



# The concentration dependent antiviral effect of ivermectin in COVID-19

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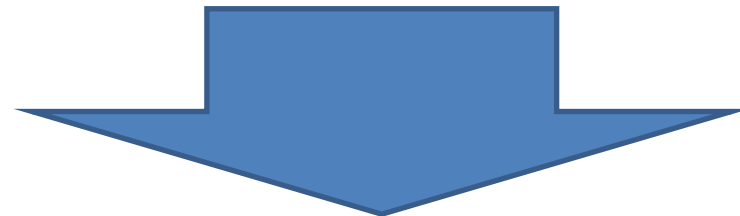
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**IVERMECTIN**  
**AGAINST COVID-19**  
COLLABORATIVE WORKSHOP

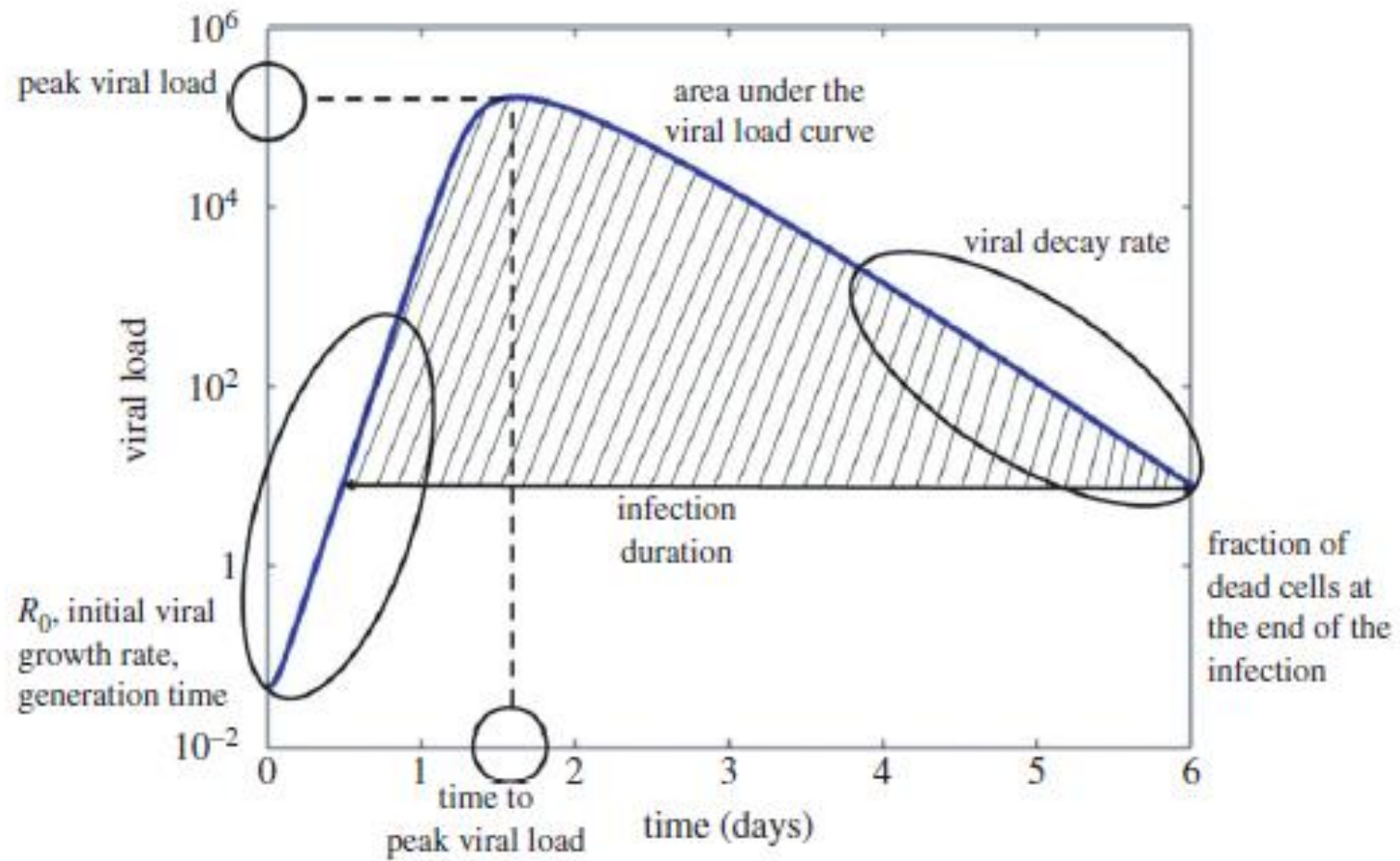
# Challenges in the assessment of antiviral effects in Acute Viral Infections

- Short incubations – rapid onset of symptoms.
- Presentation for care beyond viral load peak.
- Few time-points for viral and clinical measurement before immune control.
- Symptoms scores are poorly reliable.
- Symptoms and complications are often independent of viral peak or presence.



