MONITORING OF NATURAL SARS-COV-2 SUSCEPTIBILITY TO NIRMATRELVIR: A 4-YEARS RETROSPECTIVE STUDY

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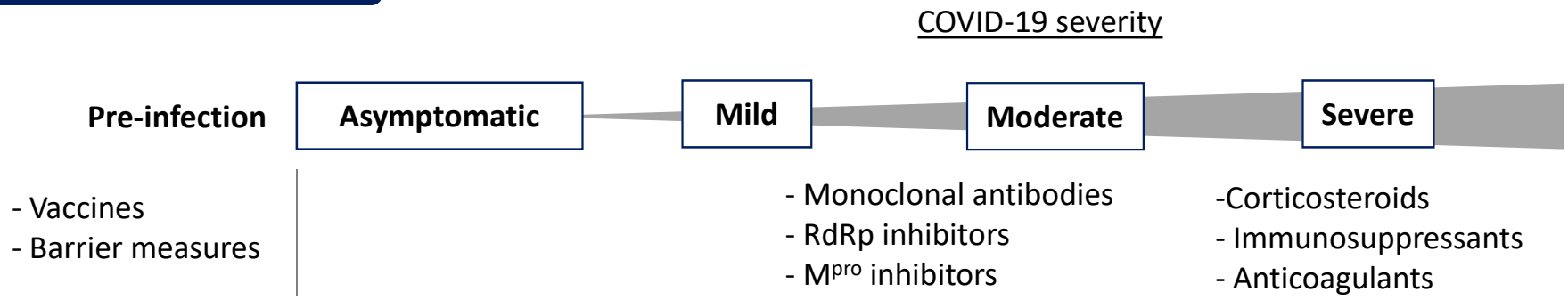
INTRODUCTION

Specific treatments for COVID-19



Adapted from Li et al. (2023)

INTRODUCTION

Specific treatments for COVID-19

COVID-19 severity

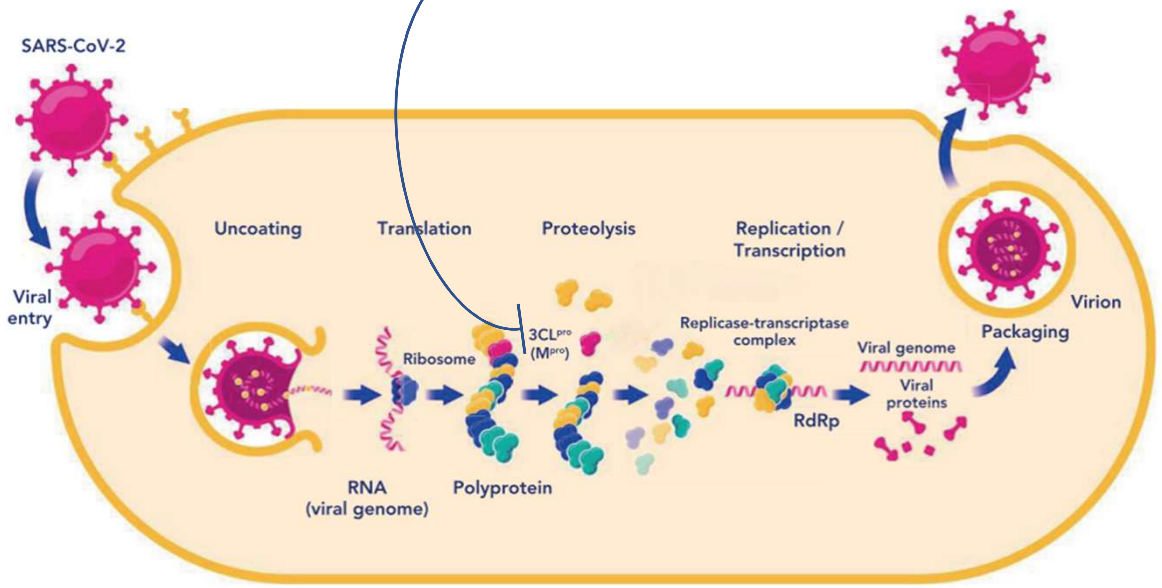
Pre-infection | **Asymptomatic** | **Mild** | **Moderate** | **Severe**

- Vaccines
- Barrier measures

- Monoclonal antibodies
- RdRp inhibitors
- **M^{pro} inhibitors:**

-Corticosteroids
- Immunosuppressants
- Anticoagulants

Nirmatrelvir (+ Ritonavir = **Paxlovid®**)



Adapted from Li et al. (2023), Pfizer (2022)

