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# Synergistic interaction between antifungal agents against *Candida guilliermondii* using pharmacodynamics-modelling approach

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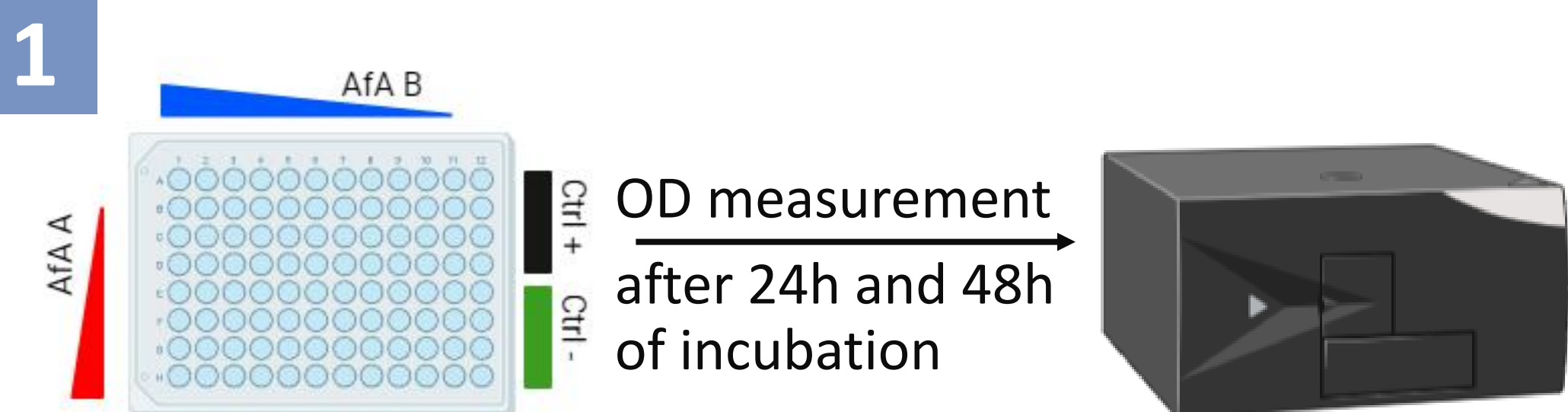
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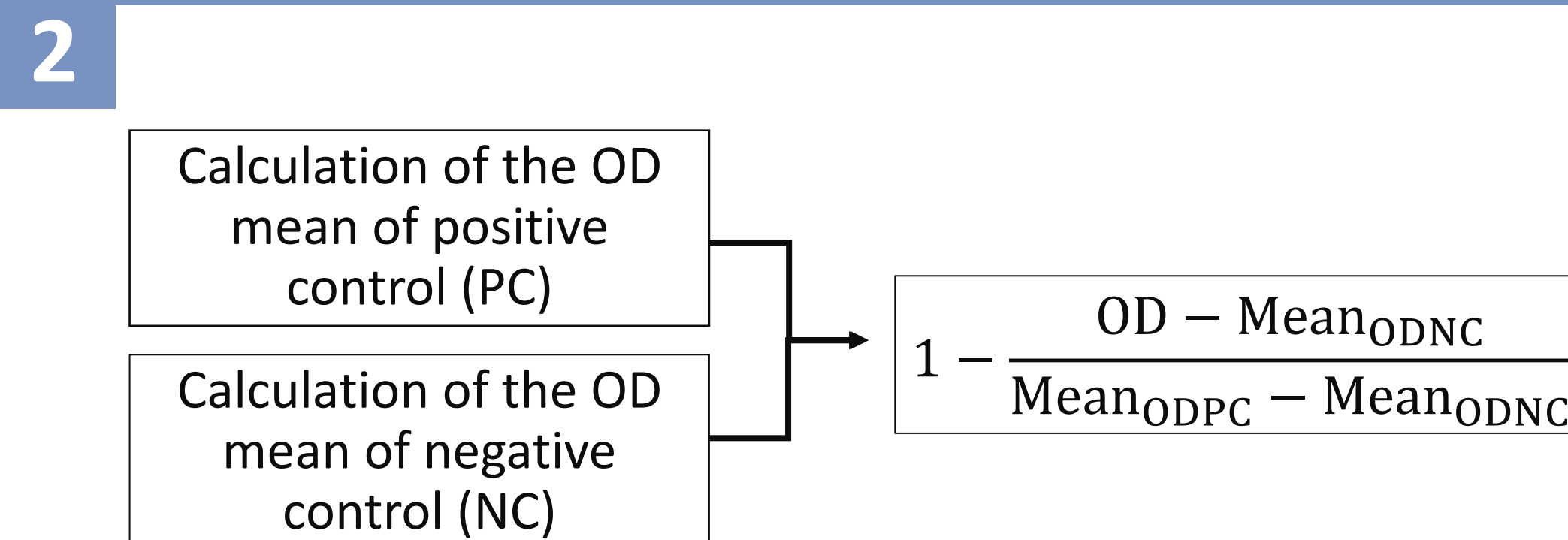
## Introduction