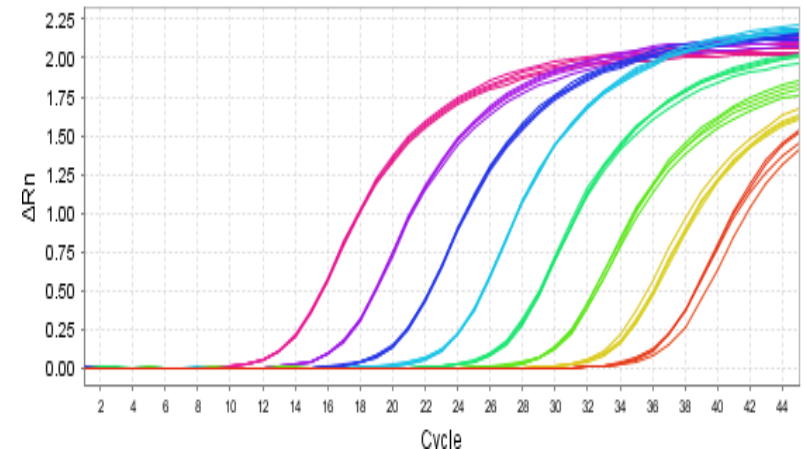
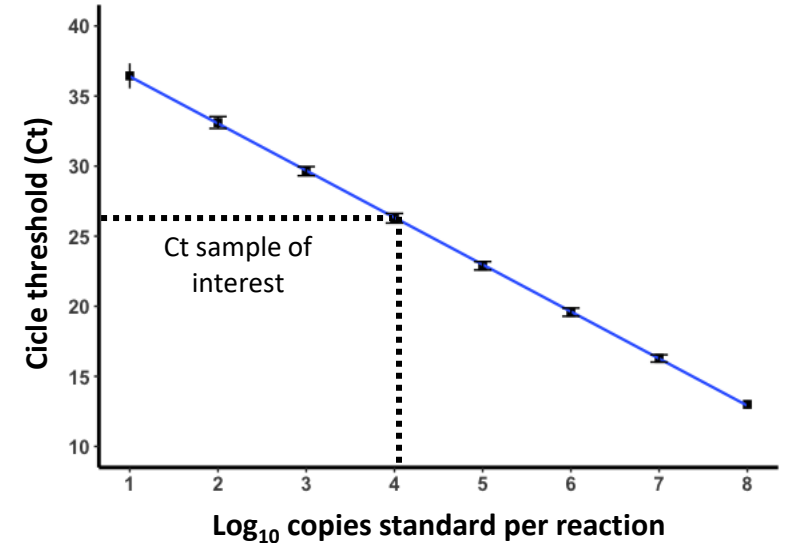
**Early cases**  
**Viral endpoints**  
**Adequate controls**

