


SOFTWARE

Open Access



# vCOMBAT: a novel tool to create and visualize a computational model of bacterial antibiotic target-binding

Vi Ngoc-Nha Tran<sup>1,2\*</sup> , Alireza Shams<sup>3</sup>, Sinan Ascioğlu<sup>4</sup>, Antal Martinecz<sup>1,10</sup>, Jingyi Liang<sup>1</sup>, Fabrizio Clarelli<sup>1</sup>, Rafal Mostowy<sup>5,6</sup>, Ted Cohen<sup>7</sup> and Pia Abel zur Wiesch<sup>1,8,9,10,11</sup>

\*Correspondence:

vi.tran@uit.no

<sup>2</sup> Department of Computer Science, Faculty of Science and Technology, UiT The Arctic University of Norway, 9037 Tromsø, Norway  
Full list of author information is available at the end of the article

## Abstract

**Background:** As antibiotic resistance creates a significant global health threat, we need not only to accelerate the development of novel antibiotics but also to develop better treatment strategies using existing drugs to improve their efficacy and prevent the selection of further resistance. We require new tools to rationally design dosing regimens from data collected in early phases of antibiotic and dosing development. Mathematical models such as mechanistic pharmacodynamic drug-target binding explain mechanistic details of how the given drug concentration affects its targeted bacteria. However, there are no available tools in the literature that allow non-quantitative scientists to develop computational models to simulate antibiotic-target binding and its effects on bacteria.

**Results:** In this work, we have devised an extension of a mechanistic binding-kinetic model to incorporate clinical drug concentration data. Based on the extended model, we develop a novel and interactive web-based tool that allows non-quantitative scientists to create and visualize their own computational models of bacterial antibiotic target-binding based on their considered drugs and bacteria. We also demonstrate how Rifampicin affects bacterial populations of Tuberculosis bacteria using our vCOMBAT tool.

**Conclusions:** The vCOMBAT online tool is publicly available at <https://combat-bacteria.org/>.

**Keywords:** Web-based tool, Computational model, Antibiotic, Pharmacodynamics, Pharmacokinetics, Binding kinetics

## Introduction

As antibiotic resistance poses a substantial worldwide health threat [1], leading academics have recently declared that we stand at the precipice of the “post-antibiotic era” [2]. To circumvent resistance, we need to limit inappropriate prescribing of existing drugs and also accelerate the development of novel antibiotics. Moreover, there is also a clear



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

need to develop better treatment strategies using existing drugs to improve their efficacy and prevent the selection of further resistance.

Even though antibiotics have been used since 1944, we are not yet able to predict how antibiotic concentration affects bacteria. That leads to our inability to design rational treatment strategies using existing drugs. That is illustrated by the fact that substantial treatment improvements have been made solely based on expert opinion even after decades of clinical practice [3–7].

Currently, most dosing recommendations are based on the selection of the best regimens during a series of trial-and-error experiments. Many candidate drug regimens fail during this testing process, and for those candidates that do succeed, the best regimen may be missed. This costly and long trial-and-error approach may also slow down the development of new antibiotics and limits the opportunities for dosing improvement of existing drugs [8]. The design of rationale dosing of new combination regimens using multiple drugs is even more complex. The nature of the drug-drug interaction may change depending on drug concentration and therefore, antibiotic synergy and antagonism cannot usually be predicted [9]. Furthermore, differences in the pharmacokinetic and pharmacodynamic profiles of drugs used in combination regimens can promote the selection of resistance during multi-drug treatment [10, 11].

We require new tools to rationally design dosing regimens that maximize the efficacy of existing antibiotics and to shorten the development process for new antibiotics [12]. The development of models that can guide the selection of optimal dosing strategies from data collected in early phases of antibiotic development (e.g. drug-target binding and transmembrane permeability, bacteriostatic and bactericidal action of living bacteria) could accelerate the drug development process and dosing design process [13]. Computational models and tools that predict relapse from pre-clinical and early clinical data would be immensely demanded [14, 15].

Mathematical models such as mechanistic pharmacodynamic drug-target binding [16] explain mechanistic details of how the given drug concentration affects its targeted bacteria. In the mechanistic models, each living bacterium has  $n$  target molecules. The models classify living bacteria into different compartments based on the number of bound target molecules [17]. They also incorporate both bacteriostatic and bactericidal action of living bacteria into their simulations. While such models have gained traction in the last years, there are no available tools to implement those models for scientists who are not experts in mathematical modelling. Developing these computational models to simulate the mechanism of drug-target binding requires both complex modeling and programming process. For healthcare providers and scientists with a non-quantitative background, creating such mathematical models for their considered drugs and bacteria is a challenging and time-consuming task.

In this work, we have devised an extension of the mechanistic binding-kinetic model that simulates the process of bacterial antibiotic target-binding. The extended model allows the incorporation of clinical drug concentration data to the original mechanistic model [17] in order to understand the effect of drug-target binding *in vivo*. Based on the extended model, we have developed an interactive web-based tool, namely vCOMBAT, to allow non-quantitative scientists to create and visualize their own computational models of bacterial antibiotic target-binding. In contrast to our previously developed

COMBAT modeling framework [18], this tool allows to incorporate antibiotic time-concentration profiles measured in patients. The tool can inform optimal dosing strategies based on antibiotic and bacteria data provided by the users. We also demonstrate how Rifampicin affects bacterial populations of Tuberculosis (TB) bacteria using our vCOMBAT tool.

## Method and implementation

### Mathematical models of drug binding kinetics

The web-based tool is built as an extension of the classic reaction kinetics model [17], where a bacterium has  $n$  target molecules binding to the antibiotic molecules. Depending on the number of bound target molecules  $x$  out of  $n$  target molecules in a bacterium, bacteria are classified into  $n + 1$  compartments  $B_x$  (where  $x$  is from 0 to  $n$ ). Living bacteria also replicate and die at a rate as functions of the bound targets  $x$ . When a bacterium duplicates, it results in two bacteria with two times of the number of target molecules in two daughter cells. However, the number of bound target molecules  $x$  in the mother cell remains constant and is distributed into the two daughter cells. The distributions are calculated based on a hypergeometric distribution function. The model is implemented as a system of ordinary differential equations as Eq. 1:

