



HAL
open science

Manogepix and amphotericin B combination is synergistic against *Candida glabrata* as evidenced by a new pharmacodynamic-modelling approach

Adrien Baillod, Vincent Aranzana-Climent, Jonathan Clarhaut, Sandrine Marchand, Kevin Brunet

► To cite this version:

Adrien Baillod, Vincent Aranzana-Climent, Jonathan Clarhaut, Sandrine Marchand, Kevin Brunet. Manogepix and amphotericin B combination is synergistic against *Candida glabrata* as evidenced by a new pharmacodynamic-modelling approach. ESCMID Global 2025, Apr 2025, Vienna, Austria. . <hal-05071394>

HAL Id: hal-05071394

<https://hal.science/hal-05071394v1>

Submitted on 16 May 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC-ND 4.0 - Attribution - Non-commercial use - No Derivative Works - International License

Manogepix and amphotericin B combination is synergistic against *Candida glabrata* as evidenced by a new pharmacodynamic-modelling approach

Adrien Baillod¹, Vincent Aranzana-Climent¹, Jonathan Clarhaut^{1,2}, Sandrine Marchand^{1,2}, Kevin Brunet^{1,3}

Contacts: adrien.baillod@univ-poitiers.fr ; kevin.brunet@univ-poitiers.fr

¹ Université de Poitiers, INSERM U1070 PHAR2, Poitiers, France

² CHU de Poitiers, service de Toxicologie-Pharmacocinétique, Poitiers, France

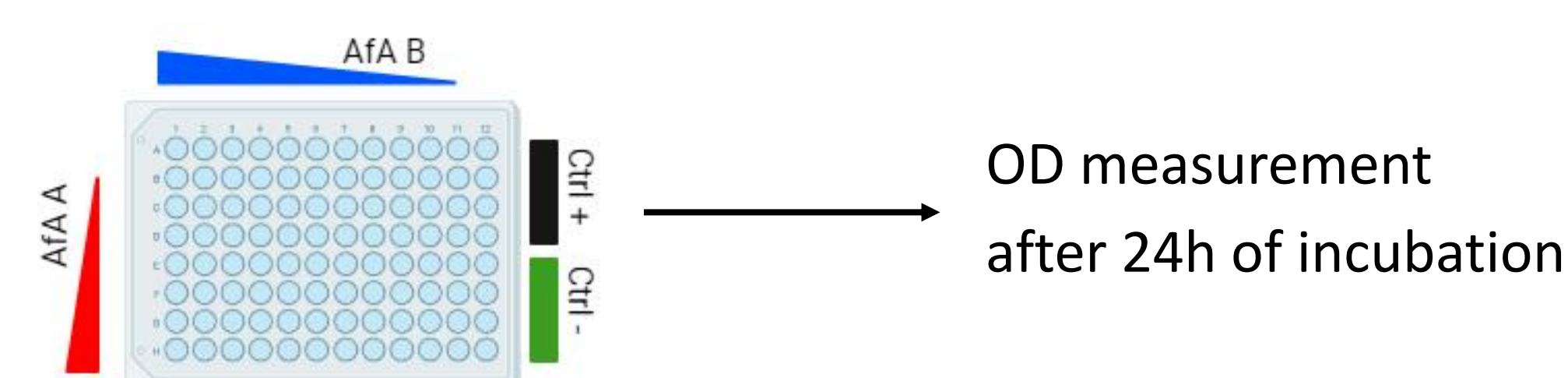
³ CHU de Poitiers, service de Parasitologie et Mycologie Médicale, Poitiers, France

Introduction

Candida glabrata is the second most common yeast species involved in candidemia. It presents high MICs for azoles and several strains have showed resistance or tolerance to echinocandins. Manogepix (MGX) is an innovative antifungal agent that disrupts the GPI-anchor biosynthesis pathway by inhibiting the GWT1 enzyme. MGX could be an alternative to treat multi-resistant *C. glabrata* strains. The aim of this study was to evaluate the potential of MGX in combination with other antifungal agents, amphotericin B (AmB), micafungin (MCF), fluconazole (FLU) and voriconazole (VRZ), to improve efficacy and/or limit the development of resistance against *C. glabrata* using a new pharmacodynamic-modelling approach to overcome the problems encountered (varied definitions of MIC, 90% or 50% growth inhibition) with FIC index analysis.