# Viral Dynamic, *the influenza model*

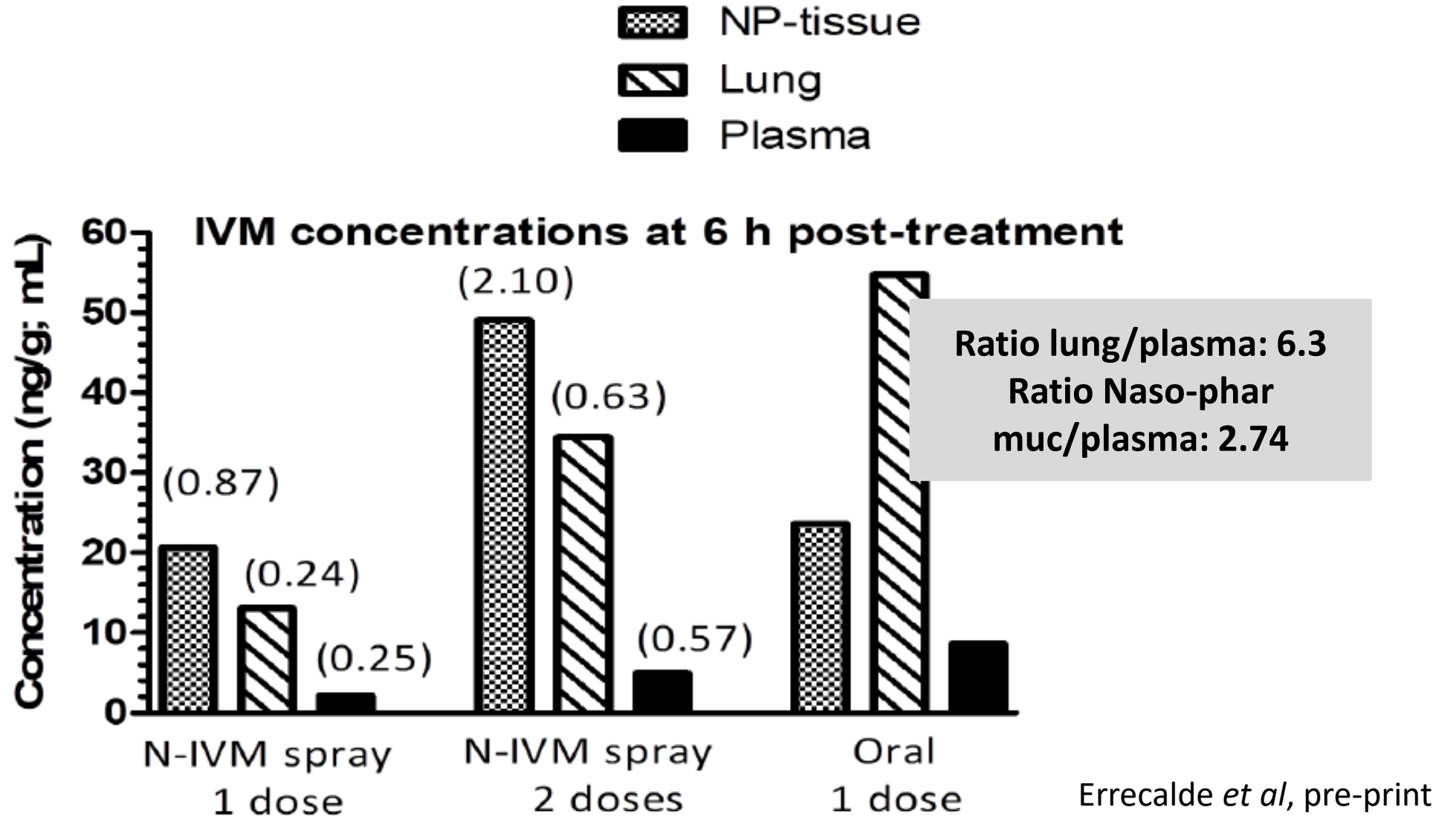


# RT-qPCR for SARS-Cov-2 viral load measurement

- Validated as laboratory-developed test according international guidelines (Burd EM, Clin Microbiol Rev. 2010):
  - Specificity: 100% (panel ADV, RV, PanCov, Flu B, H1N1, H3, MWV)
  - Dinamic range:  $\log_{10}$  1 – 8 copies/reaction
  - Precision: CV 2.35% - 1.04%
  - Efficiency: 99%
- *In-house* SARS-CoV-2 RNA standard
- Human target as normalizer to compensate variability in purification step, ARN integrity and quantity in the sample.

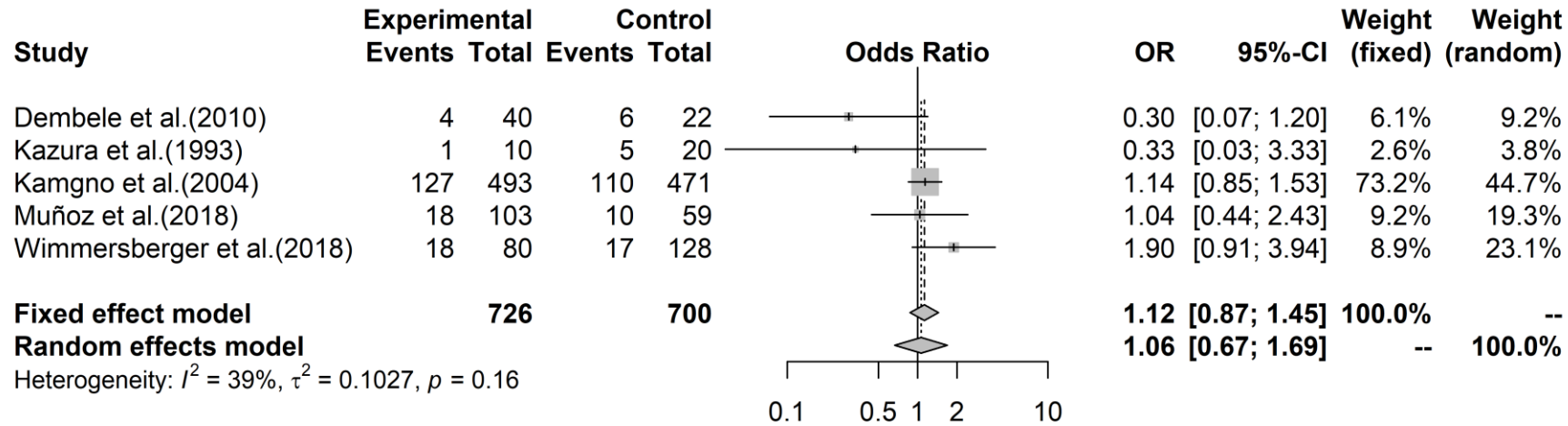


# IVM tissue concentration. *Swine model*



# Safety data on high dose IVM

- Smit M *et al.* 600µg/kg for 3 days in adults with malaria. Clin Pharmacol Ther, 2018
- Krolewiecki *et al.* 600µg/kg for 3 days in children with *T. trichiura*. Ct.gov ID: NCT04041453
- Navarro *et al.* Systematic Review. JAC 2020
- Wimmersberger *et al.* 200, 400 y 600 µg/kg días in children with *T. trichiura*. CID 2018



<b>Study Design</b>	<b>Prospective, open, randomized, controlled</b>
<b>Primary goal</b>	<b>To assess the effect of IVM on the evolution of VL of SARS-CoV-2.</b>
<b>Secondary goals</b>	<b>Symptoms, severity of disease, safety, antibody response, PK/PD inferences.</b>
<b>Sample size</b>	<b>45 subjects.</b> <b>Group A: 30 treated with 600µg/kg x 5 days (6mg tabs)</b> <b>Group B: 15 untreated controls.</b>

# Main entry criteria

## **Inclusion criteria:**

1. Patients of both genders, aged between 18 and 69.
2. Hospitalized patients with symptoms onset 5 days before executing the Informed Consent.
3. No comorbidities affecting the patient 's prognosis, rendering them high risk patients.