$$\begin{aligned}
 \frac{dB_x}{dt} &= \frac{k_f}{Vn_A}(n-x+1)AB_{x-1} - k_rxB_x - \frac{k_f}{Vn_A}(n-x)AB_x \\
 &\quad + k_r(x+1)B_{x+1} + \rho_x - r_xB_x \frac{C - \sum_{j=0}^n B_j}{C} - d_xB_x \\
 \frac{dA}{dt} &= -\frac{k_f}{Vn_A} \left( AT + \sum_{x=0}^{n-1} (n-x)AB_x \right) + k_r \left( AT + \sum_{x=1}^n xB_x \right) \\
 \frac{dT}{dt} &= -\frac{k_f}{Vn_A}AT + k_rAT + \sum_{x=0}^n d_x(n-x)B_x \\
 \frac{dAT}{dt} &= \frac{k_f}{Vn_A}AT - k_rAT + \sum_{x=0}^n d_xxB_x \\
 \rho_x &= 2 \sum_{i=x}^n f_{i,x}r_iB_i \frac{C - \sum_{j=0}^n B_j}{C}
 \end{aligned} \tag{1}$$

where  $B_x$  is the bacteria population with  $x$  bound targets;  $n$  is the number of targets per bacterium;  $k_f$  is the binding rate;  $k_r$  is the unbinding rate;  $V = e^{-15}[L/bacterialcell]$  is the average intracellular volume; and  $n_A = 6 \times e^{23}$  is the Avogadro number;  $C$  is the carrying capacity of total bacterial population;  $A$  is the drug concentration;  $T$  is the target concentration;  $A_T$  is the bound target concentration;  $\rho_x$  is the total rate with which replication creates new bacteria with  $x$  bound target;  $r_x$  and  $d_x$  are the replication and death rate of bacteria with  $x$  bound targets, respectively;  $f_{i,x}$  is the hyper-geometric distribution function.

We develop vCOMBAT as an extension of the classic reaction kinetics model [17]. In our extension of the model, instead of calculating antibiotic concentration  $A$  from Eq. 1, users can supply their own measured concentration data to the model. The benefit of incorporating external drug concentration data into the model is to make the model

more flexible so that the user can supply the drug concentration data from their measurements or computation from a pharmacokinetic model. By using the clinical/measured concentration data, the model can reflect the bacteria population of the in vivo environment. By computing the concentration data from a pharmacokinetic model, it allows the users to test the effects of drug concentration data from different pharmacokinetic models.

### Rifampicin test case

TB is currently the bacterial infection with the highest number of infections in the world. Even though antibiotics drugs to treat TB are used for many decades, the treatment success rate is low. Understanding how anti-tuberculosis drugs affect the total bacterial population in TB patients helps to guide the design of dosing strategies. Rifampicin is one of the most effective antibiotics to treat TB due to its safety and tolerability of its high-dose treatment and its low production cost [19]. There are currently several clinical trials on assessing increasing the doses on rifampicin and, therefore, it is a huge interest to model Rifampicin actions on TB [20].

The pharmacokinetic-pharmacodynamic model is intended to capture and simulate the decrease in the number of bacteria in the cavity walls in the lungs of the tuberculosis patients in response to rifampicin exposure. Table 1 summarizes the parameter values of Rifampicin and TB bacteria used in Eq. 1.

### Webtool implementations

In order to make the vCOMBAT tool accessible to on-line users, it is important to have a response time (i.e., computation runtime of the model to produce results) as fast as possible. Choosing a high-performance math library for numerical computation to solve our ODE system is one of the solutions to enhance its time performance. The original model was built

**Table 1** Model-parameter values when using Rifampicin in TB patients. These values are identified from the literature

Parameter	Description	Unit	Value	References
$A$	Antibiotic concentration	mg/L	e.g., 5 mg/L	Measured/external source
$B_0$	Starting population	Number of bacteria	$1e^6$	Assumption
$n$	Target molecules	Molecules	100	Assumption
$D_0$	Maximum death rate	$s^{-1}$	$1.6e^{-5}$	[28]
$R_0$	Maximum replication rate	$s^{-1}$	$9.25833e^{-6}$	[28]
$k_T$	Killing threshold		99	From $f_c$ of Eq (3) [29] $MIC = \frac{k_0 f_c}{1-f_c}$
$r_T$	Replication threshold		98	From $f_c$ of Eq (3) [29] $MIC = \frac{k_0 f_c}{1-f_c}$
$k_f$	Binding rate	$M^{-1}s^{-1}$	$1.2e^6$	[30]
$k_r$	Unbinding rate	$s^{-1}$	0.001284	[30]
$W$	Drug molecular weight	g/mol	822.94	[31]
$C$	Carrying capacity	Bacteria/ml	$1e^9$	[29]
$V$	Intracellular volume	L/bacterial cell	$1e^{-15}$	[29]
$MIC$	Minimum inhibitory concentration	mg/L	0.4	[28]

in R environment because R provides a vast amount of supported statistical tools and packages which makes it straightforward to program mathematical models [21]. However, R is also known for its low performance compared to other programming languages [22].

To provide high performance and short computational time, GNU Scientific Library (GSL) [23] is chosen as a numeric software package to solve our large ODE system described in Section Mathematical models of drug binding kinetics. The model has ODE system with 104 equations for 104 variables: 101 bacteria compartments  $B_x$  (where  $x$  varies from 0 to 100), the drug concentration  $A$ , the target concentration  $T$  and the bound target concentration  $AT$  as in Eq. 1 where the drug concentration  $A$  can be supplied by the user with their own measured concentration data.

To solve the ODE system, we use the driver *gsl\_odeiv2\_driver\_alloc\_y\_new* from GSL library [23] that wraps the evolution, control and stepper objects. The chosen step function is the explicit embedded Runge-Kutta method *gsl\_odeiv2\_step\_rk2*. The desired absolute and relative error limits for the driver are set as  $e^{-5}$ .

Antibiotic concentrations  $A$  are measured/supplied in different time points separated by a time interval (e.g., every hour or every day). In order to incorporate the external concentration data into the original model, the concentration values  $A(t)$  at time  $t$  are calculated by a linear function of the two measured concentration data points  $A(t_1)$  and  $A(t_2)$ , where  $t_1 < t < t_2$ .

## Results

In this section, we demonstrate how our vCOMBAT model estimates bacteria population when using Rifampicin to treat TB patients. Then, we evaluate the results by comparing the simulated outputs of vCOMBAT model with the traditional pharmacodynamic model [24]. We also conduct experiments to analyze the correctness and time performance of the extended model.