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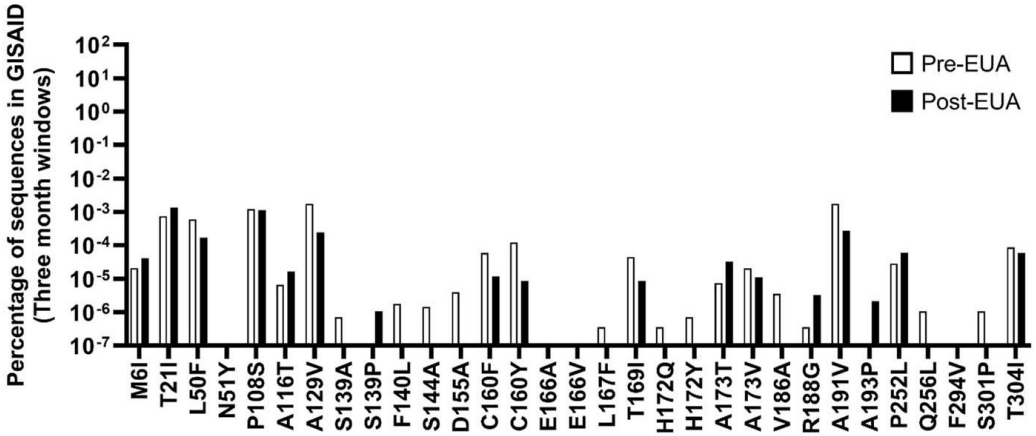

Analysis of sequences in GISAID:

- **Low prevalence** of worldwide mutations on **Mpro** (0.5%)
- Similar mutation prevalence **before and after the Paxlovid emergency use authorisation** (EUA)

Iketani et al. (2022)

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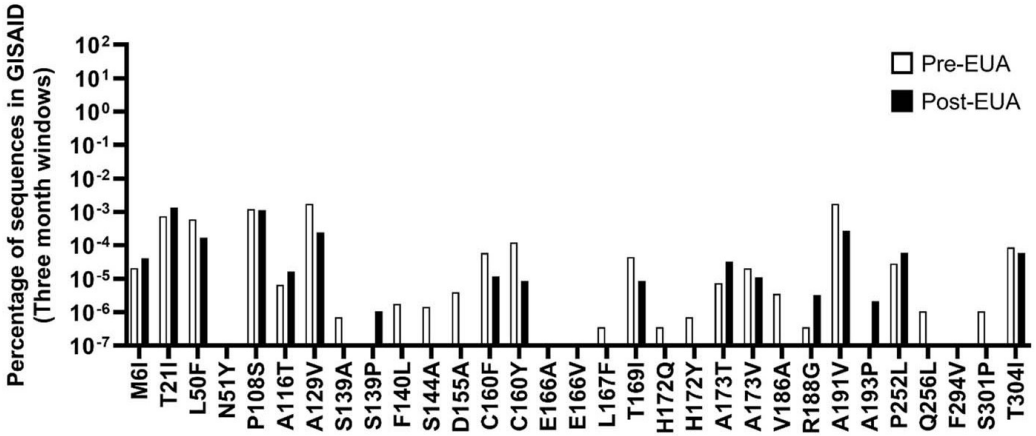

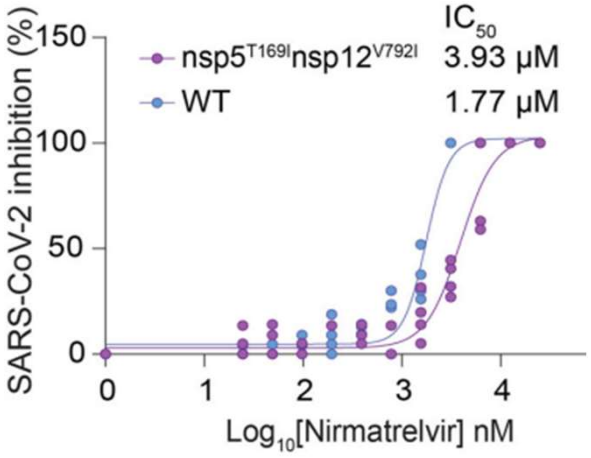

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- **Few phenotypic tests** performed

Iketani et al. (2022), Nooruzzaman et al. (2024)