## **Exclusion Criteria:**

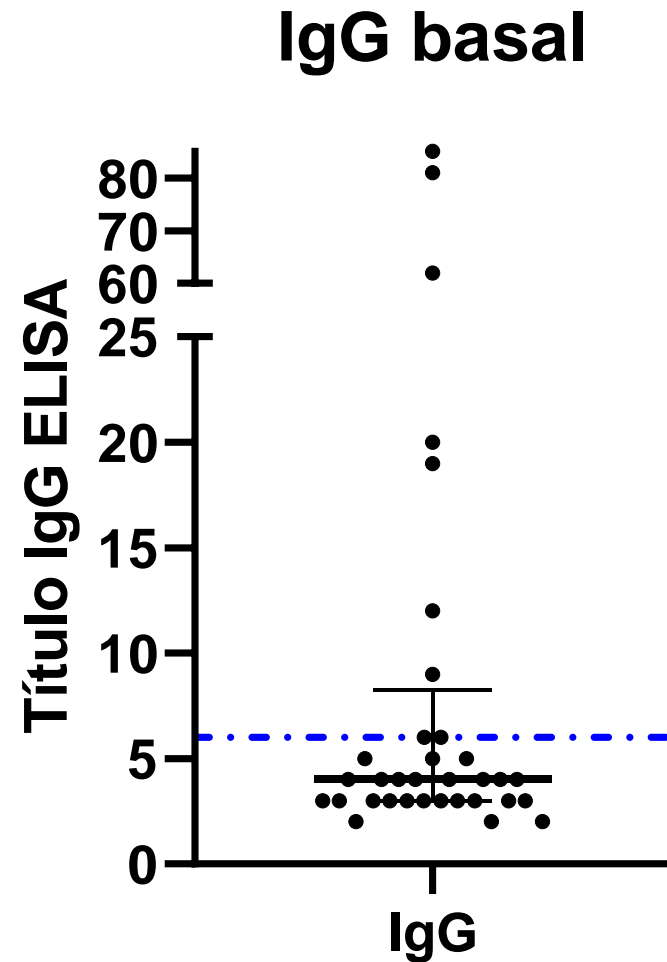
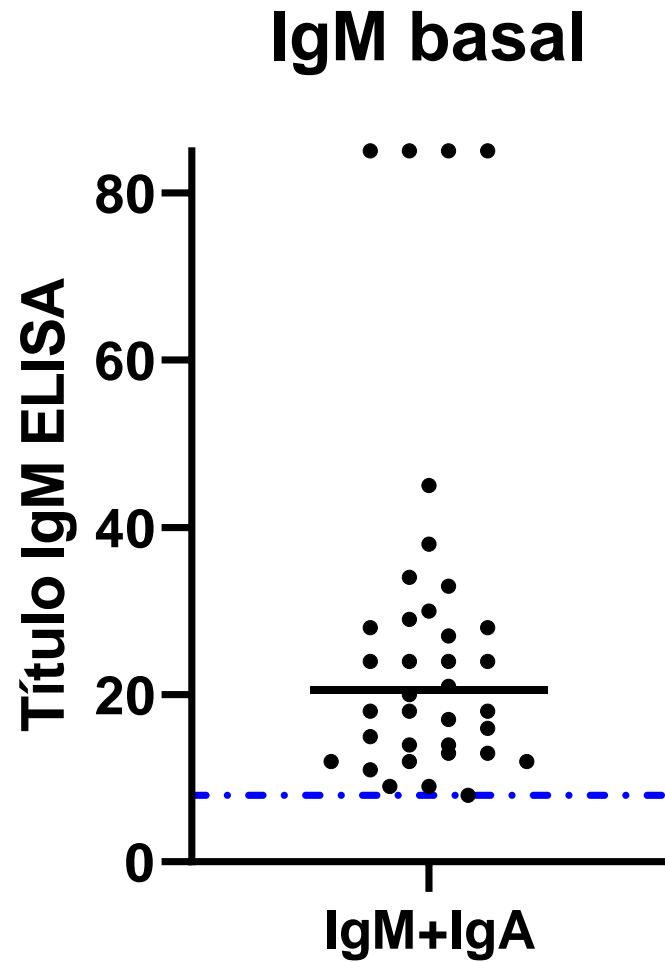
1. Patients meeting COVID-19 severity criteria, with respiratory distress or requiring intensive care.
2. Using medications having potential activity against SARS-CoV-2 such as hydroxychloroquine, chloroquine, lopinavir, ritonavir, remdesivir, azithromycin in the last 3 months.
3. Use of immunodepressants (including systemic corticosteroids) in the last 30 days.
4. Pregnancy or breastfeeding.



