paradigm in drug development in which the progression of candidates depended on a sequential decision-making process; that is, each phase is considered as a discrete step that is successfully completed as soon as predefined targets or criteria are met. However, this approach does not provide the flexibility that is required to rapidly and effectively assess multiple new combination regimens in a single development program. Yet, new anti-TB drugs or combinations are still assessed according to the same linear pathway before

moving to large trials in which the new drug is added to, or used as substitution for, one of the drugs in the standard regimen [10,11]. Most alarming is the lack of a strong scientific basis for the selection of doses and dosing regimens for TB, which is one of the major poverty-related diseases.

#### **PreDiCT-TB: a quantitative framework for TB drug development**

A robust quantitative framework is required to integrate data and facilitate effective translation of preclinical findings to humans. To that purpose, PreDiCT-TB, an Innovative Medicines Initiative (IMI)-funded project comprising pharmaceutical research and development (R&D) and academic partners, has proposed the development of model-informed approaches to address some of the existing gaps in TB drug development. In particular, attention is given to opportunities for improved evidence generation as well as evidence synthesis for the evaluation of new, more effective combinations of treatments. PKPD–disease modelling and simulation have been established as powerful tools for the characterisation of efficacy and safety in other therapeutic areas [12,13]. Their impacts on therapeutics and drug development have been reviewed extensively elsewhere [14]. A formal modelling framework that integrates data arising from novel or existing preclinical models and historical clinical studies is envisaged to inform decision-making at different stages of development; that is, optimisation of experimental protocols and sampling schemes and the design of the subsequent studies or termination of the project [15]. Most importantly, it enables comprehensive evaluation of the dose rationale [16].

Within PreDiCT-TB, a set of carefully selected anti-TB drugs (licensed and unlicensed) is being evaluated using standard and novel preclinical models. In parallel, a comprehensive database comprising individual patient data from historical clinical trials will be established for use as a reference for evaluating the performance of multiple anti-TB drug regimens, as assessed by preclinical models. These results will be used to refine experimental protocol conditions and identify experimental designs that are most informative; that is, provide evidence of the underlying concentration–effect relations or support the translation of drug effects in humans [17]. Both preclinical and clinical data will then contribute to the development and validation of a PKPD–disease modelling and simulation framework, which is intended to support the progression of candidate molecules into clinical development. Among the key deliverables of the consortium are the evaluation of (adaptive) study designs and translational research platforms for novel combination therapies for TB (Figures 1 and 2). An overview of current recommendations for the implementation of a model-informed approach as envisaged by PreDiCT-TB is presented in Table 1.

#### **Evidence generation and synthesis at candidate selection**

The availability of preclinical models that reflect key human pathological features of TB infection would be a valuable tool for translating PKPD concepts, offering a strong rationale for clinical trial designs [18,19]. If designed properly, such experiments could also facilitate the characterisation of PKPD relations of drugs in combination therapies, providing insight into exposure levels that correspond with optimal effect. Based on this approach, preclinical findings should form the basis for dose selection in humans and support the design of subsequent clinical studies [18].

TB has seen many exciting advances in preclinical research [20,21]. *In vitro* and animal models are becoming more sophisticated and have enabled us to generate more insight regarding the immunopathology of the disease and the interaction between various *Mycobacterium tuberculosis* (Mtb) subpopulations [22]. However, given the major differences in TB susceptibility and histopathology that currently exist between animal models, it is unlikely that a single experimental system will become available that could fully mimic the infection process in humans. In addition, large variability is observed in *in vivo* efficacy studies depending on the choice of Mtb strain [23]. In most cases, these experiments rely on limited information about drug combinations, range of doses, or dosing intervals. Consequently, the translation of preclinical data to inform suitable combinations and appropriate dosing regimens in clinical trials is anything but accurate.