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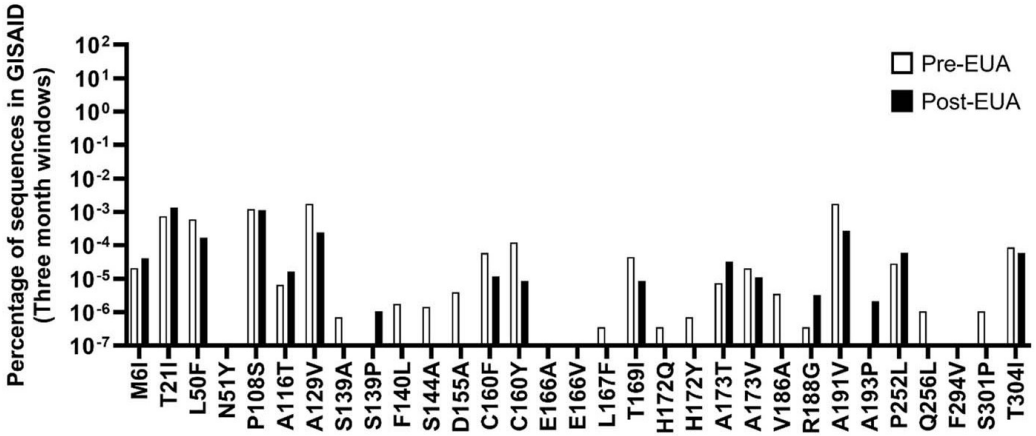

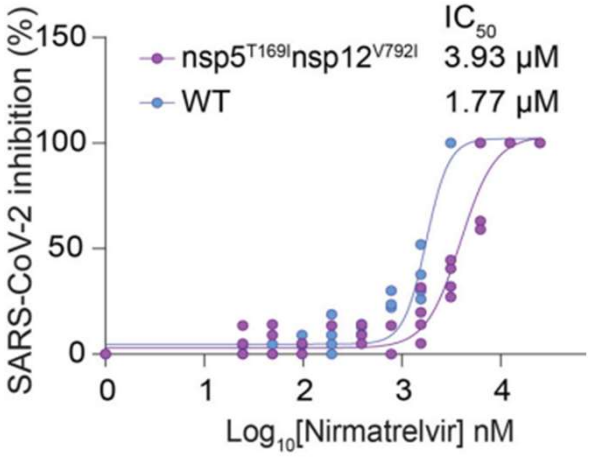

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The **phenotypic** and **genotypic** monitoring is essential

Iketani et al. (2022), Nooruzzaman et al. (2024)

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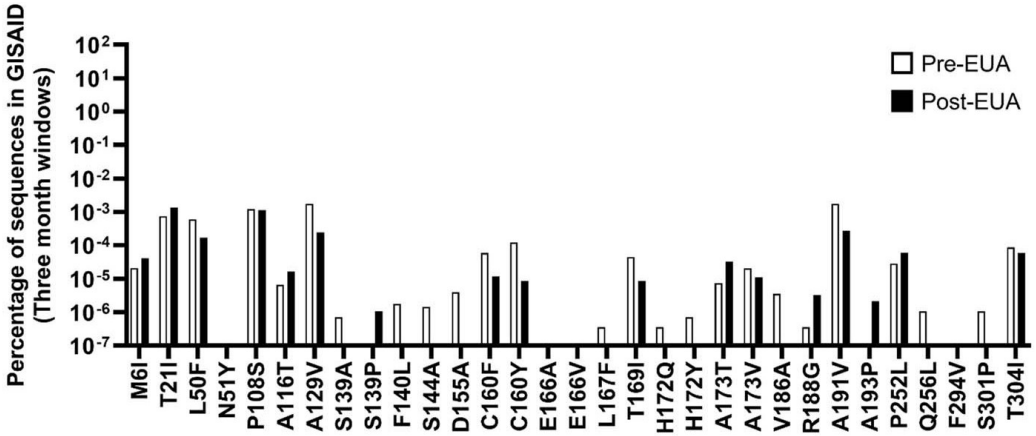

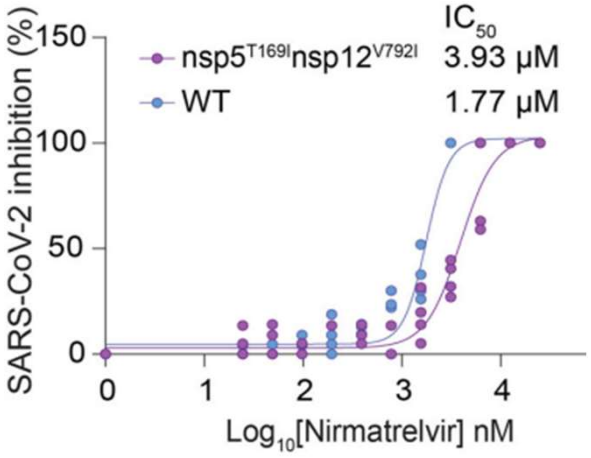

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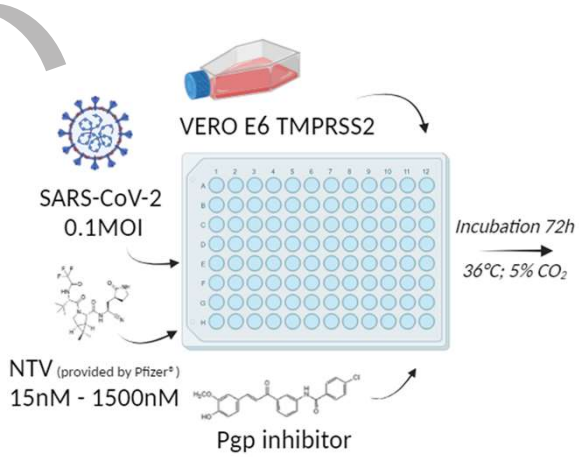
Objective: Assess the **phenotypic susceptibility to Nirmatrelvir** (NTV) of **clinical SARS-CoV-2 strains** circulating in the **South of France from 2020 to 2023.**