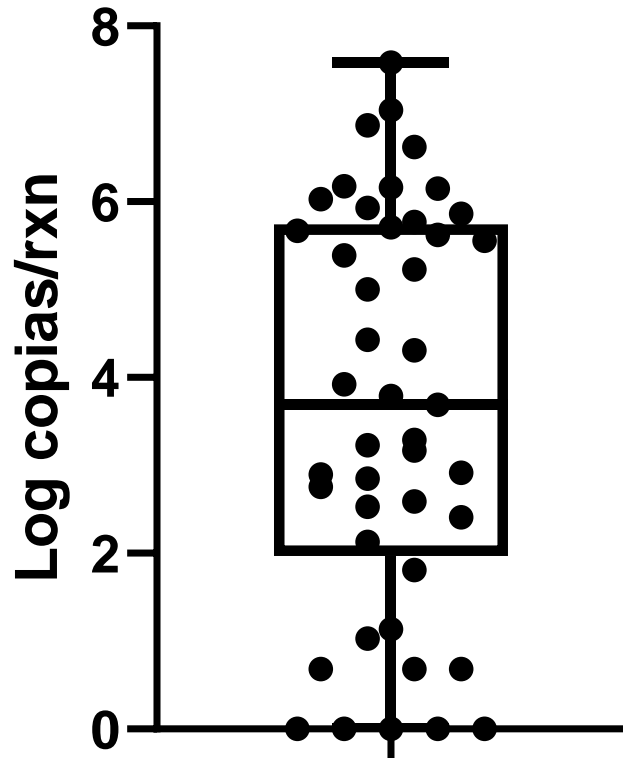
# Baseline characteristics

	Control (n = 15)	Ivermectin (n = 30)
Age (years)	38,1 ± 11,7	42,3 ± 12,8
Sex (f:m) (%)	(33:67)	(50:50)
Days since symptoms onset	3,6 ± 1,4	3,5 ± 1,0
Baseline VL(copies/reaction)	5,39 ± 1,56 (n = 12)	4,18 ± 1,60 (n = 20)
Radiologic pulmonary abnormalities	6 (40%)	14 (47%)
Sat O2<94%	0	1 (3%)
Comorbidities		
Overweight	8 (53%)	6 (20%)
Obesity I	2 (13%)	11 (47%)
Obesity II	1 (7%)	1 (3%)
Obesity III	1 (7%)	1 (3%)
Hypertension	3 (20%)	3 (10%)
Diabetes	1 (7%)	6 (20%)
WHO ordinal scale category 3	13 (87%)	29 (97%)
WHO ordinal scale category 4	2 (13%)	1 (3%)