### Model estimation of Rifampicin

In this section, we demonstrate the use of the vCOMBAT tool for antibiotic Rifampicin treatment in TB patients. We have the vCOMBAT model parameters from Table 1 and the antibiotic concentration over time from the published compartmental pharmacokinetic model from Strydom et al. [25]. The compartmental pharmacokinetic model can be used to simulate antibiotic levels in different kinds of infected tissue in the lungs of TB patients. Open cavities in the lungs are considered to be the source of the sputum which is often measured in tuberculosis clinical trials [13, 26]. Therefore, we have chosen to model the antibiotic concentrations in the tissue of cavity walls. We simplify the compartmental model to our requirement by using only absorption, plasma, and tissue compartments without using a compartment chain for the absorption as Eq. 2:

$$\begin{aligned} \frac{dA_{abs}}{dt} &= input(t) - k_a A_{abs} \\ \frac{dA_{plasma}}{dt} &= k_a A_{abs} - \frac{CL}{V_S} A_{plasma} \\ \frac{dA_{tissue}}{dt} &= k_{pl-tissue} \left( R \frac{A_{plasma}}{V_S} - A_{tissue} \right) \end{aligned} \quad (2)$$

The parameters of Eq. 2 are published by Strydom et al. [6], where  $input(t)$  is the input function, to be able to implement daily doses of drugs into the absorption compartment;  $A_{abs}$ ,  $A_{tissue}$ , and  $A_{plasma}$  are antibiotic concentrations in the absorption, plasma and tissue compartments, respectively;  $k_a = 1.55[h^{-1}]$  is the absorption rate of the drug from absorption compartment;  $CL = 5.72[L/h]$  is the clearance rate of the drug from the plasma compartment;  $V_s = 52.3[L]$  is the volume of distribution in liters;  $R = 0.614$  is the penetration coefficient into the tissue (cavity wall);  $k_{pl-tissue} = 1.98[h^{-1}]$  rate of drug moving from plasma to tissue. For the estimates, we simulated doses of Rifampicin as 10 mg/kg bodyweight (standard dose) for a 60 kg person [27].

We use the antibiotic concentration over time generated from the compartmental pharmacokinetic model as concentration input for the vCOMBAT model. The simulated bacteria population over time by the vCOMBAT model is presented in Fig. 1. The results show that the bacteria population reduces but then relapses approximately after day two when a patient is treated with only a single dose of Rifampicin (600 mg). The results also show that with repeated doses of Rifampicin daily (i.e., 600 mg every day in 4 days), the bacteria population keeps being reduced through 4 days until 0.6% of the original population.

### Comparison of vCOMBAT to a traditional pharmacodynamic model

In this section, we compare the output of our vCOMBAT model - a mechanistic pharmacodynamic model with the traditional pharmacodynamic model by Aljayyousi et al. [24]. Mechanistic models provide a deep understanding of drug action and capture various pharmacodynamic effects [16]. Traditional models, on the other hand, are simpler but limited due to several assumptions that are likely invalid in reality. e.g., There is no cellular growth or death meaning that the total number of target molecules is constant. Traditional models are, therefore, not able to capture the pharmacodynamic effects such as post-antibiotic and inoculum effect [16].

The traditional model by Aljayyousi et al. [24] develops the relationships of the antibiotic concentration and the net growth (elimination) rate of Mycobacterium tuberculosis bacteria exposure to Rifampicin as in Eq. 3, where  $A$  is the antibiotic concentration in [mg/ml],  $B(t)$  represents of bacterial density over time in [ $ml^{-1}$ ],  $r$  is growth rate of bacteria in [ $day^{-1}$ ],  $EC_{max}$  is the maximum elimination rate in [ $day^{-1}$ ], and  $EC_{50}$  is the half-maximal effective concentration in [mg/L]. Aljayyousi et al. [24] found the values of  $EC_{max} = 1.82$ ,  $EC_{50} = 0.51$ , and  $r = 0.8$  by fitting their clinical data into their model. With concentration  $A$  provided by the compartmental pharmacokinetic model [25] described in Section Model estimation of Rifampicin and the known parameters, the bacteria population over time  $B(t)$  by the traditional model [24] is computed as Eq. 3.

$$\begin{aligned} \delta(A) &= -r + \frac{EC_{max}A}{EC_{50} + A} \\ \frac{dB(t)}{dt} &= -\delta(A)B(t) \end{aligned} \quad (3)$$