MATERIAL AND METHODS

Phenotypic susceptibility assay by Real-Time Cellular Analysis (RTCA)

Respiratory samples from patients hospitalised in the **Lyon area** from **2020 to 2023** (n=411).
Selected based on:
- **Ct < 25**
- **Local epidemiology**



Agilent

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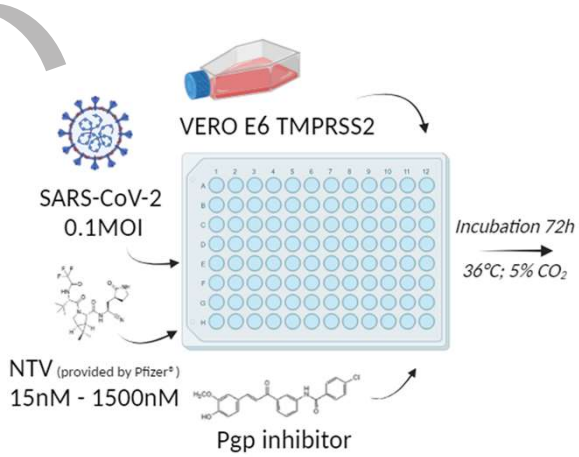

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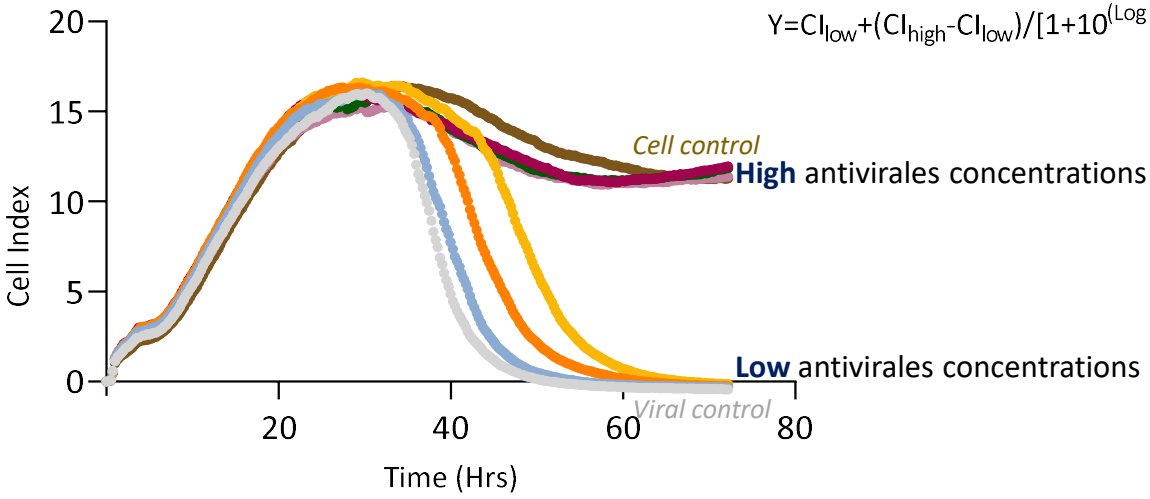
Doses-Responses Curves

$$Y=CI_{low}+(CI_{high}-CI_{low})/[1+10^{(Log\ IC50-X)}]$$



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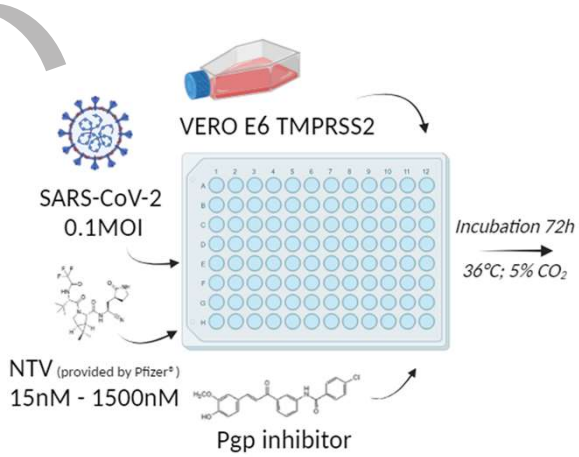