*Candida guilliermondii* is a yeast species involved in candidemia. It presents high MICs for echinocandins, the first-line treatment, and several strains showed tolerance to amphotericin B (AmB). The objective of this study was to test *in vitro* combinations of antifungal agents against clinical isolates of *C. guilliermondii* by using an innovative pharmacodynamics-modelling approach to evaluate the interactions between antifungal agents. This approach is used to replace the fractional inhibitory combination index (FICI), which is unusable due to the varied definitions of MIC (Minimum Inhibitory Concentration) for antifungal agents, such as 90% or 50% growth inhibition.

## Materials and methods



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



**Step 2:** Computation of the growth inhibition percentage at each tested antifungal agent(s) concentrations<sup>1</sup>

**3**

$$E_{\text{monoth}} = \frac{E_{\text{max}} * C^H}{EC_{50}^H + C^H}$$

**Step 3:** Modelling and simulation of the monotherapy effect for all antifungals, strains, time, combinations

**4**

$$E_{A|B} = \frac{E_{\text{max}_A} * C_A^{H_A}}{\left( EC_{50_A} * \left( 1 + \frac{INT_{AB} * C_B^{H_{INT,AB}}}{EC_{50_{INT,AB}}^{H_{INT,AB}} + C_B^{H_{INT,AB}}} \right) \right)^{H_A}} + C_A^{H_A}$$

$$E_{\text{Comb}} = E_{A|B} + E_{B|A} - E_{A|B} * E_{B|A}$$

**Step 4:** Modelling and simulation of the combination effect for all antifungals, strains, time, concentration combination

**5**

$$\text{Effect improvement} = E_{A \text{ and } B} - \max(E_A, E_B)$$

**Step 5:** Computation of the difference of effect (effect improvement = increase of growth inhibition) between the combination and the best monotherapy effect of the same combination

### Microbiological materials:

Checkerboard assays were performed using RPMI medium and 5 different antifungal combinations :

- AmB/micafungine (MICA)
- AmB/fluconazole (FLU)
- AmB/voriconazole (VORI)
- MICA/FLU
- MICA/VORI

**11 *C. guilliermondii*** strains were tested, ATCC 6260 and 10 clinical isolates including 3 azole-resistant strains ( $MIC_{\text{FLU}} > 16$  mg/L and  $MIC_{\text{VORI}} > 0,25$  mg/L).