PKPD–disease models can be developed to systematically characterise the differences in disease condition and evaluate the impact of combination therapies on the PKPD relation of backbone treatment in various animal models. It can be anticipated that the use of such models may allow: (i) the refinement of experimental protocols, consequently reducing the sample size needed in preclinical studies without compromising the precision of information derived from the experiment; (ii) inform prioritisation of the best drug combinations to be tested in clinical development; and (iii) systematically evaluate the performance of various preclinical models against available human data. Even if shortcomings were found in the translation of findings, the use of a model-informed approach does represent a considerable improvement in terms of the 3 Rs (reduction, replacement, and refinement).

#### **Evidence generation and evidence synthesis during clinical drug development**

Once the best predictive preclinical models are identified, clinical trial simulations (CTS) can be harnessed to evaluate an unlimited number of experimental scenarios (i.e., drug combinations, dose selection, sampling times, and sample sizes) in a systematic manner to identify the best clinical study design. For example, CTS has been successfully used to support selection of the dose range of antibiotics in Phase II/III studies by integrating data on the distribution of minimum inhibitory concentration (MIC) for clinical isolates with the PD target(s) developed from animal models of infection and PK characteristics of the compound [24]. By contrast, Phase II studies have often ignored PK variability and other sources of variation in treatment response in the target patient population, which need to be accounted for when exploring the dose–exposure–response relation. The impact of CTS during clinical development by means of providing stronger support for regulatory approval and labelling has been

established in other therapeutic areas [12,25] and acknowledged by regulatory agencies [26]. Given that only a limited number of combinations can be tested in humans, it is crucial to harness methods that facilitate more robust study design and dose-range selection before the start of the trial. If necessary, data from Phase IIa can be used prospectively to refine the PKPD–disease model and increase its performance to assess the most appropriate Phase IIb and III study protocol (i.e., patient population, dose, sample size, sampling time, treatment duration, and drug combinations). Moreover, additional factors, such as different compliance patterns and other comorbidities, can be included into the simulation scenarios when evaluating the dose rationale for antibiotics that are used in a chronic manner. Ultimately, this approach allows one to explore the impacts of critical factors on treatment response and address crucial questions regarding the experimental protocol before the trial is conducted.

Results from Phase II and III trials have been traditionally reported without linking treatment outcome with individual drug exposure. However, the availability of such data could explain the variability in response and, hence, provide insight into whether any unsuccessful trial outcome might be attributed to underexposure to the drugs, rather than the novel regimen truly being inferior to the standard of care. Considering the cost and burden of Phase II and III trials, the integration of PK to efficacy trials should become a mandatory component of clinical protocols. MIDs can be implemented that require sparse PK sampling, yielding accurate and precise estimation drug exposure in individual patients [27]. A PKPD analysis can subsequently be performed to evaluate the relation between drug exposure and clinical response.

Another important aspect regarding the evaluation of clinical response is the lack of consensus regarding the relevance of different endpoints in clinical trials (e.g., colony-forming unit count versus time to positivity). The concurrent use of different measures and regimen has made the comparison of historical and modern clinical trials challenging [28]. Rather than neglecting historical data, *in silico* models can be used to characterise the relation between different measures of bacterial load [29]. The availability of such models will enable researchers to utilise as many existing data as possible to inform decision-making in TB drug development in a more robust manner.

#### **Challenges for the implementation of a model-informed approach at candidate selection**

The success of the proposed model-informed approach depends on the availability of suitable experimental data for the development of robust *in silico* models. This requirement is not trivial, in that most experimental protocols might only provide insight into the underlying PKPD relations. These limitations are often determined by costs and time constraints. However, even when full PKPD relations are characterised, discrepancies between animal models still pose a major challenge in extrapolating model predictions into clinical doses. Difference in bacterial strain (e.g., H37Rv versus Erdman), pathology (e.g., absence versus presence of necrotic lesions) or treatment condition (e.g., onset and duration of treatment) can yield significantly different PKPD parameters and, hence, varying predictions of the clinical dose.

Efforts are being made within PreDiCT-TB to overcome some of these challenges. The consortium has identified a range of *in vitro* and *in vivo* models and performed a variety of experiments to compare the differences in PKPD relations of various anti-TB regimens. Even though the current clinical regimens with isoniazid, rifampicin, ethambutol, and pyrazinamide are not truly optimised, evidence of differences in the PK and PD of standard drugs across experimental models will provide insight into the sensitivity and specificity of these models to detect the bactericidal, bacteriostatic, and sterilising activity of compounds currently used in humans.