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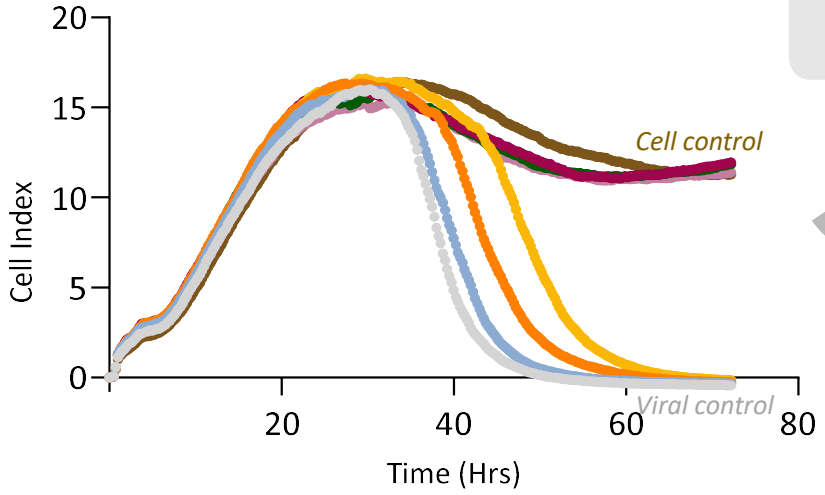
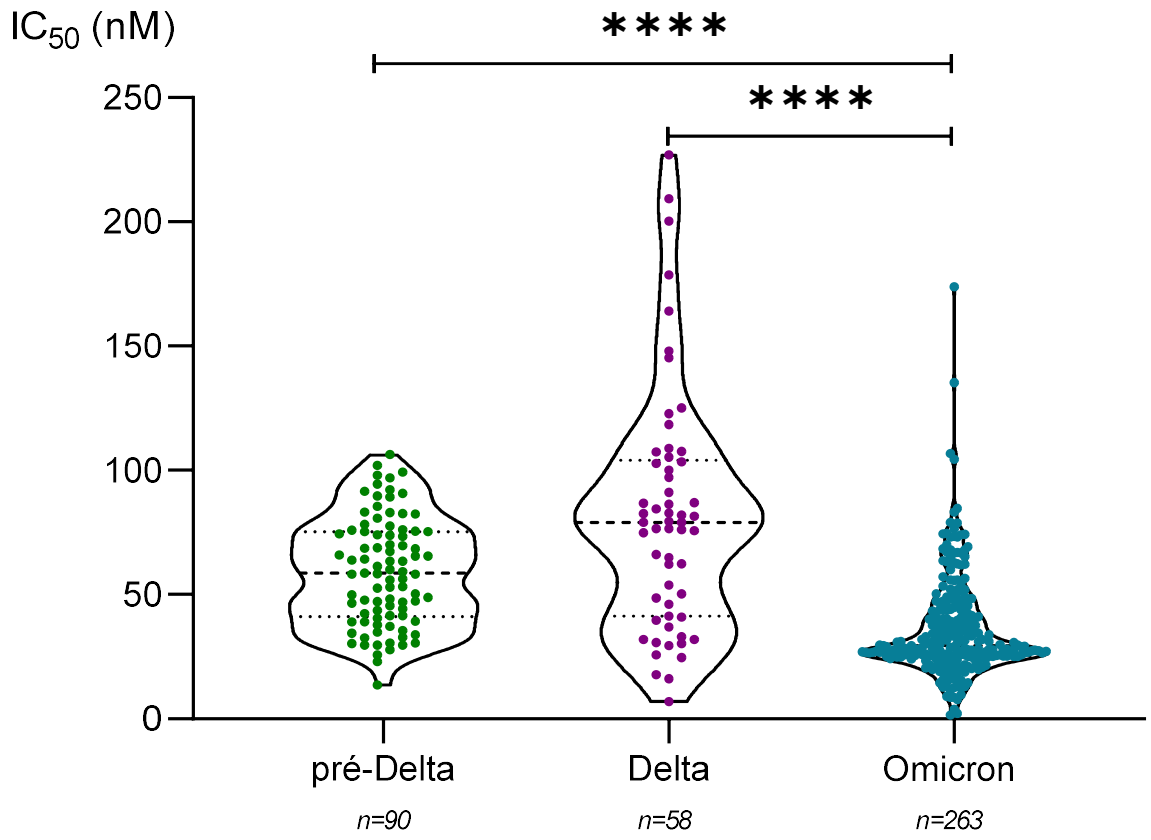


Half maximal inhibitory concentration (IC_{50})