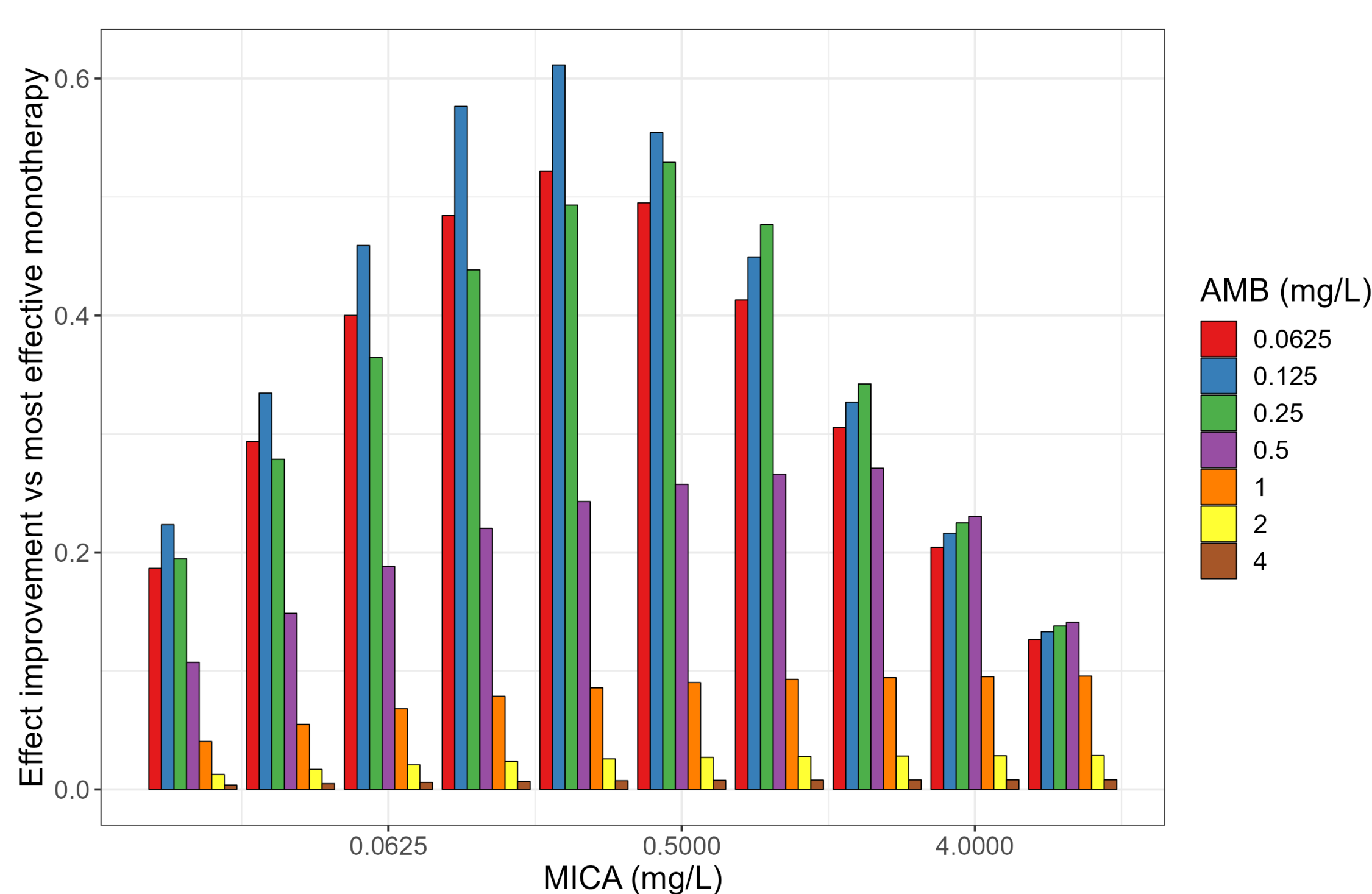
### Mathematical methods and software:

An Emax model was fitted to monotherapy data. It was modified following the GPDI<sup>2</sup> method to fit combination data. Modelling and simulation were performed with R<sup>3</sup> version 4.3.2.

## Results

We developed models that successfully described the effect of the five combination therapies at 70 different concentration combinations against the 11 strains. From the final models, we were able to quantify the **improvement of the effect of the combination** in comparison to the **most efficient monotherapy** at equivalent concentrations. Representative data for one strain are showed in Figure 1.

After data analyzing, **synergy** was defined as an improvement of at least **20%** for the concentration combination in comparison to the most efficient monotherapy.