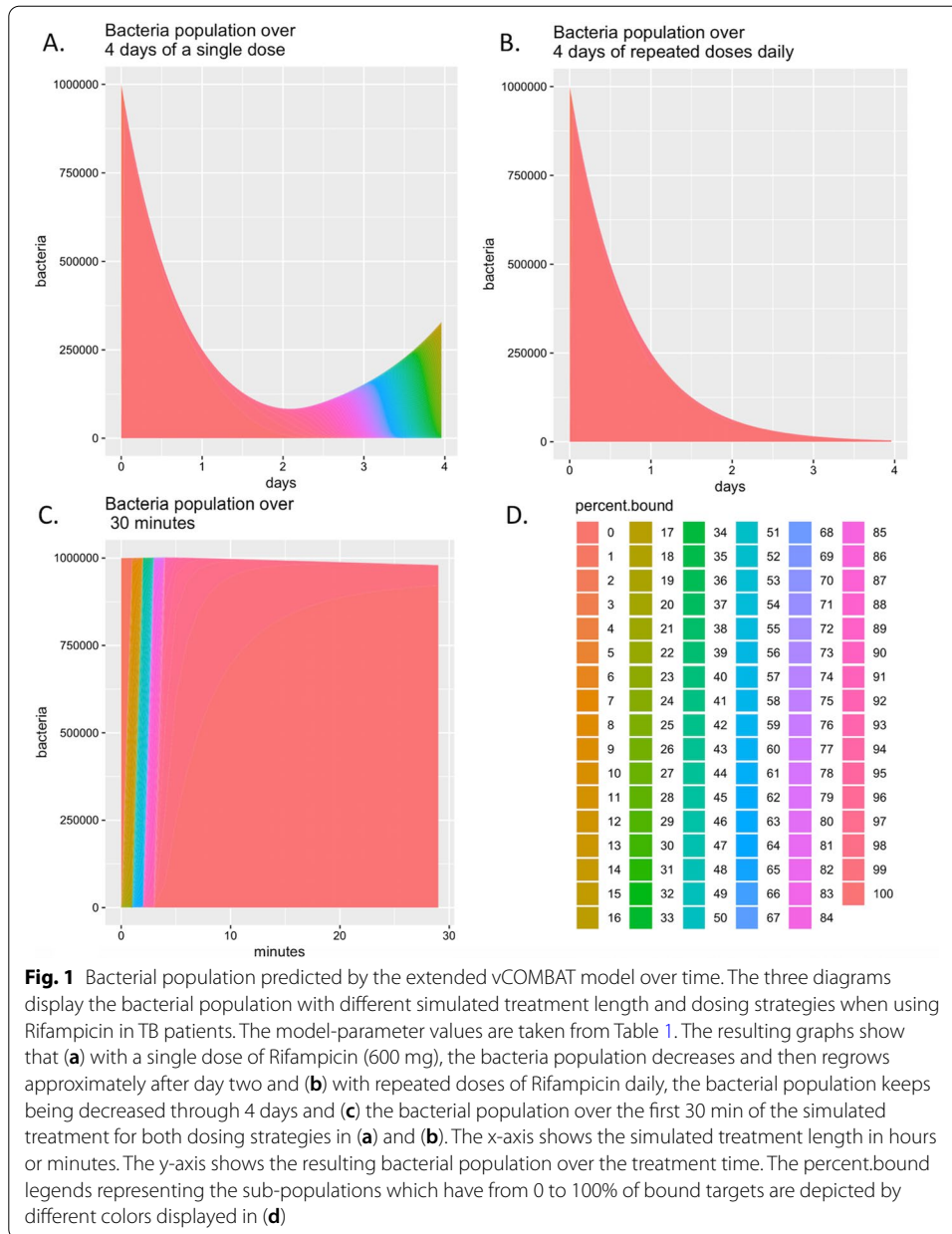
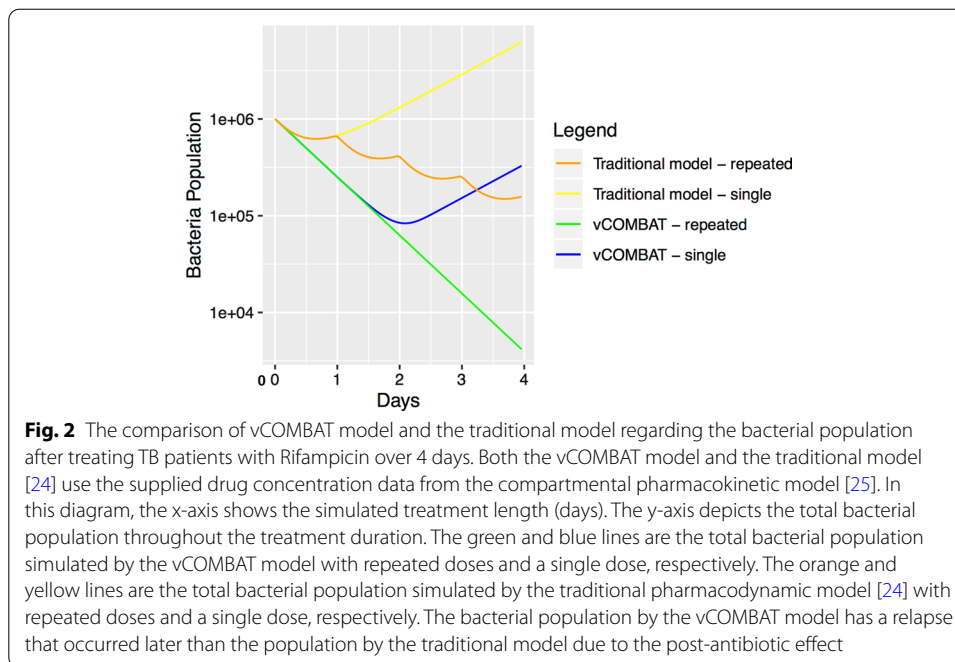


Figure 2 displays the bacteria population after treating TB patients with Rifampicin over 4 days by our mechanistic vCOMBAT model and the traditional model [24]. We notice that for a single-dose treatment (600 mg of Rifampicin) with the vCOMBAT model, the total bacteria population reduces for 2 days before bacteria regrow while with the traditional model, the population decreases and then increases after approximately 18 h. This can be explained by the post-antibiotic effect [16] which the mechanistic models can capture. The post-antibiotic effect is the delay of the bacterial regrowth after bacteria are exposed to antibiotics. The bound drug-target molecules require a certain time to unbind and free the targets, as well as the drug molecules need time to leave the cell.





Therefore, the vCOMBAT model in Fig. 2 has the bacteria regrown later than the bacteria in the traditional model.

#### Model computational correctness

In this section, we analyze the performance of the original and extended vCOMBAT models. We design the three test cases for three scenarios with model parameters from Table 2. Test case 1 has no bacterial growth and death; test case 2 is a normal scenario where there is bacterial growth and death while test case 3 has a high initial antibiotic concentration which shows the effect on the bacteria subpopulations from different percentages of bound targets. To validate the results from the extended model, we compare the output of the original and the extended model for the three designed test cases. The antibiotic concentration input for the extended model is generated by the original model. In this way, we expect that the outputs of the two models are similar. Figure 3 demonstrates the effect of model parameters on the total bacteria population and bacterial population with different percentages of bound targets. The results from Fig. 3 show that both the original model and the extended model provide similar results in terms of the bacterial population and percentage bound target for all three test cases.