RESULTS

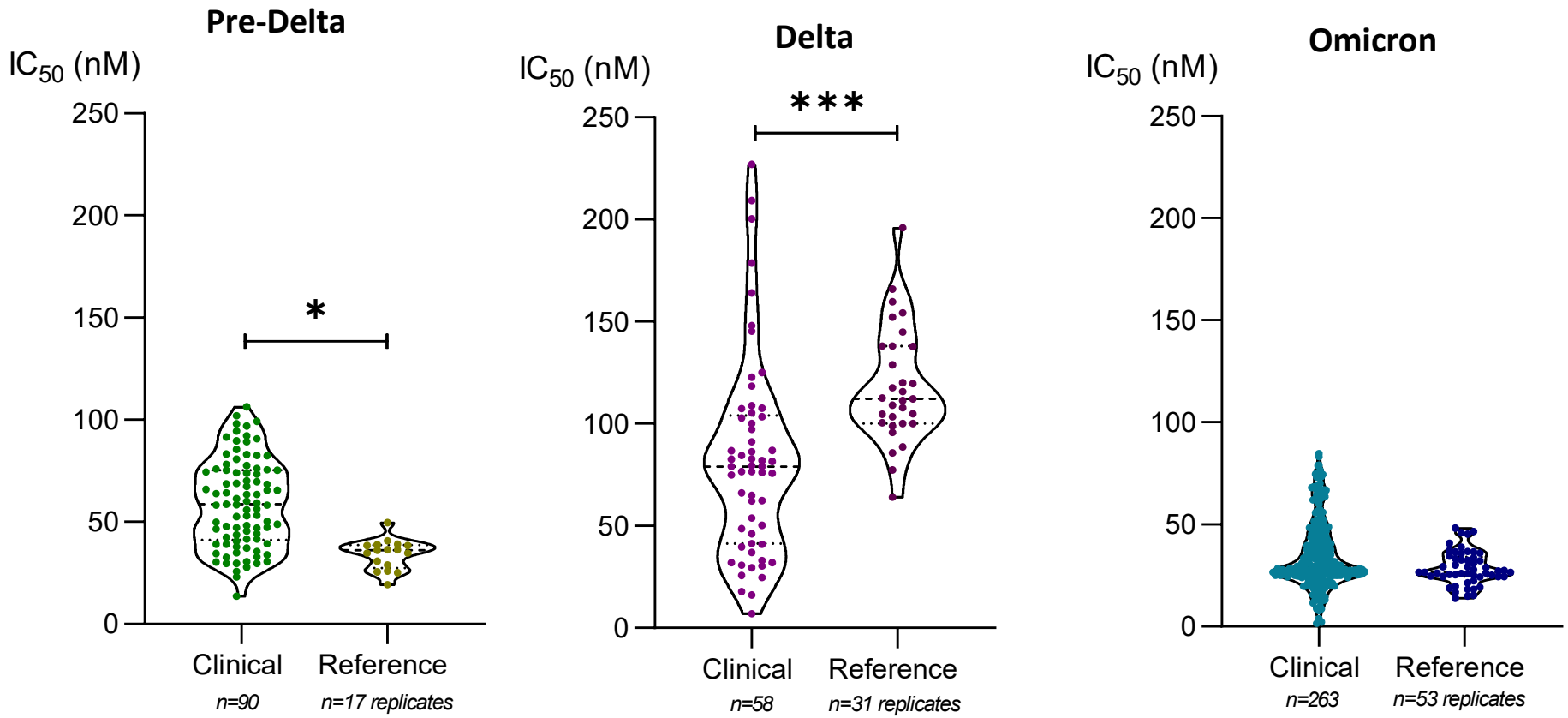
Natural phenotypic susceptibility of SARS-CoV-2 to NTV



More **heterogeneous** IC_{50} for Delta with a higher median.
No significant differences between **pre-delta and delta medians**, **unlike omicron**.

RESULTS

Results compared with a reference strain



Differences between clinical and reference median IC_{50} highlight **clinical variability**

RESULTS

Interpretation thresholds for IC_{50}

- Median clinical strains + 3 to 5* standard deviation clinical strains
- Median reference strain + 3 to 5* standard deviation reference strain
- 2.5* median reference strain (Stanford University)
- 3* median reference strain (WHO)