Materials and methods

1 Study of the *in vitro* activity of antifungal combinations by checkerboard assays



Checkerboard assays were performed using RPMI medium and 4 different antifungal combinations :

- MGX/AmB
- MGX/FLU
- MGX/MCF
- MGX/VRZ

12 isolates of *C. glabrata* (including 2 echinocandin-resistant strains, 2 azole-resistant strains and the ATCC 2950 reference strain) were studied.

2 Interpretation of checkerboards using pharmacodynamic-modelling approach

Growth inhibition was modelled using the GDPI model¹ (Eq.1). The effect of combination was modelled with Bliss independence (Eq.2). A new index was developed, named effect improvement (EI) (Eq.3), which compares the effect of the combination with the effect of the best monotherapy at equivalent concentration.

$$1 \quad E_{A|B} = \frac{Emax_A * C_A^{H_A}}{\left(EC50_A * \left(1 + \frac{INT_{AB} * C_B^{H_{INT,AB}}}{EC50_{INT,AB} + C_B^{H_{INT,AB}}} \right) \right)^{H_A}} + C_A^{H_A}$$

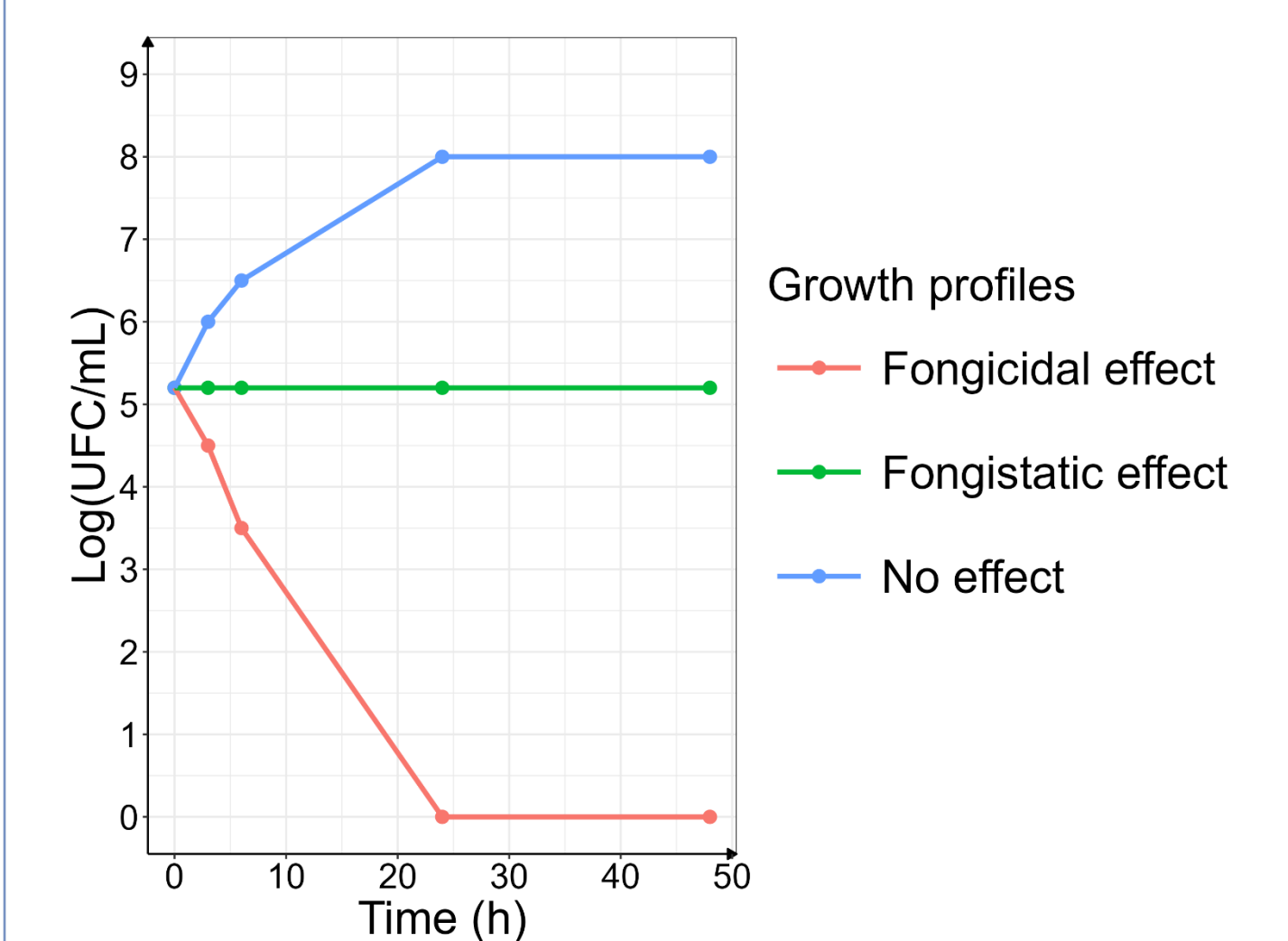
$$2 \quad E_{AandB} = E_{A|B} + E_{B|A} - E_{A|B} * E_{B|A}$$