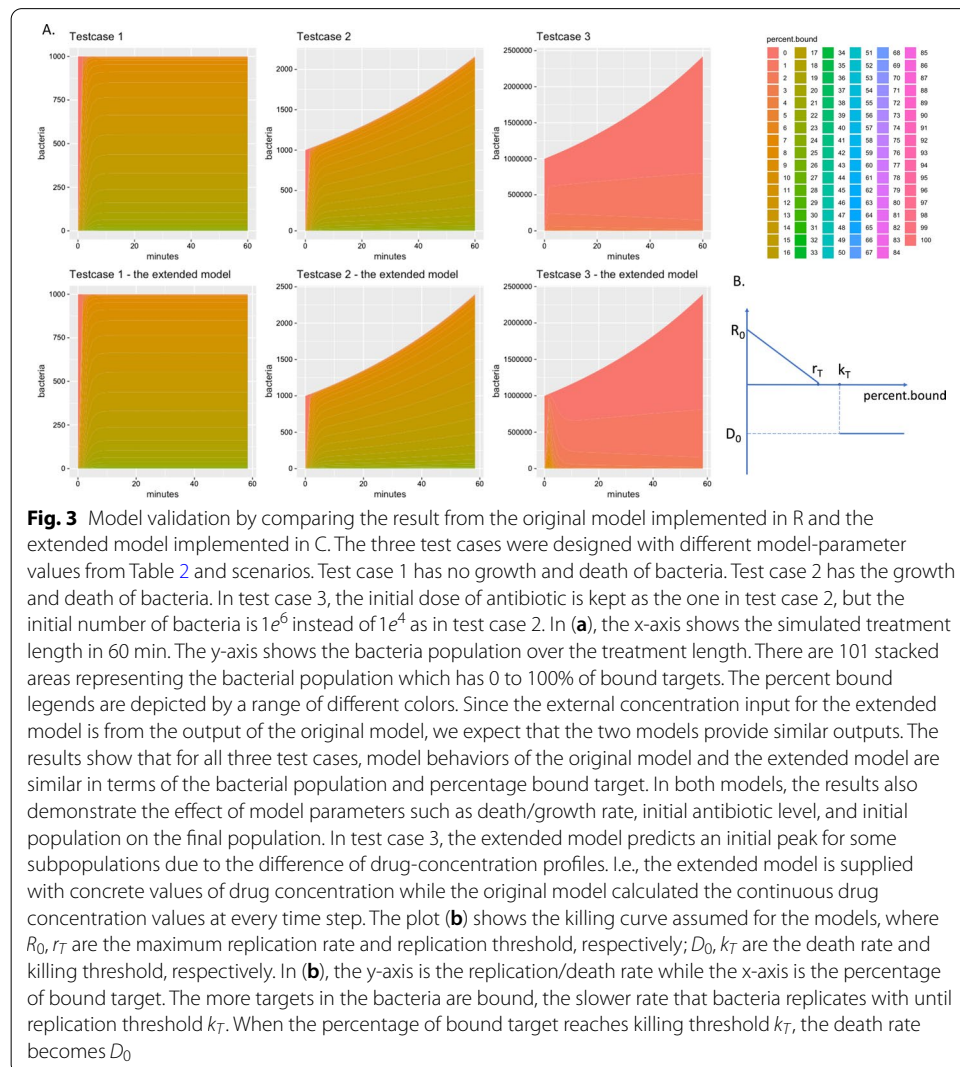
#### Model performance analysis

We also analyze the performance of our extended model together with the original model in two environments: R and C. We conduct the experiments to measure computation runtime of the original model and the extended model in different environments. The original model is implemented in both R programming language and C programming language. The extended model is implemented in C environment.



**Table 2** Model-parameter values of the three test cases used for model validation and performance analysis

Parameter	Testcase 1	Testcase 2	Testcase 3
Starting population	$1e^6$	$1e^6$	$1e^6$
Initial antibiotic level (mol/cell)	$1e^3$	$1e^3$	$1e^6$
Simulated treatment length (s)	86400	86400	86400
Target molecules	100	100	100
Maximum kill rate	0	0.001	0.001
Killing threshold	50	60	60
Replication threshold	50	50	50
Maximum replication rate	0	0.00025	0.00025
Binding rate	1	1	1
Unbinding rate	0.01	0.01	0.01
Drug Molecular Weight	555.5	555.5	555.5
Carrying capacity	$1e^9$	$1e^9$	$1e^9$
Intracellular volume	$1e^{-15}$	$1e^{-15}$	$1e^{-15}$

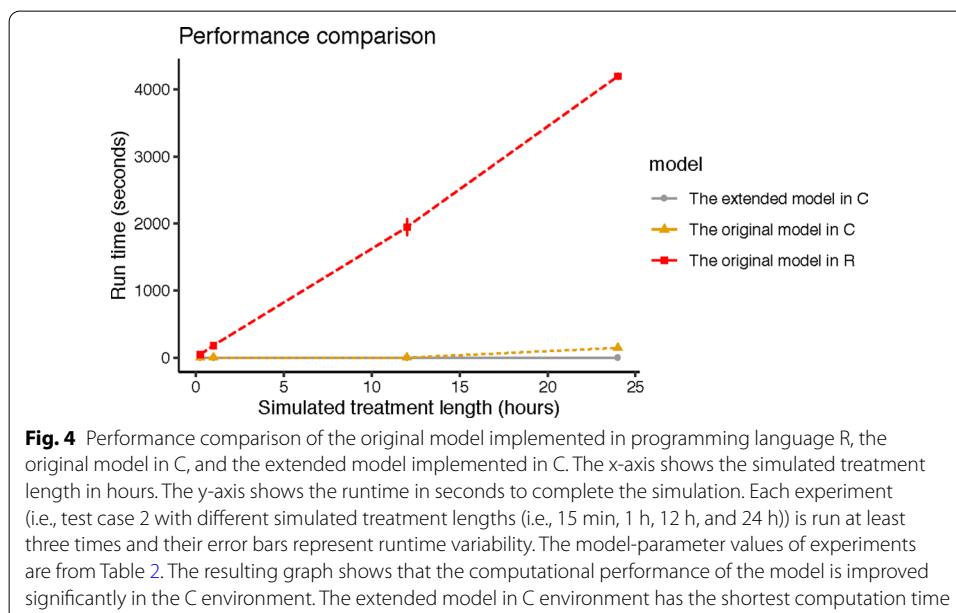


**Environmental set-up** In R environment, we used library *deSolve* to solve our ODE system and *tictoc* to measure the runtime of simulations. In C environment, we used GNU Scientific Library *GSL* 2.5 to solve ODE systems. The parameters of the experiments are from Test case 2 of Table 2. Test case 2 was chosen as a typical scenario where there are growth and death of bacteria. Each experiment was run at least three times to measure the mean runtime and its variability. All experiments were conducted on an Intel platform with one Intel Core i7 processor (4 cores, 2GHz speed, and 8 GB DDR3).

**Time performance** The performance of the original model and the extended model are illustrated in Fig. 4. The experimental results show that the computational model requires significant processing time in R environment as compared to C environment. e.g., to simulate 24-h treatment length, the computation time needs a maximum of 4252 s in R and a maximum 150 s in C. Since the computation time (runtime) is proportional to the simulated treatment length, the longer the simulated treatment length is, the longer computational time is required. The performance of the extended model in C environment is approximately 28 times faster the conducted experiments for the original model in R environment. By improving the performance, the model results are accessible to users in a shorter time. Moreover, the timely model is also beneficial in the scenario where processing algorithms require running the model with several iterations.

#### vCOMBAT model as a scientific web-based tool

We develop a web-based tool to provide a user-friendly, scientific platform to create pharmacodynamic models and simulate them using our simulation software. This online tool also provides data visualization of the simulation results based on input parameter-values of the chosen drug compounds, bacteria type, and treatment length. The tool illustrates critical information such as bacteria population, drug concentration and complex bound target over treatment length to assist the design of dosing regimens.