RESULTATS

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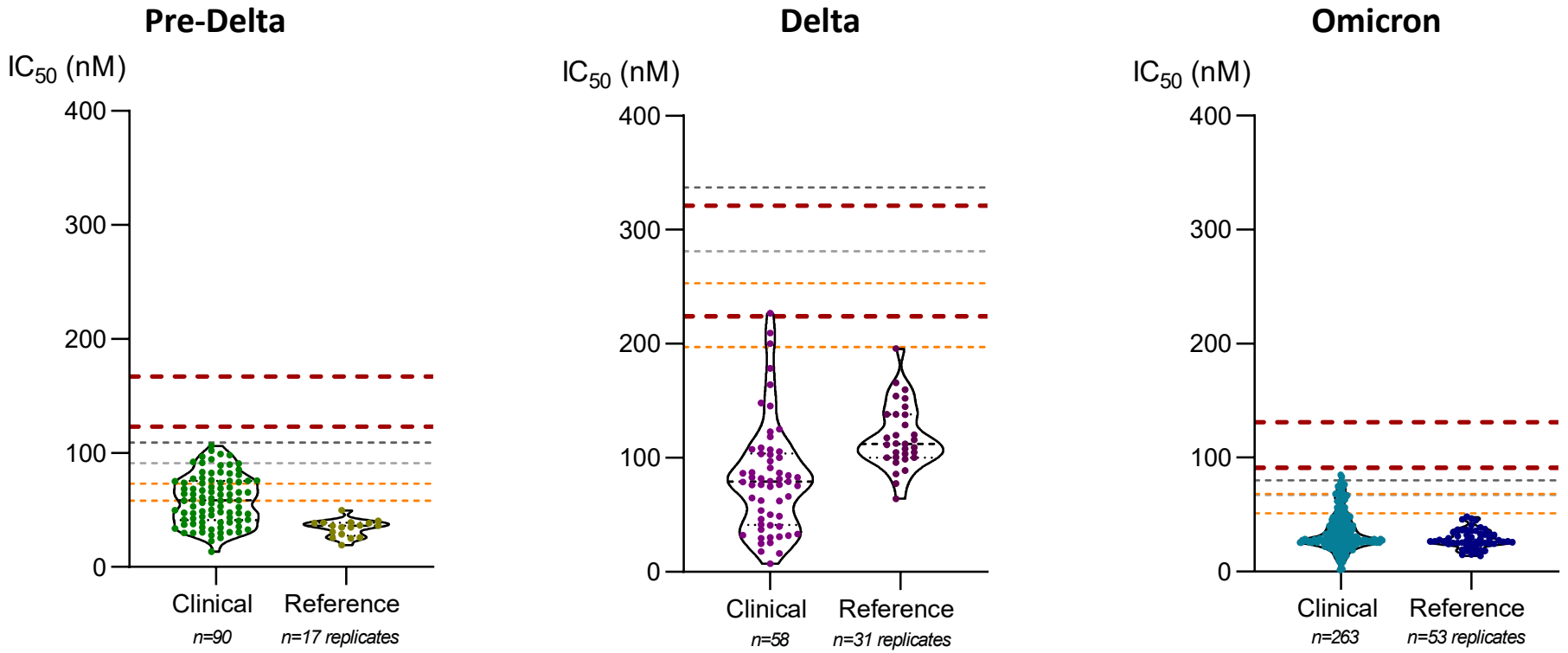
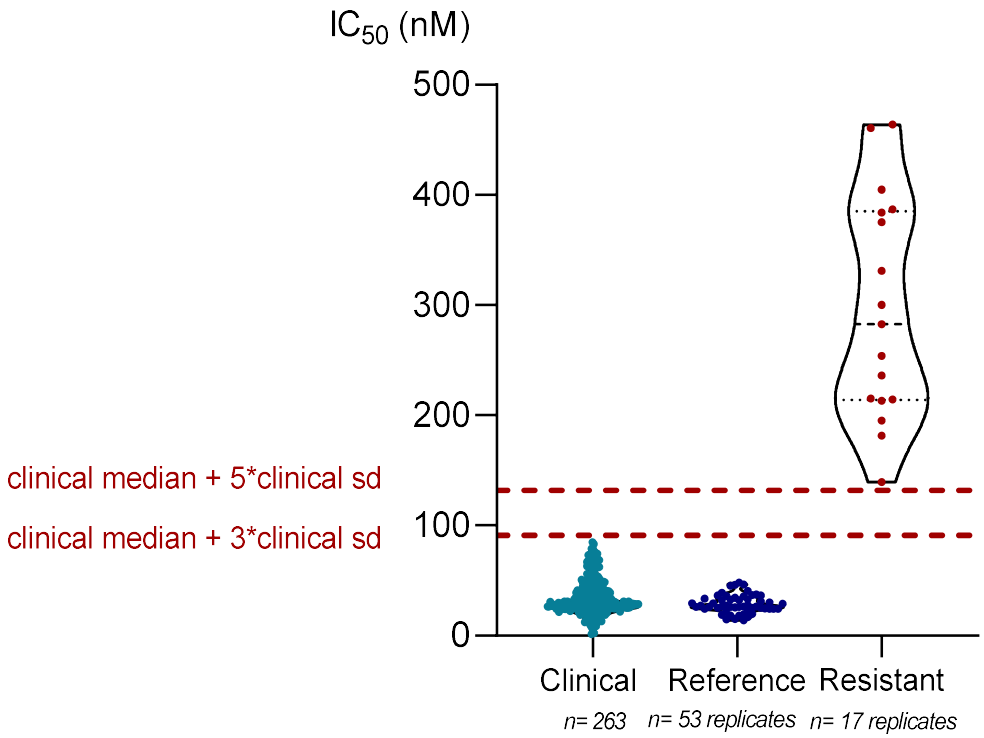