#### **Challenges for the implementation of a model-informed approach in clinical drug development**

Most of the known issues for the clinical development of anti-TB agents cannot be overcome by PreDiCT-TB alone. First, variability in PK continues to be overlooked. Collection of individual drug exposure is not included as a standard procedure in clinical protocols and blood sampling might not even be feasible in high-burden countries, where most Phase III TB trials are performed. In addition, even if individual PKPD data were collected, such as sputum conversion, information from a single measurement at the time of relapse would be insufficient to allow the development of predictive models for the detection of relapse. In addition to further understanding of the underlying biological mechanisms of relapse, it is crucial to obtain repeated microbiological data during treatment and follow-up. From a drug development perspective, what appears to become clear from early bactericidal activity (EBA) studies is that information on early bactericidal activity might not be a suitable descriptor of the processes associated with relapse. Another important limitation of EBA studies is that the PKPD relation based on drug levels in plasma might not describe tissue exposure. Similarly, a viable colony-forming unit count in sputum might not represent the whole *Mtb* population in the human lung.

Despite such limitations, the opportunity to replace the empirical basis upon which doses are selected will represent an important advancement for therapeutics with novel anti-TB drugs. Last, but not least, the consortium has managed to collate data from historical studies, creating a pool of individual patient-level data that will facilitate the evaluation of the proposed framework for drug combinations.

#### **Consequences for regulatory approval**

Clearly, translation of the advancements obtained so far with regard to our increased understanding of the pathophysiology of infection by *Mtb* and improved knowledge of drug disposition and PKPD properties in tissues and target organs demands more than just the effective implementation of the MID3 concepts highlighted above. Regulatory acceptance and guidance needs to evolve to ensure that lessons from this growing field are embedded into the drug approval process. A proactive attitude by regulatory authorities has been observed over the past few

years, in that a concept paper and new guidance have been issued that focus on the development of entirely new regimens to treat TB, rather than focusing on single medicines.

Recently, the European Medicines Agency (EMA) opened a consultation for updating the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections [30]. Whereas the use of *in vitro* PD models, such as the hollow fibre system, has been endorsed for dose selection early on during the development program, further insight from translational pharmacology and clinical trial simulations might have an important role in minimising the extent of dose- and/or regimen-finding clinical trials. Therefore, to be effective, the new guidance should establish the mechanisms by which novel approaches for data generation and integration will be considered in future regulatory submissions. In this respect, a dialogue between public-private initiative partnerships and regulatory agencies is timely and crucial. Most importantly, regulators and experts need to weigh the importance of alternative endpoints and study designs for the approval of new medicines or combinations of medicines along with the role of biomarkers to predict the efficacy and effectiveness of alternative regimens during clinical development.

### Concluding remarks

Improved efficiency in the development of drug combinations is urgently needed for the advancement of new treatments for TB. PreDiCT-TB has been created to overcome some of the crucial gaps during early drug development and revolutionise the way evidence is generated and integrated to support the progression of candidate molecules into humans. The implementation of a model-informed approach to the design, analysis, and interpretation of experimental data during preclinical phases of development will provide a more robust basis for the selection of suitable combinations and translate the appropriate dosing regimens for first-time use in patients. In conjunction with clinical trial simulations, PreDiCT-TB expects to demonstrate the relevance of more informative clinical trial designs and offer regulatory agencies a stronger scientific basis for the approval of treatments in a therapeutic area that has remained neglected for the past four decades.