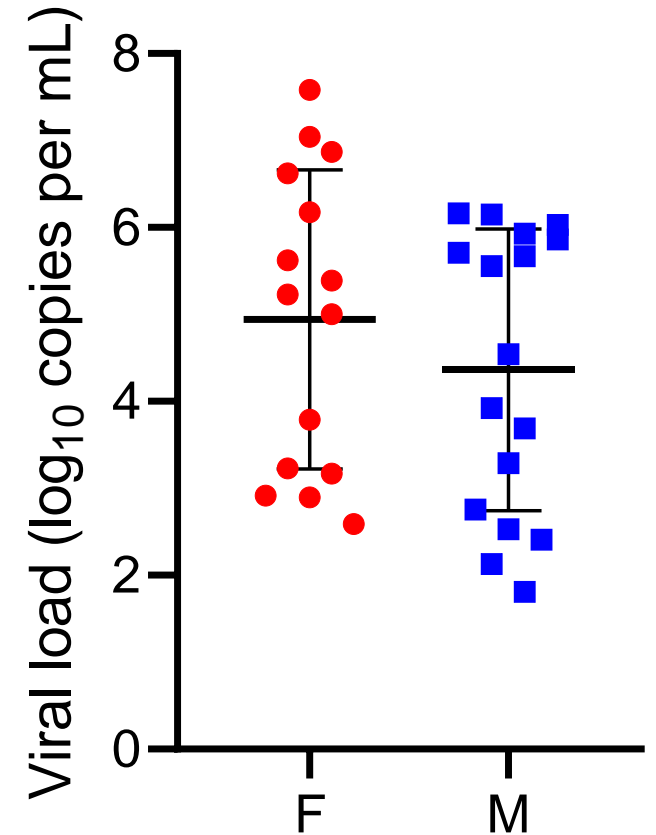
# Antibody responses at baseline



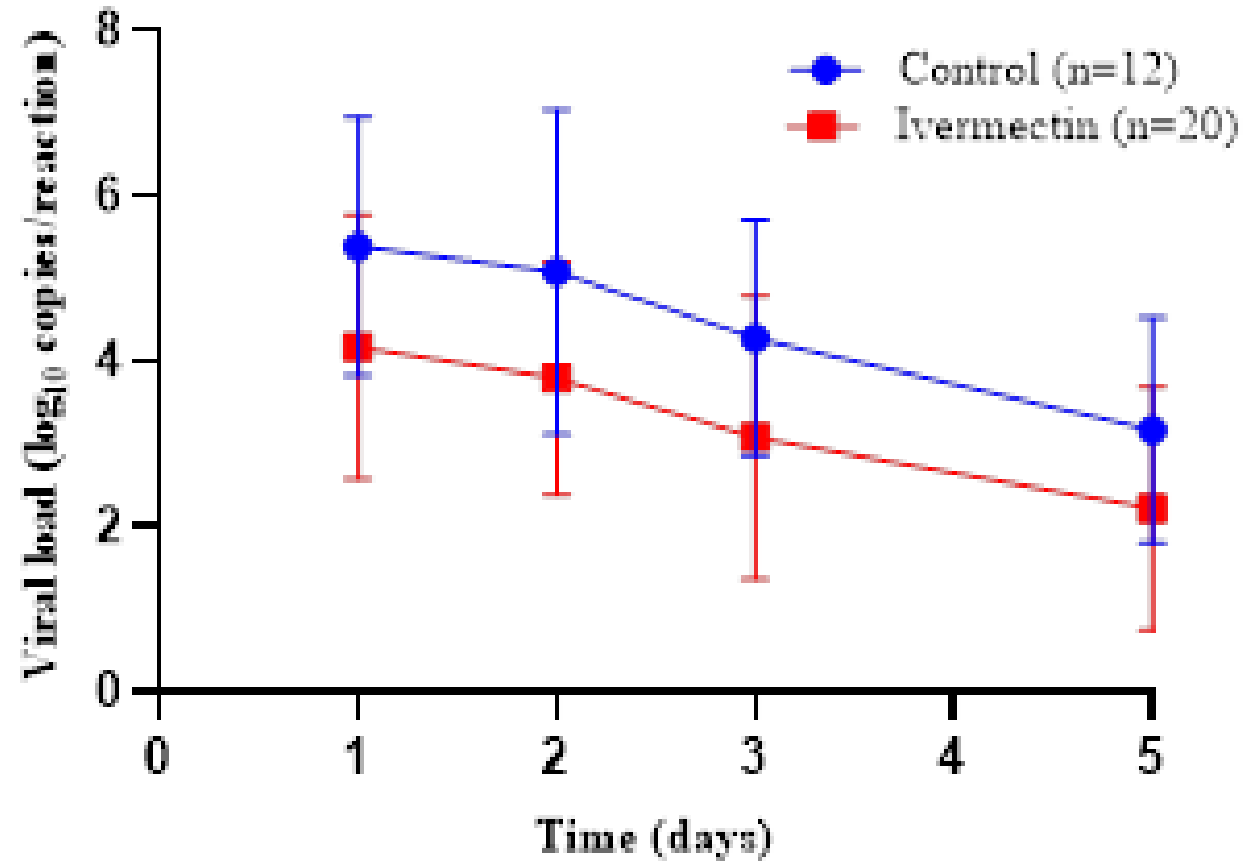
# SARS-CoV-2 viral load at baseline



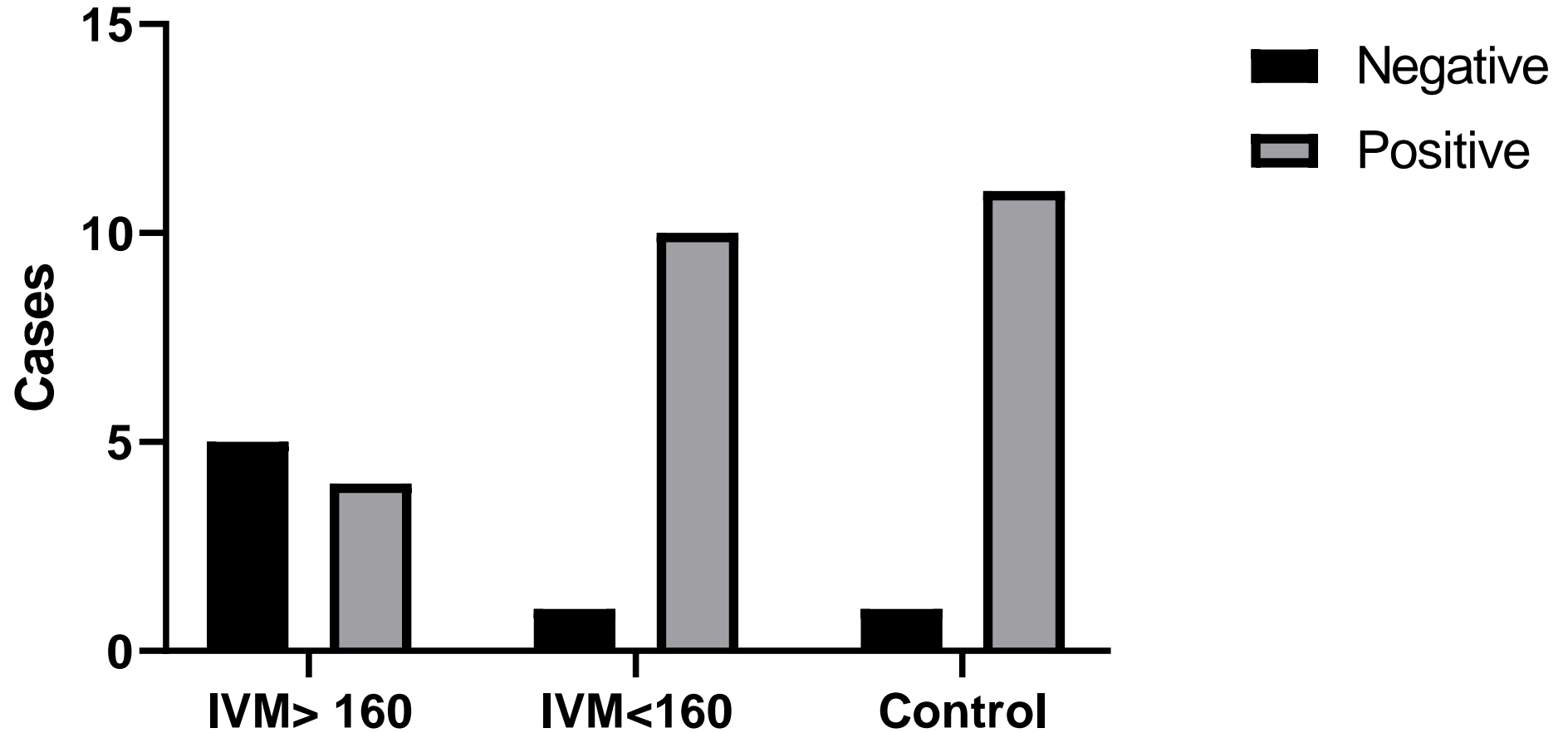
- Large variability.
- 20% of cases with VL <LOQ at baseline.