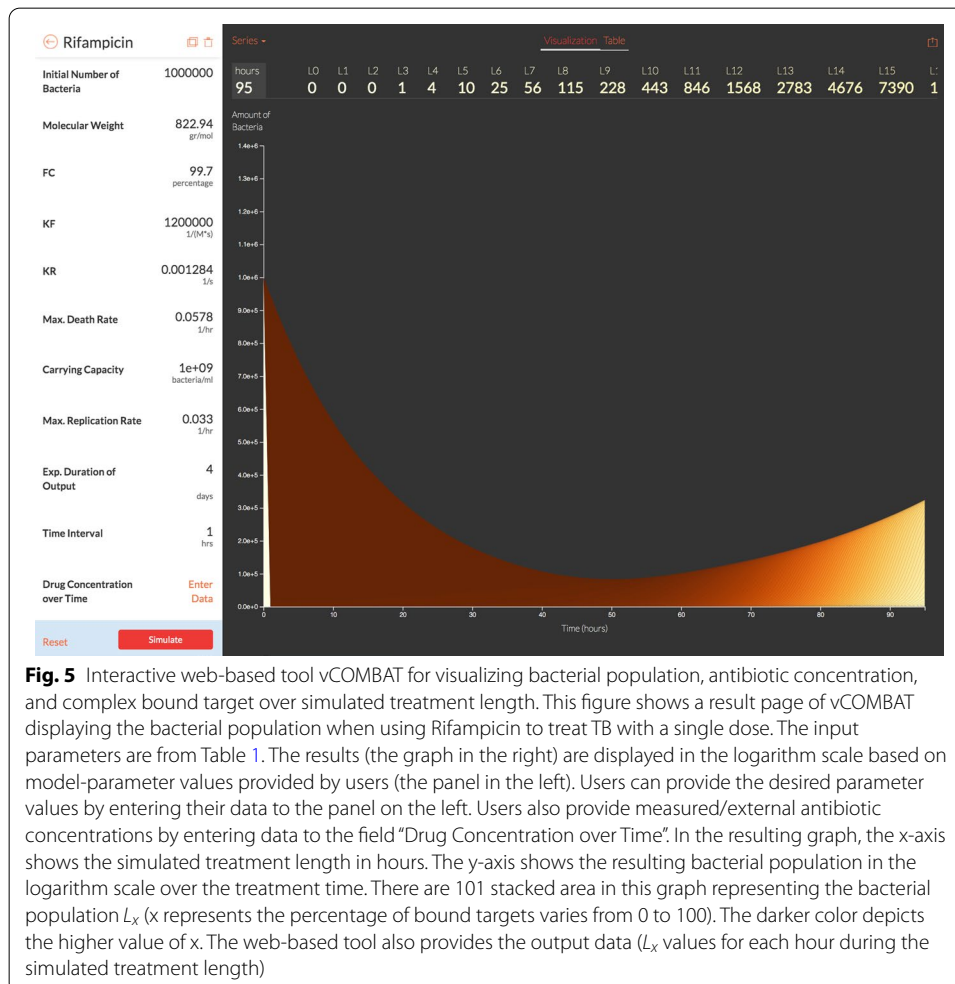


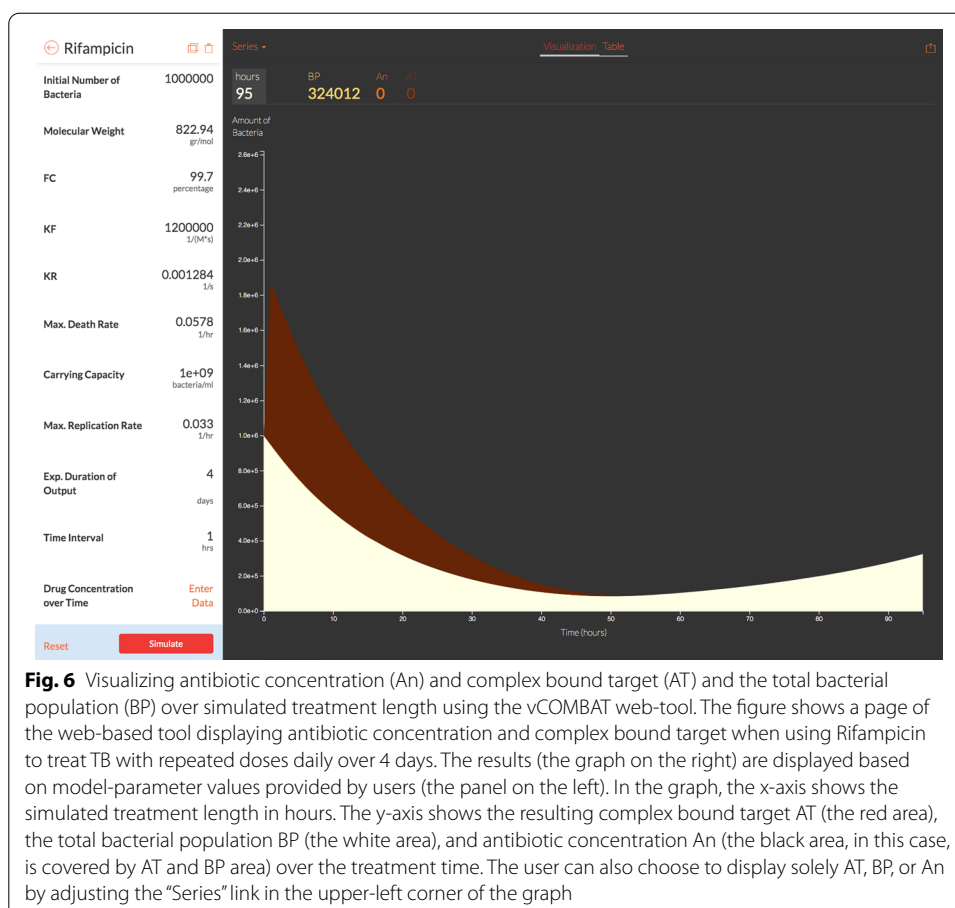
Figures 5 and 6 are the sample pages visualizing the effect of a single dose of Rifampicin on a typical Tuberculosis patient over 4 days.

The web tool can be accessed at <https://combat-bacteria.org/>. The tutorial providing step-by-step instructions for using the features of the interactive vCOMBAT web-based tool is in the supplementary document (Additional file 1).

## Discussion

In the real scenario using Rifampicin to treat TB, the output of the vCOMBAT model and tool are compared with the output of the traditional pharmacodynamic model [24]. Both models can predict the relapse from a single-dose Rifampicin at different time points. The difference is accounted for by the post-antibiotic effect. The vCOMBAT model is a mechanistic pharmacodynamic model that can capture the post-antibiotic effect where bacterial regrowth is delayed. The result from the vCOMBAT tool can aid the selection of an optimal drug dosing by informing which dosing regimens can terminate the bacterial population and clear an infection. It can also predict





relapse from pre-clinical and early clinical data and therefore, shorten the development process for new antibiotics.