$$3 \quad Effect\ improvement = E_{AandB} - \max(E_{A|B=0}, E_{B|A=0})$$

Mathematical methods and software:

Modelling and simulation were performed with R² version 4.3.2.

3 Time kill curves of MGX/AmB combination



Time kill curves (TKC) assays were performed using RPMI medium and MGX/AmB combination.

6 isolates of *C. glabrata* (including 2 echinocandin-resistant strains, 2 azole-resistant strains and the ATCC 2950 reference strain) were studied.

Results

We developed a model that successfully described the effect of the four combination therapies against the 12 strains.

We were able to quantify the **improvement of the antifungal effect** (named **effect improvement**) due to the combination in each well of the checkerboard in comparison to the most effective monotherapy at equivalent concentrations.

Comparing the best effect improvement for each strain, the combination with the higher effect improvements was **MGX/AmB** (Figure 1).

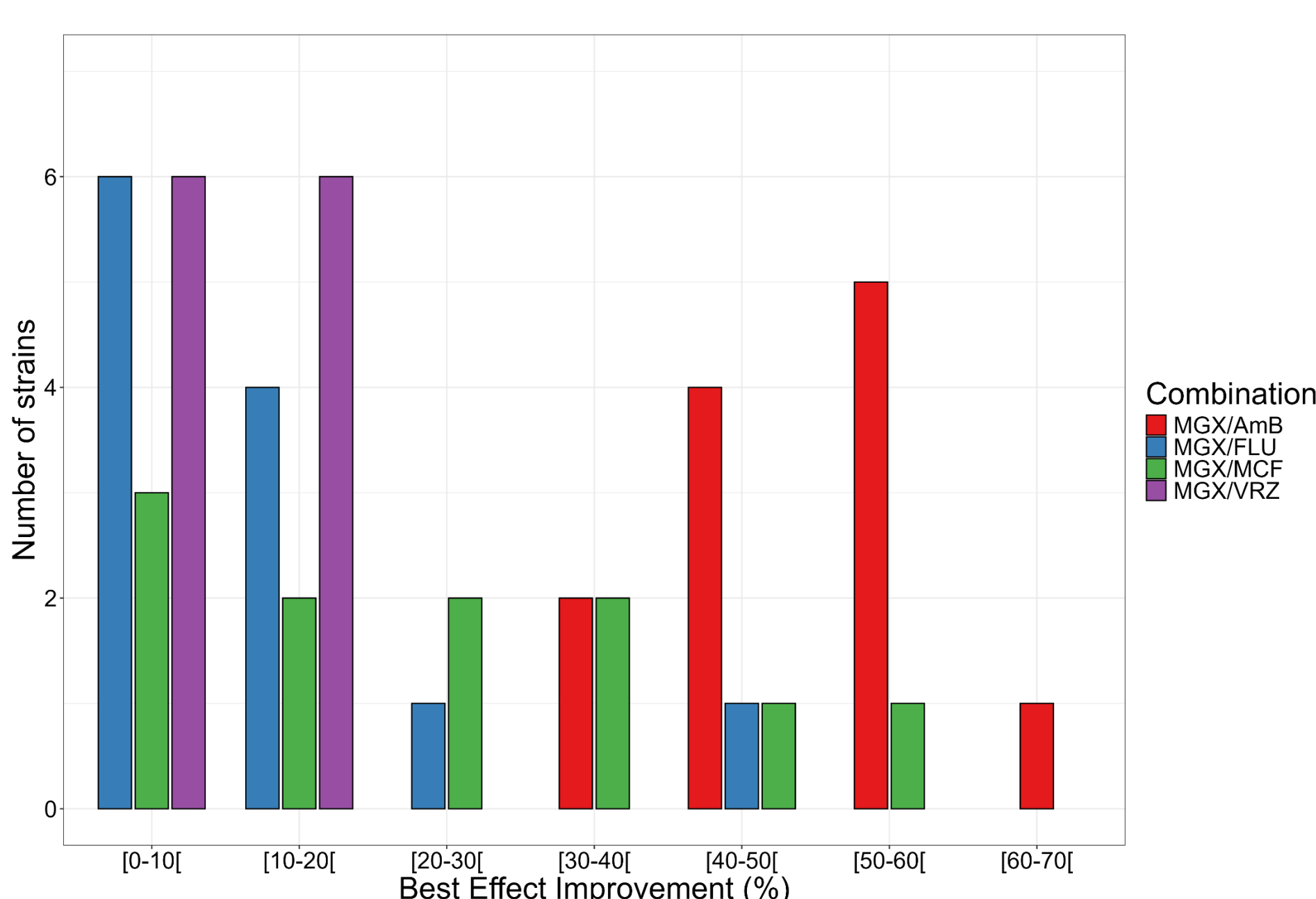


Figure 1: Cumulative representation of the best effect improvement for all strains for each combination of antifungals.

The best effect improvements were observed for combinations of MGX concentrations **between 1/8 of its MIC and its MIC** and AmB concentrations **between 1/2 and 1/8 of its MIC** (Figure 2).