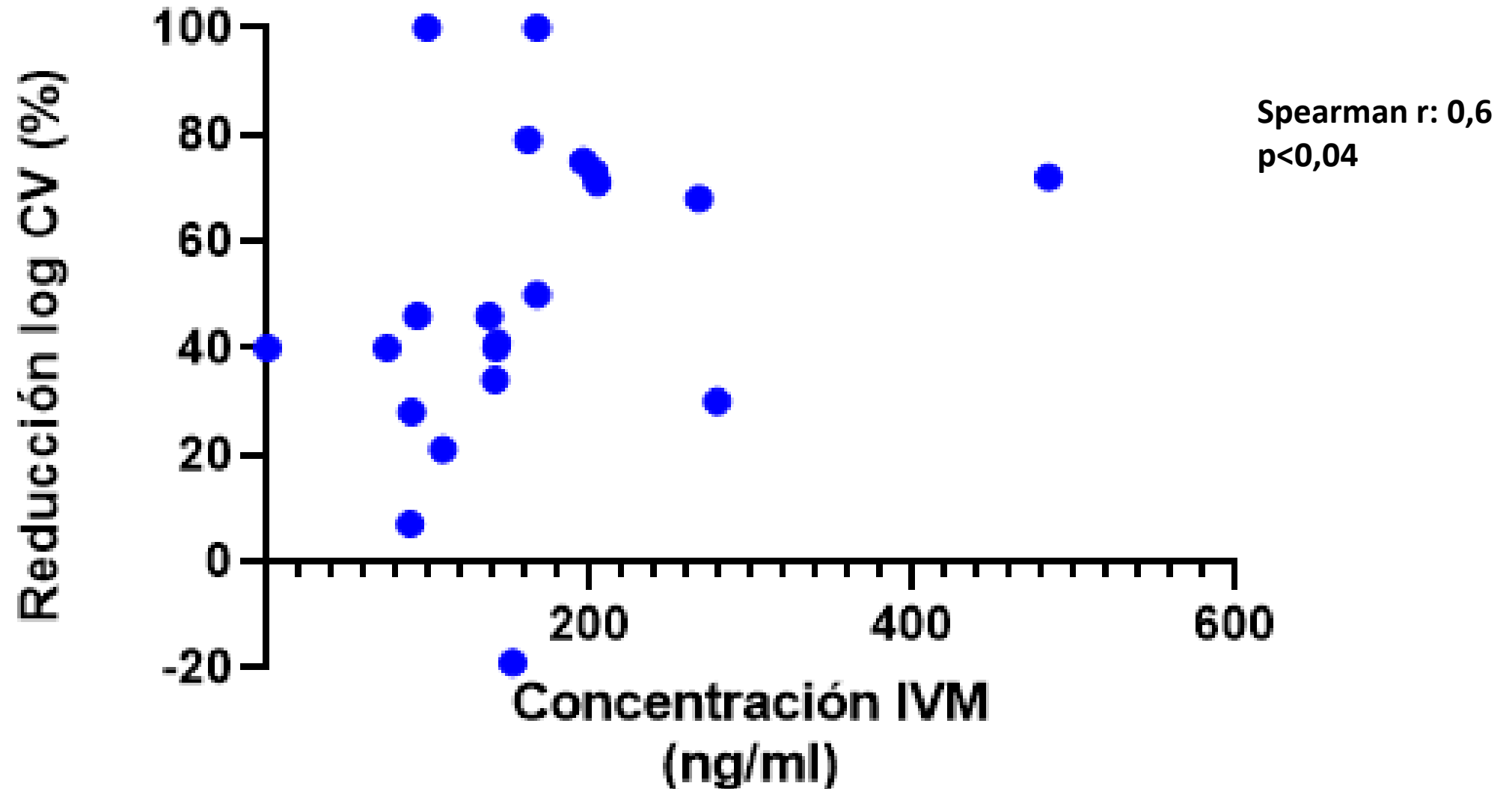
# Results: viral load dynamics



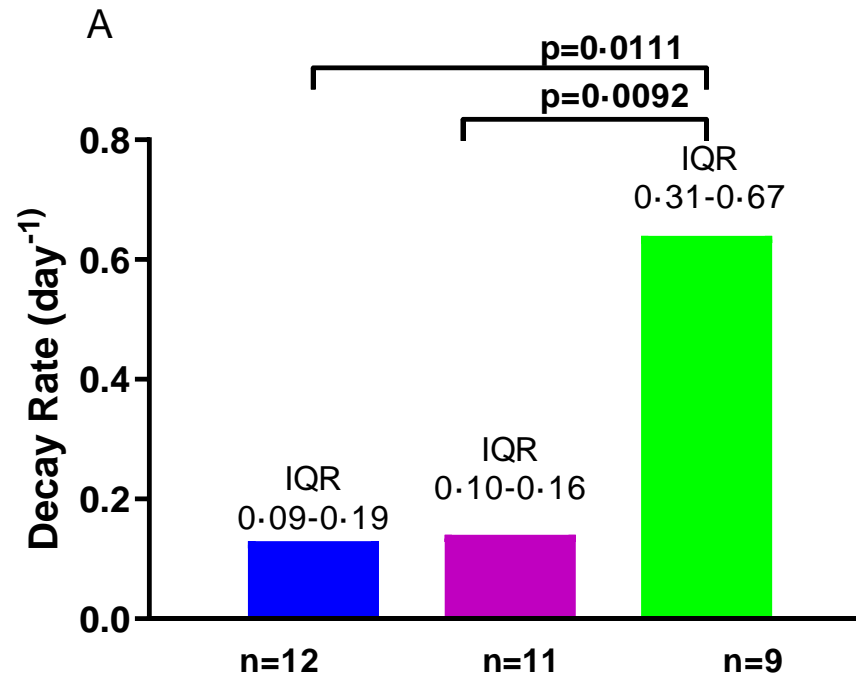
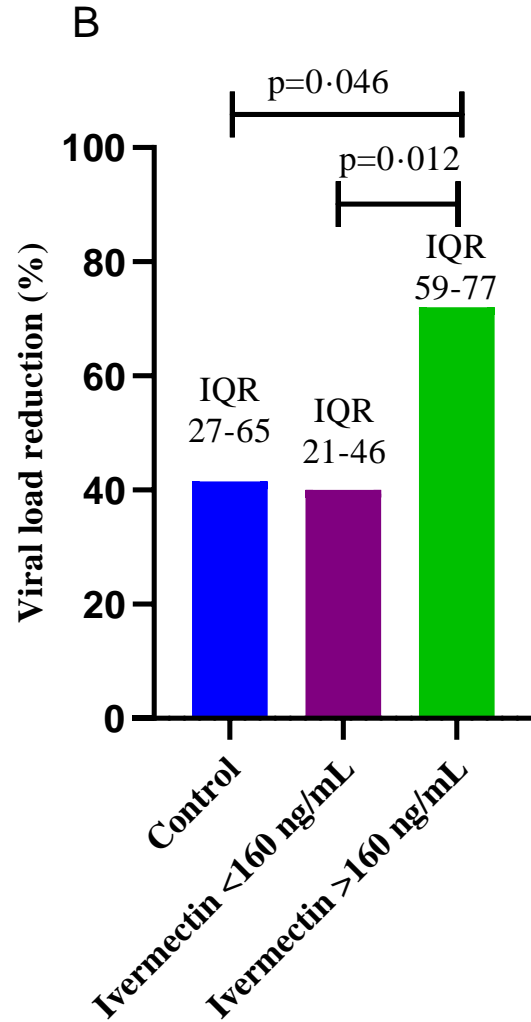
# Qualitative viral load response on day-5



# Results: concentration dependent VL reduction



# Dinámica de CV en subgrupos



# Conclusions

- An antiviral activity of IVM on SARS-CoV-2 was identified.
- The antiviral activity was concentration dependent.
- Aproximadamente la mitad de la población alcanzó niveles adecuados de droga en sangre para una actividad antivira  
Approximately half of the treated population achieved adequate IVM concentrations.
- IVM was well tolerated.
- The findings have potential clinical and epidemiologic implications.
- This trial was designed to test antiviral activity but not clinical endpoints.



# Acknowledgements

## Universidad de Salta

Ruben Cimino, Pedro Fleitas, Liz Nallim, Victor Claros

## CIVETAN-Tandil

Carlos Lanusse, Adrian Lifschitz, Nacho Alvarez  
Laura Ceballos

## Hosp Garrahan

Andrea Mangano, Matias Moragas

## CEMIC

Ricardo Valentini, Pablo Bonvehi

## ELEA – Phoenix

Eduardo Spitzer, Marcelo Tinelli, Marcelo Guthmann

## Universidad Nacional de La Plata

Jorge Errecalde

## Universidad Nacional de Quilmes

Daniel Lopez, Hernan Farina, Georgina Cardama

## Hospital Muñiz

Ruben Solari, Germán Astudillo

## Fundación Mundo Sano

Silvia Gold, Graciela Ciccía , Ignacio Demarco, Alicia Bagnoli

**This Project has grant support from Agencia Nacional de Ciencia y Técnica, MINCyT, Argentina and ELEA/Phoenix Argentina**

Thanks

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