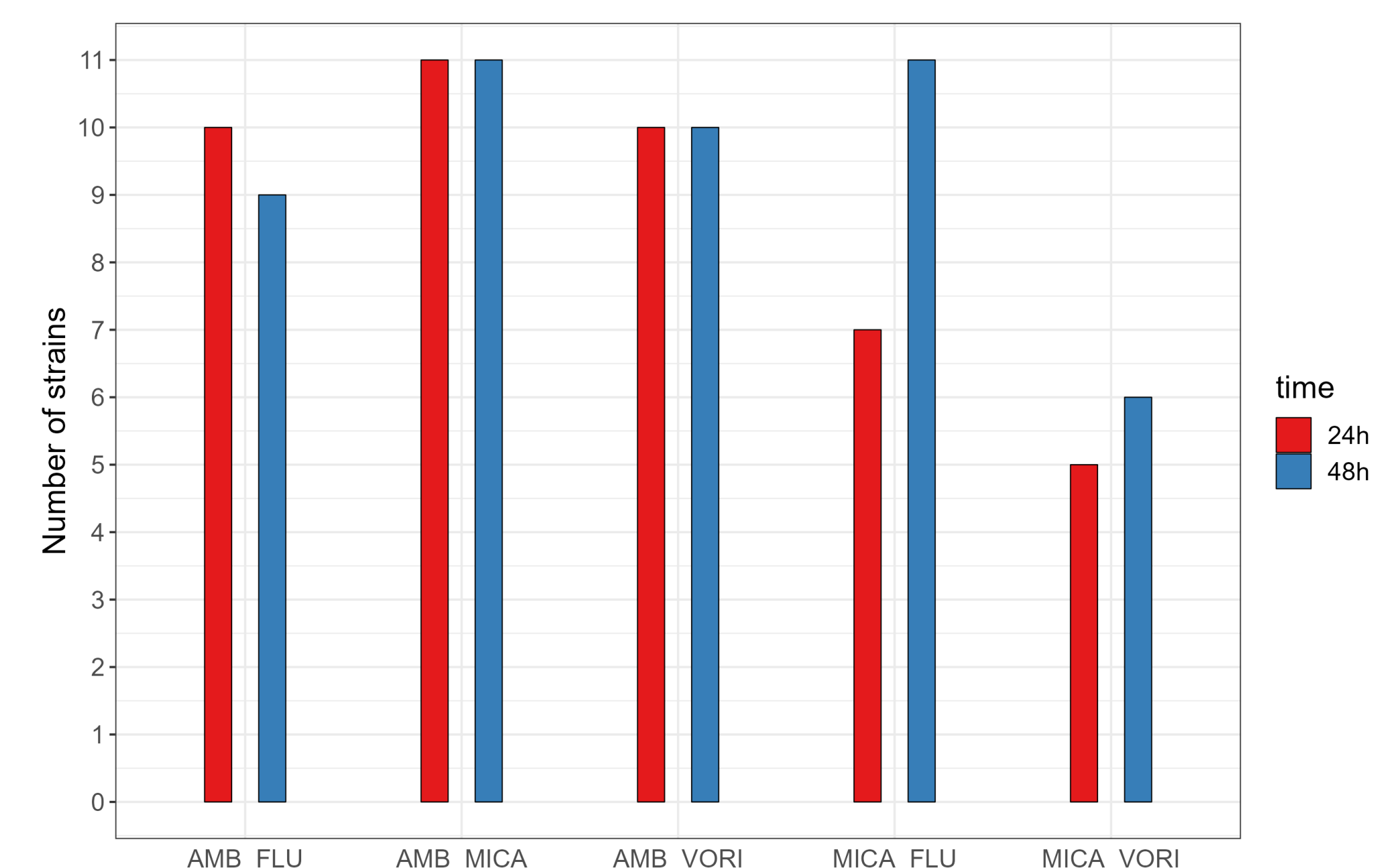


**Figure 1:** Representative data for one combination (AMB/MICA) against one strain (G9) at one time (48h).

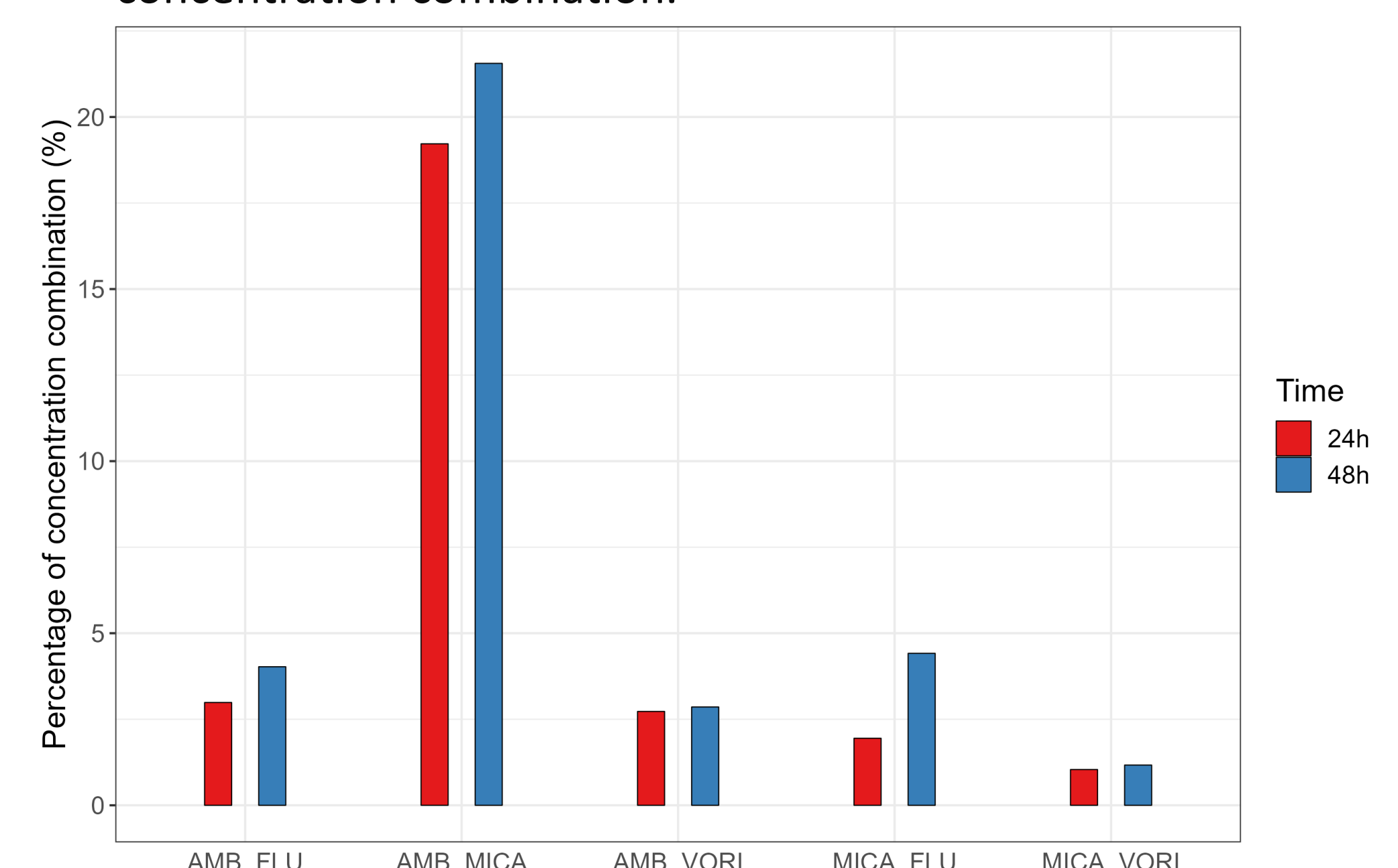
The model suggested synergy for (Figure 2) :

- The majority of strains for the **AmB/azole combinations**, including azole-resistant strains.
- Every strains for **AMB/MICA combination** at both 24h and 48h.
- Several strains for MICA/FLU combination.

The **AMB/MICA combination** was the combination with the highest number of concentration combinations that showed synergy (Figure 3).



**Figure 2:** Number of strains with at least one synergistic concentration combination.



**Figure 3:** Percentage of synergistic concentration combinations for every strains.

## Conclusion

The pharmacodynamics-modelling approach allowed us to evaluate combined effect of antifungal agents without the need to binarize our results as necessitated by traditional methods such as the fractional inhibitory combination index (FICI). The model suggested **synergy** for the majority of strains for the **AmB/azole** (9/11 strains) and **AmB/MICA** (11/11 strains) combinations, including azole-resistant strains. The model suggested that **AMB/MICA** was the combination with the **most effective concentration combinations** against the tested strains. No tested combination exhibited antagonism.

## References

- 1) EUCAST\_E.Def\_7.4\_Yeast\_definitive\_revised\_2023
- 2) Wicha et al. [10.1038/s41467-017-01929-y](https://doi.org/10.1038/s41467-017-01929-y)
- 3) R Core Team (2023) <https://www.R-project.org/>



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