The vCOMBAT tool run time varies by the values of the model parameters. For the model of using Rifampicin to treat TB patients, the runtime is longer (e.g., 15 min of simulation for 4 days of simulated treatment length) than the sample test cases due to the values of killing and replication threshold. The combination of Rifampicin drug and TB has extreme values of killing and replication threshold (i.e., TB bacterium are killed when 99 of its 100 free target molecules are bound). That means at every time step, the ODE solver has to compute 99 sub-populations of compartments  $B_x$  and assure their precision at the same time. However, the tool runtime (i.e., 15 min) is still considerably quick given the long simulated treatment length (i.e., 4 days).

The vCOMBAT tool provides a user-friendly and scientific platform for non-quantitative scientists and healthcare providers to create and visualize their own binding kinetic models for their considered drugs and bacteria. Moreover, with a timely and interactive tool, it also opens a wide range of opportunities to further use the vCOMBAT model in practices. The model can predict the drug efficacy for a large selection of dosing regimens and guide the choice of optimal doses. It can also be integrated with machine learning techniques to automatize the process of selecting optimal dosing.

## Conclusion

This work developed an extension of the mechanistic binding-kinetic model that simulates the process of bacterial antibiotic target-binding and presents the effect of drug actions on bacterial population over time. Based on the vCOMBAT model, we developed an interactive online tool that allows scientists and healthcare providers to create and visualize their own binding-kinetic models in a quick response time. We also demonstrated how the vCOMBAT tool simulates and visualizes the effect by different dosing strategies of Rifampicin on TB bacterial populations.

In the future, this work will be developed further to devise a framework to assist the process of choosing the optimal dosings. In the case where there is a wide range of possible dosings to be considered, modeling and selecting the optimal dosing from all the dosing possibilities are significantly more complex. Our ultimate aim is to make the process of selecting optimal dosing less time-consuming which is critical in improving patient well-being.

## Availability and requirements

Project name: vCOMBAT.

Project home page: <https://combat-bacteria.org/>.

Operating system(s): Platform independent.

Programming language: C.

Other requirements: GNU version 8 or higher.

License: GNU GPL.

Any restrictions to use by non-academics: vCOMBAT is publicly available for non-commercial users.

## Abbreviations

vCOMBAT: Visualize computational model of bacterial antibiotic target-binding; ODE: Ordinary differential equation; GNU: GNU's not unix; TB: Tuberculosis.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12859-021-04536-3>.

**Additional file 1:** The tutorial of vCOMBAT web-based tool.

## Acknowledgements

Not applicable.

## Authors' contributions

Conceptualization: PAzW and TC. Data curation: VT, AM, JL, FC and PAzW. Formal analysis: VT and PAzW. Investigation: VT and PAzW. Methodology: VT, TC and PAzW. Software: VT, AS, RM, SA. Validation: VT, AM and PAzW. Writing: VT and PAzW. Project administration and supervision: PAzW. Funding acquisition and resources: PAzW and TC. All authors read and approved the final manuscript.

## Funding

This work was funded by Bill and Melinda Gates Foundation Grant OPP1111658 (to T.C. & PAzW), Research Council of Norway (NFR) Grant 262686 (to PAzW), JPI-EC-AMR (Project 271176/H10), Polish National Agency of Academic Exchange and the European Molecular Biology Organisation. The publication charges for this article have been funded by a grant from the publication fund of UiT The Arctic University of Norway. The funders had no role in study design, data collection and analysis, result interpretation, or preparation of the manuscript.

## Availability of data and materials

The vCOMBAT online tool is freely accessible at <https://combat-bacteria.org/>. The software source code is uploaded to the git repository: <https://github.com/vitrann/vCOMBAT>.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Author details

<sup>1</sup>Department of Pharmacy, Faculty of Health Sciences, UiT The Arctic University of Norway, 9037 Tromsø, Norway.

<sup>2</sup>Department of Computer Science, Faculty of Science and Technology, UiT The Arctic University of Norway, 9037 Tromsø, Norway. <sup>3</sup>Polytechnique Montréal, Montreal, QC H3T 1J4, Canada. <sup>4</sup>Integrated Digital Media Department, New York University, New York, USA. <sup>5</sup>Malopolska Centre of Biotechnology, Jagiellonian University, Kraków, Poland. <sup>6</sup>Department of Infectious Disease Epidemiology, Imperial College London, St Mary's Campus, London, UK. <sup>7</sup>Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, USA. <sup>8</sup>Centre for Molecular Medicine Norway, Nordic EMBL Partnership, Blindern, 0318 Oslo, Norway. <sup>9</sup>Department of Biology, The Pennsylvania State University, University Park, PA 16802, USA. <sup>10</sup>Huck Institutes of the Life Sciences, The Pennsylvania State University, University Park, PA 16802, USA. <sup>11</sup>Division of Infection Control, Norwegian Institute of Public Health, Oslo, Norway.