RESULTS

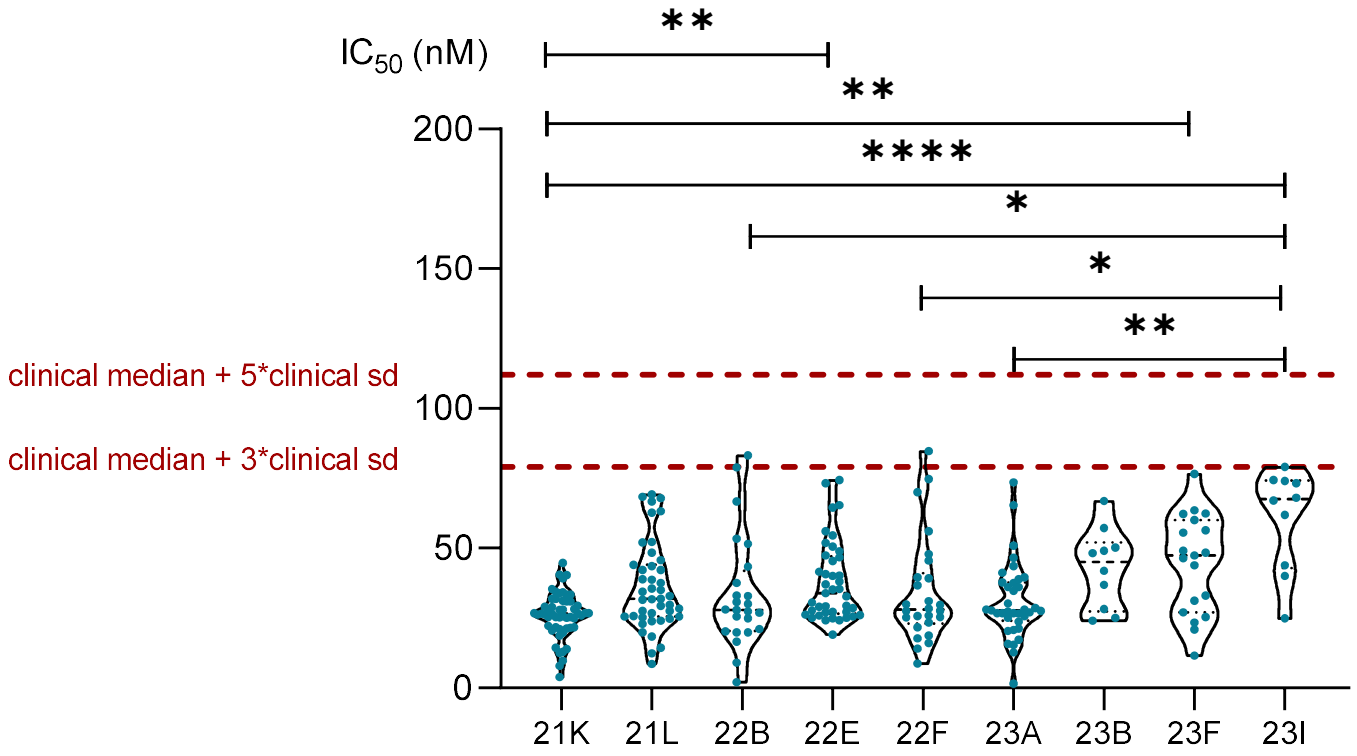
Omicron-resistant strain



Resistant control correctly classified as resistant → validity of **clinical thresholds**

RESULTATS

Phenotypic susceptibility of different Omicron clades to NTV



Higher IC_{50} median of the **most phylogenetically** distant clades

DISCUSSION AND CONCLUSION

- **SARS-CoV-2 remained susceptible to NTV until 2024**, despite increased IC_{50} in recent clades
- **Ongoing monitoring is essential** to track susceptibility evolution
- Our assay enables **rapid detection of NTV resistance mutations** and could help prevent their spread
- Limitations: **resistance thresholds must be standardised**, and **phenotypic data correlated with clinical outcomes**
- Next steps: focused testing in **immunocompromised patients treated with Paxlovid®**
- Clinical failures with Paxlovid remain rare worldwide, but **resistance emergence is still possible**

OPTICOV
Optimizing COVID-19 antiviral therapy

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