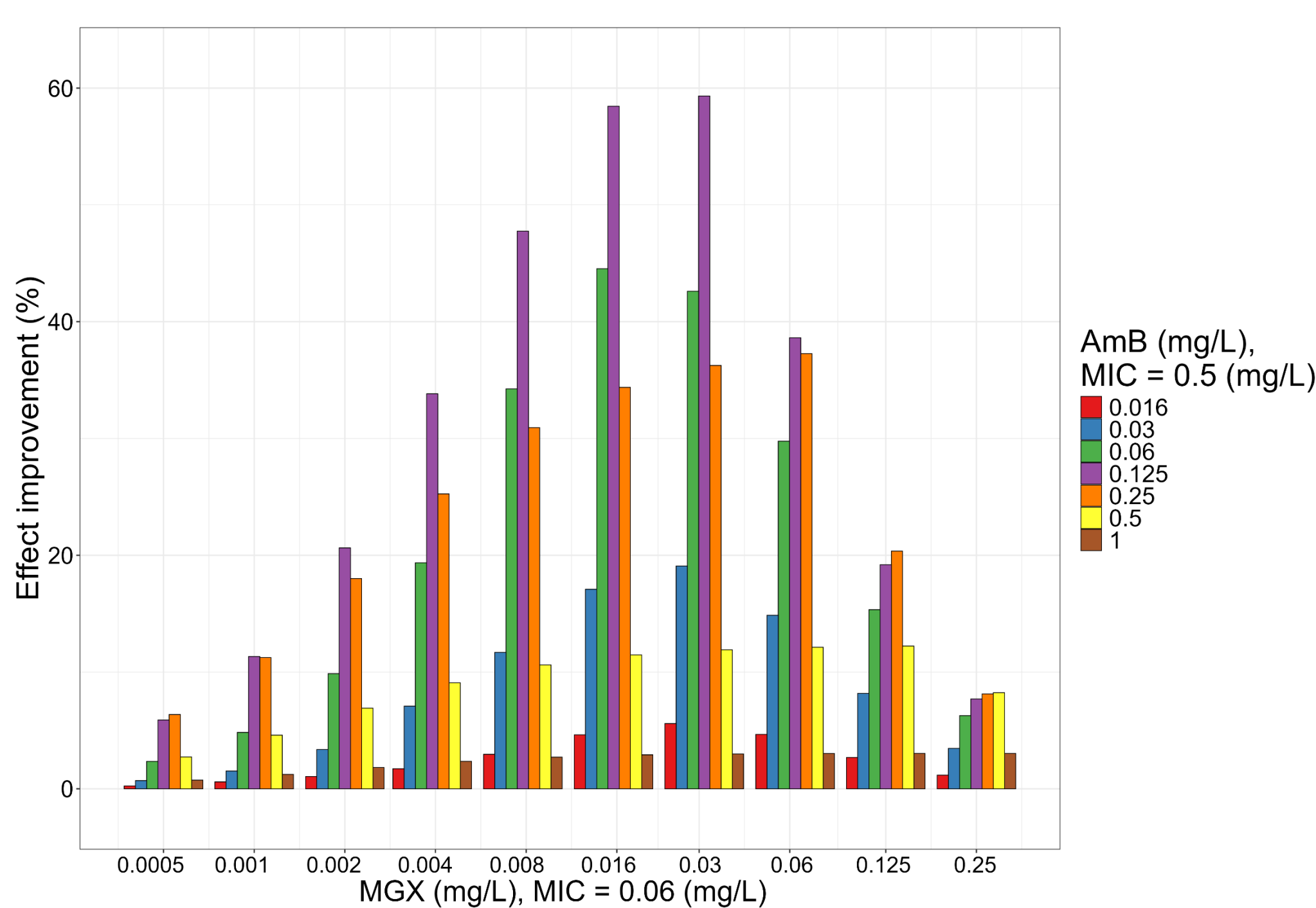


Figure 2: Effect improvement values for each well of the MGX/AmB checkerboard against one strain of *C. glabrata*.

The **MGX/AmB combination synergy** was confirmed in TKC. Use of **AmB concentrations 8 to 4 fold lower than its MIC** improved the efficacy of MGX compared to monotherapy.

For example, against one of the strains, use of **0,125 mg/L of AmB (1/4 of its MIC)** in combination with MGX at its MIC reduced the fungal load in the TKC by more than **99%** (Figure 3).