### Acknowledgements

The research leading to these results received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115337, the resources of which comprise financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

### References

- Ginsberg, A.M. *et al.* (2007) Challenges in tuberculosis drug research and development. *Nat Med.* 13, 290–294
- Gillespie, S.H. *et al.* (2014) Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *New Engl. J. Med.* 371, 1577–1587
- Jawahar, M.S. *et al.* (2013) Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. *PLoS ONE* 8, e67030
- Jindani, A. *et al.* (2014) High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *New Engl. J. Med.* 37, 1599–1608
- Merle, C.S. *et al.* (XXXX[LM1]) A four-month gatifloxacin-containing regimen for treating tuberculosis. *New Engl. J. Med.* 371, 1588–98
- Arrowsmith, J. (2011) Trial watch: Phase II failures: 2008-2010. *Nat. Rev. Drug Discov.* 10, 328–329
- Hay, M. *et al.* (2014) Clinical development success rates for investigational drugs. *Nat. Biotechnol.* 32,40–51
- Phillips, P.P. *et al.* (2012) Innovative trial designs are practical solutions for improving the treatment of tuberculosis. *J. Infect. Dis.* 205, S250–257
- Fox, W. *et al.* (1999) Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *Int. J. Tuberc. Lung Dis.* 3, S231–279
- Leibert, E. *et al.* (2014) New drugs to treat multidrug-resistant tuberculosis: the case for bedaquiline. *Ther. Clin. Risk Manag.* 10, 597–602
- Lewis, J.M. and Sloan, D.J. (2015) The role of delamanid in the treatment of drug-resistant tuberculosis. *Ther. Clin. Risk Manag.* 11, 779–791
- Lee, J.Y. *et al.* (2011) Impact of pharmacometric analyses on new drug approval and labelling decisions: a review of 198 submissions between 2000 and 2008. *Clin. Pharmacokinet.* 50, 627–635
- Stone, J.A. *et al.* (2010) Model-based drug development survey finds pharmacometrics impacting decision making in the pharmaceutical industry. *J. Clin. Pharmacol.* 50, 20S–30S
- Marshall, S.F. *et al.* (2015) Good practices in model-informed drug discovery and development (MID3): practice, application and documentation. *CPT Pharmacometrics Syst. Pharmacol.* 5, 93–122
- Sahota, T. *et al.* (2015) Model-based prediction of the acute and long-term safety profile of naproxen in rats. *Br. J. Pharmacol.* 172, 3861–7
- Sahota, T. and Della Pasqua, O. (2012) Feasibility of a fixed-dose regimen of pyrazinamide and its impact on systemic drug exposure and liver safety in patients with tuberculosis. *Antimicrob. Agents Chemother.* 56, 5442–5449
- Della Pasqua, O. (2013) From animal to humans and back. *Drug Discov. Today: Technol.* 10, e315–e317
- Gumbo, T. *et al.* (2015) Nonclinical models for antituberculosis drug development: a landscape analysis. *J. Infect. Dis.* 211, S83–S95
- Warner, D.F. and Mizrahi, V. (2014) Shortening treatment for tuberculosis—to basics. *New Engl. J. Med.* 371, 1642–1643
- Davies, G.R. (2013) Bridging the gap in the fight against tuberculosis. *Drug Discov. Today.* 10, e359–e364
- Franzblau, S.G. *et al.* (2012) Comprehensive analysis of methods used for the evaluation of compounds against *Mycobacterium tuberculosis*. *Tuberculosis* 92, 453–488
- Hammond, R.J. *et al.* (2015) Phenotypic resistance in mycobacteria: is it because I am old or fat that I resist you? *J. Antimicrob. Chemother.* 70, 2823–2827
- De Groote, M.A. *et al.* (2012) Importance of confirming data on the *in vivo* efficacy of novel antibacterial drug regimens against various strains of *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.* 56, 731–738
- Drusano, G.L. *et al.* (2001) Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. *Antimicrob. Agents Chemother.* 45, 13–22
- Milligan, P.A. *et al.* (2013) Model-based drug development: a rational approach to efficiently accelerate drug development. *Clin. Pharmacol. Ther.* 93, 502–514
- Manolis, E. and Herold, R. (2011) Pharmacometrics for regulatory decision making: status and perspective. *Clin. Pharmacokinet.* 50, 625–626
- Magis-Escorra, C. *et al.* (2014) Population pharmacokinetics and limited sampling strategy for first-line tuberculosis drugs and moxifloxacin. *Int. J. Antimicrob. Agents* 44, 229–234
- Bonnett, L.J. and Davies, G.R. (2015) Quality of outcome reporting in Phase II studies in pulmonary tuberculosis. *Trials* 16, 518