Received: 3 August 2020 Accepted: 14 December 2021

Published online: 06 January 2022

## References

1. Nations U. 2020. <http://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/>.
2. Woolhouse M, Farrar J. Policy: an intergovernmental panel on antimicrobial resistance. *Nature*. 2014;509(7502):555–7. <https://doi.org/10.1038/509555a>.
3. Boeree MJ, Diacon AH, Dawson R, Narunsky K, Du Bois J, Venter A, Phillips PPJ, Gillespie SH, McHugh TD, Hoelscher M, Heinrich N, Rehal S, Van Soolingen D, Van Ingen J, Magis-Escurra C, Burger D, Van Balen GP, Aarnoutse RE. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med*. 2015;191(9):1058–65. <https://doi.org/10.1164/rccm.201407-1264OC>.
4. Lan AJ, Colford JM, Colford JM. The impact of dosing frequency on the efficacy of 10-day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: a meta-analysis. *Pediatrics*. 2000. <https://doi.org/10.1542/peds.105.2.e19>.
5. Roord JJ, Wolf BH, Gossens MM, Kimpen JL. Prospective open randomized study comparing efficacies and safeties of a 3-day course of azithromycin and a 10-day course of erythromycin in children with community-acquired acute lower respiratory tract infections. *Antimicrob Agents Chemother*. 1996;40(12):2765–8. <https://doi.org/10.1128/AAC.40.12.2765>.
6. Deun AV, Salim MAH, Kumar Das AP, Bastian I, Portals F. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh A standardised approach may provide a reasonable alternative to individualised treatment of MDR-TB in resource-poor settings. However, DOTS- plus programmes in resource-p. *Int J Tuberc Lung Dis*. 2004;8(5):560–7.
7. WHO: The Shorter MDR-TB Regimen. [http://www.who.int/tb/Short\\_MDR\\_regimen\\_factsheet.pdf?ua=1](http://www.who.int/tb/Short_MDR_regimen_factsheet.pdf?ua=1)
8. Horsburgh CR, Barry CE, Lange C. Treatment of tuberculosis. *N Engl J Med*. 2015;373(22):2149–60. <https://doi.org/10.1056/NEJMr1413919>.
9. Ankamah P, Levin BR. Two-drug antimicrobial chemotherapy: a mathematical model and experiments with *Mycobacterium marinum*. *PLoS Pathog*. 2012. <https://doi.org/10.1371/journal.ppat.1002487>.
10. Zhang Q, Lambert G, Liao D, Kim H, Robin K, Tung C-K, Pourmand N, Austin RH. Acceleration of emergence of bacterial antibiotic resistance in connected microenvironments. *Science*. 2011;333(6050):1764–7. <https://doi.org/10.1126/science.1208747>.
11. Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: strategies to beat multidrug-resistant tuberculosis. *Science*. 2002;295(5562):2042–6. <https://doi.org/10.1126/science.1063814>.
12. Norrby SR, Nord CE, Finch R. Lack of development of new antimicrobial drugs: a potential serious threat to public health. *Eur Soc Clin Microbiol Infect Dis (ESCMID)*. 2005. [https://doi.org/10.1016/S1473-3099\(05\)01283-1](https://doi.org/10.1016/S1473-3099(05)01283-1).
13. Davies G, Boeree M, Hermann D, Hoelscher M. Accelerating the transition of new tuberculosis drug combinations from phase ii to phase iii trials: new technologies and innovative designs. *PLoS Med*. 2019;16(7):1–10. <https://doi.org/10.1371/journal.pmed.1002851>.
14. Zhang R. Pharmacodynamics which trails are your drugs taking? *Nat Chem Biol*. 2015;11:382–3.
15. Lienhardt C, Nahid P. Advances in clinical trial design for development of new tb treatments: a call for innovation. *PLoS Med*. 2019;16(3):1–5. <https://doi.org/10.1371/journal.pmed.1002769>.
16. Clarelli F, Liang J, Martinecz A, Heiland I, Abel zur Wiesch P. Multi-scale modeling of drug binding kinetics to predict drug efficacy. *Cell Mol Life Sci*. 2020;77(3):381–94. <https://doi.org/10.1007/s00018-019-03376-y>.
17. Abel Zur Wiesch P, Abel S, Gkotz S, Ocampo P, Engelstädter J, Hinkley T, Magnus C, Waldor MK, Udekwi K, Cohen T. Classic reaction kinetics can explain complex patterns of antibiotic action. *Sci Transl Med*. 2015;7(287):1–12. <https://doi.org/10.1126/scitranslmed.aaa8760>.
18. Clarelli F, Palmer A, Singh B, Storfli M, Lauksund S, Cohen T, Abel S, PazW. Drug-target binding quantitatively predicts optimal antibiotic dose levels in quinolones. *PLoS Comput Biol*. 2020.

19. Grobbelaar M, Louw GE, Sampson SL, Helden PD, Donald PR, Warren RM. Evolution of rifampicin treatment for tuberculosis. *Infect Genet Evol.* 2019;74: 103937. <https://doi.org/10.1016/j.meegid.2019.103937>.
20. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, Kibiki GS, Churchyard G, Sanne I, Ntinginya NE, Minja LT, Hunt RD, Charalambous S, Hanekom M, Semvua HH, Mpagama SG, Manyama C, Mtafya B, Reither K, Wallis RS, Venter A, Narunsky K, Mekota A, Henne S, Colbers A, van Balen GP, Gillespie SH, Phillips PPJ, Hoelscher M. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis.* 2017;17(1):39–49. [https://doi.org/10.1016/S1473-3099\(16\)30274-2](https://doi.org/10.1016/S1473-3099(16)30274-2).
21. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2014.
22. Aruoba SB, Fernández-Villaverde J. A comparison of programming languages in economics. *J Econ Dyn Control.* 2015;58:265–73. <https://doi.org/10.1016/j.jedc.2015.05.009>.
23. Galassi M. GNU scientific library reference manual. 2018. <https://www.gnu.org/software/gsl/>.
24. Aljayyousi G, Jenkins VA, Sharma R, Ardrey A, Donnellan S, Ward SA, Biagini GA. Pharmacokinetic-Pharmacodynamic modelling of intracellular Mycobacterium tuberculosis growth and kill rates is predictive of clinical treatment duration. *Nat Sci Rep.* 2017;7(1):1–11. <https://doi.org/10.1038/s41598-017-00529-6>.
25. Strydom N, Gupta SV, Fox WS, Via LE, Bang H, Lee M, Eum S, Shim TS, Barry CE, Zimmerman M, Dartois V, Savic RM. Tuberculosis drugs' distribution and emergence of resistance in patient's lung lesions: a mechanistic model and tool for regimen and dose optimization. *PLoS Med.* 2019;16(4):1–26. <https://doi.org/10.1371/journal.pmed.1002773>.
26. Dooley KE, Hanna D, Mave V, Eisenach K, Savic RM. Advancing the development of new tuberculosis treatment regimens: the essential role of translational and clinical pharmacology and microbiology. *PLoS Med.* 2019;16(7):1–14. <https://doi.org/10.1371/journal.pmed.1002842>.
27. Van Ingen J, Aarnoutse RE, Donald PR, Diacon AH, Dawson R, Plemper van Balen G, Gillespie SH, Boeree MJ. Why do we use 600 mg of rifampicin in tuberculosis treatment? *Clin Infect Dis.* 2011;52(9):194–9. <https://doi.org/10.1093/cid/cir184>.
28. Cadosch D, Abel zur Wiesch P, Kouyos R, Bonhoeffer S. The role of adherence and retreatment in de novo emergence of MDR-TB. *PLoS Comput Biol.* 2016;12(3):1–19. <https://doi.org/10.1371/journal.pcbi.1004749>.
29. Abel zur Wiesch P, Clarelli F, Cohen T. Using chemical reaction kinetics to predict optimal antibiotic treatment strategies. *PLoS Comput Biol.* 2017;13(1):1–28. <https://doi.org/10.1371/journal.pcbi.1005321>.
30. Wehrli W. Kinetic Studies of the Interaction between Rifampicin and DNA-Dependent RNA Polymerase of Escherichia coli. *Biol Res.* 1977;330:325–30.
31. COMPOUND SUMMARY of Rifampicin. (2019). <https://pubchem.ncbi.nlm.nih.gov/compound/Rifampicin> Accessed 01 Apr 2020.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