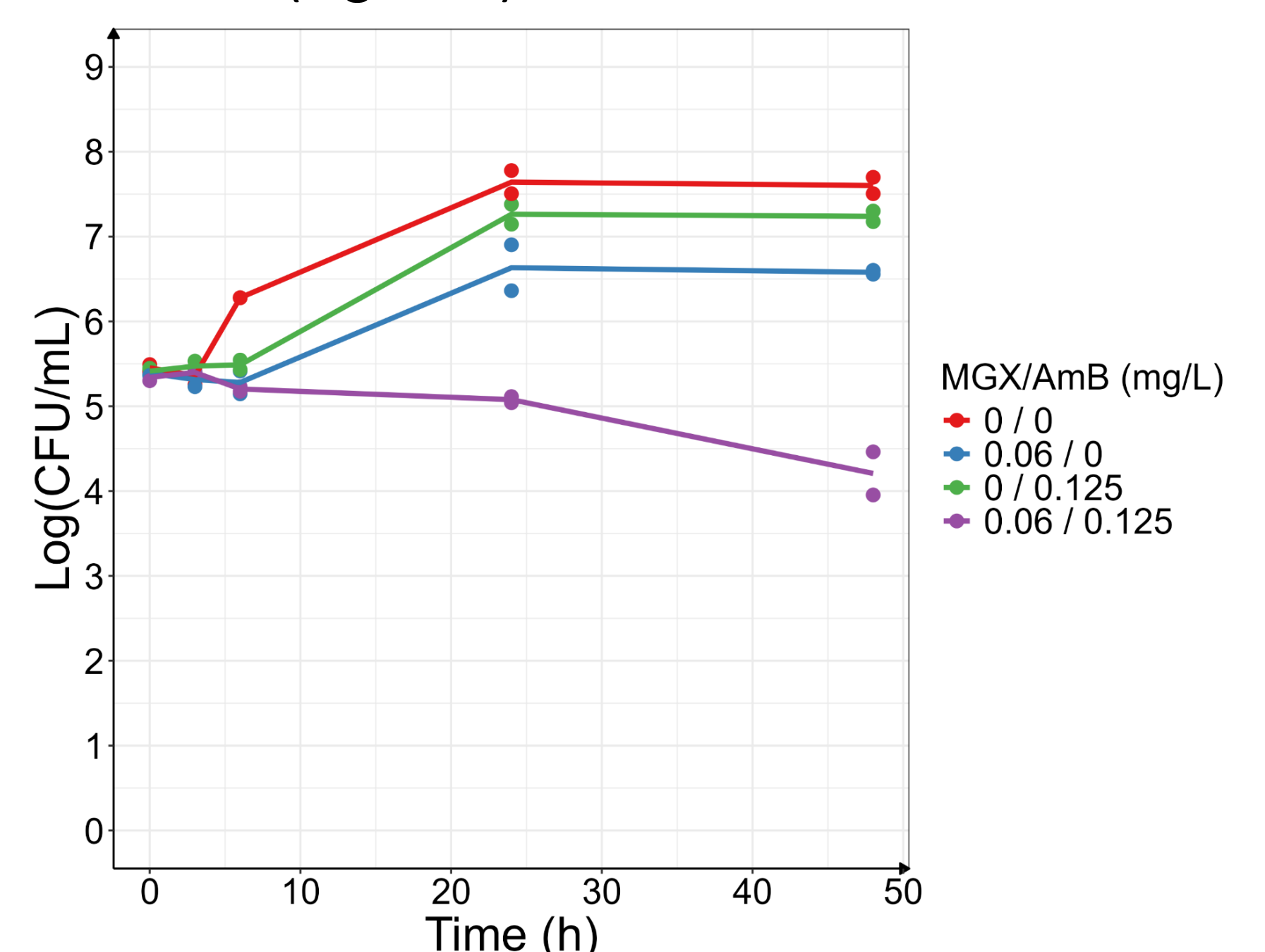


Figure 3: Time kill curve for the combination of 0.06 mg/L of MGX and 0,125 mg/L of AmB against one strain of *C. glabrata* (n=2).

Conclusion

We have developed an **innovative and robust checkerboard analysis model** for antifungal agent combinations analysis. The analysis showed that **MGX/AmB combination** appears to be the best combination on the twelve tested strains of *C. glabrata*. The model supposed that the use of **low doses of AmB and MGX** could improve the effect of both monotherapies. These results were confirmed by the TKC assays in which the use of **low doses of AmB** improved the effect of MGX at its MIC concentration. The MGX/AmB combination appears very promising to **treat *C. glabrata*** and reduce the risk of resistance development.

1) Wicha et al. [10.1038/s41467-017-01929-y](https://doi.org/10.1038/s41467-017-01929-y)

2) R Core Team (2023) <https://www.R-project.org/>

Funding: This project (DACOSID) benefits from financial support from the Région Nouvelle-Aquitaine as part of its "Recherche et Plateformes" Call for Projects.