- 29 Bowness, R. *et al.* (2015) The relationship between Mycobacterium tuberculosis MGIT time to positivity and cfu in sputum samples demonstrates changing bacterial phenotypes potentially reflecting the impact of chemotherapy on critical sub-populations. *J. Antimicrob. Chemother.* 70, 448–455
- 30 Committee for Medicinal Products for Human Use (CHMP) (XXXX[LM2]) *Addendum to the 'Guideline on the Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections' to Address the Clinical Development of New Agents to Treat Disease due to Mycobacterium tuberculosis*, European Medicines Agency
- 31 Gobburu, J.V. and Lesko, L.J. (2009) Quantitative disease, drug, and trial models. *Annu. Rev. Pharmacol. Toxicol.* 49, 291–301

**Figure 1.** [LM3]Diagram describing the individual components of the integrated pharmacokinetics/pharmacodynamics (PKPD)–disease modelling and simulation framework. The disease model encompasses the natural growth and elimination rate of *Mycobacterium tuberculosis* (Mtb) in the absence of antibiotics. The drug model characterises the PK and PKPD properties as well as any covariate effects on the disposition or PD of the drug. In addition to the disease and drug components, a trial model is used to assess treatment performance in the context of a clinical trial protocol. Among other factors, a trial model allows the assessment of the impact of dropouts, inclusion/exclusion criteria, or compliance on trial outcome. Adapted from [31].

**Figure 2.** [LM4]A schematic overview of how a pharmacokinetics/pharmacodynamics (PKPD)–disease modelling and simulation framework can be applied to translate preclinical findings and identify the appropriate doses and dosing regimens for tuberculosis drugs for first-time use in patients from preclinical experiments. Assuming the availability of data supporting the characterisation of dose/exposure–response relations *in vitro* and *in vivo* (A), *in silico* models can be developed that characterise the PK and PKPD properties of the drug combinations of interest (B). After correcting for the interspecies differences in physiology and/or physiochemical properties, parameter estimates can subsequently be used to either scale preclinical findings to humans or to facilitate the translation of drug effects taking into account differences between experimental and clinical conditions. Clinical trial simulations can be performed to inform the range of doses of each antibiotic that is expected to yield exposure levels (shaded green area) that are associated with the desired effect (dashed line) in preclinical experiments (C).

**Table 1. Overview of recommendations of how a model-based approach can be used to address the current gaps in various stages of TB drug development**

Development stage	Current gaps	Recommendations for the implementation of MID3
Preclinical	Limited value of preclinical experimental protocol designs, which often do not provide insight into the PK and PKPD relations	Adapt experimental protocols to ensure characterisation of the PKPD relations while allowing for experiments with fewer animals and optimised sampling and dosing schedules
	Lack of quantitative methods to systematically integrate PK or PKPD findings arising from different experimental models	Develop integrated models for the systematic evaluation of the implications of differences across species and/or experimental conditions
Clinical	Uncertainty about the predictive value of preclinical experiments and lack of tools to account for uncertainties into the decision-making process	Incorporation of historical data and mechanism-based and physiologically based PK (PBPK) models into the dose rationale in patients
	Progression of a compound into clinical development based on a weak dose rationale and lack of understanding of the relation between drug exposure and clinical outcome (i.e., relapse or time to positivity)	Focus on the underlying PKPD relation and monitoring of PK and PD over time using a sparse sampling strategy; in addition, availability of longitudinal data at individual patient level might provide an opportunity to assess the impact different sources of variability during Phase II or III trials
	Lack of systematic (quantitative) integration of historical data, partly because of the use of different clinical measures (endpoints) in old and recent clinical trials	Explore the utility of mechanism-based parameterisation that supports the characterisation of bacterial growth and killing as the primary processes underlying time to positivity





Figure 2

