Viral dynamics of SARS-CoV2 and role of antiviral treatments

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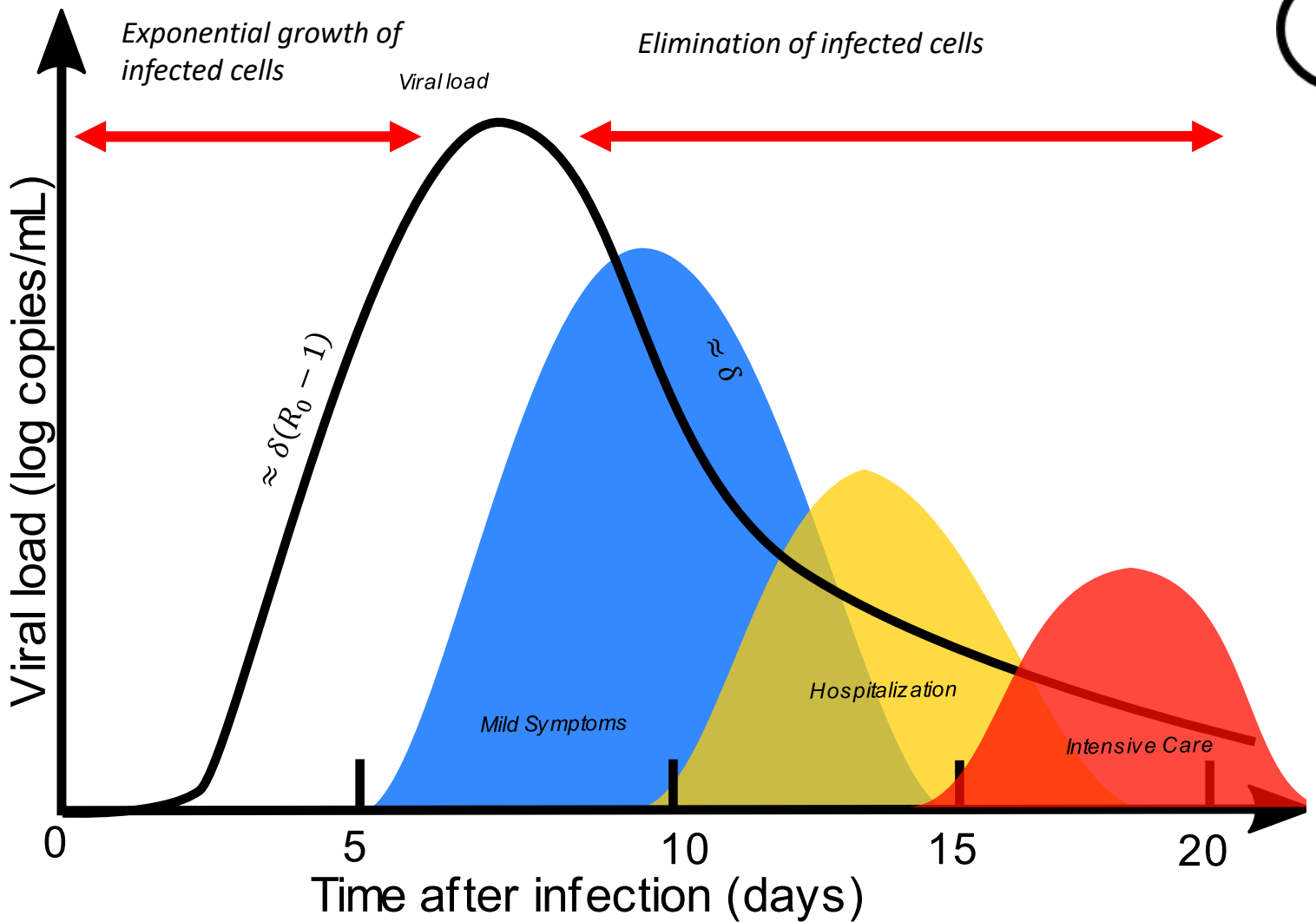
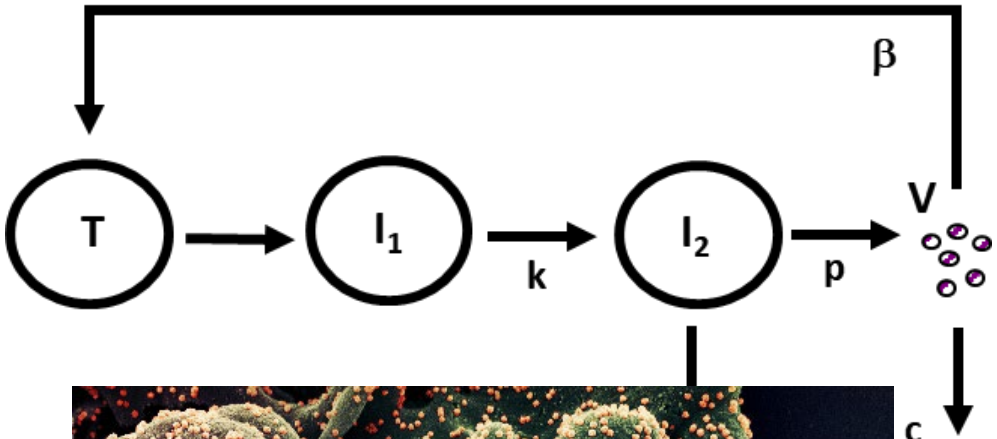
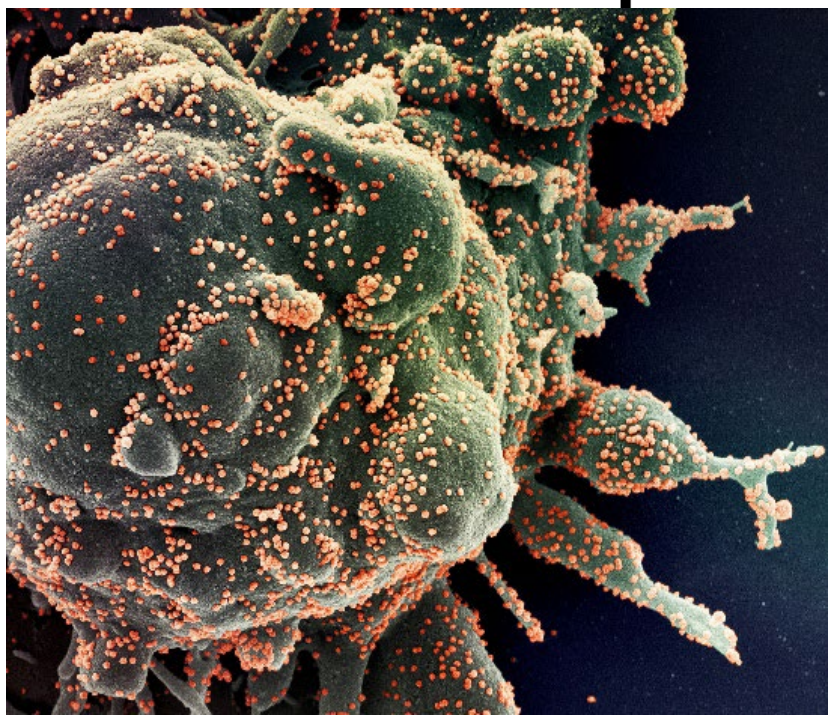
Viral dynamics during acute infection

Peak viral load ≈ Target cell exhaustion

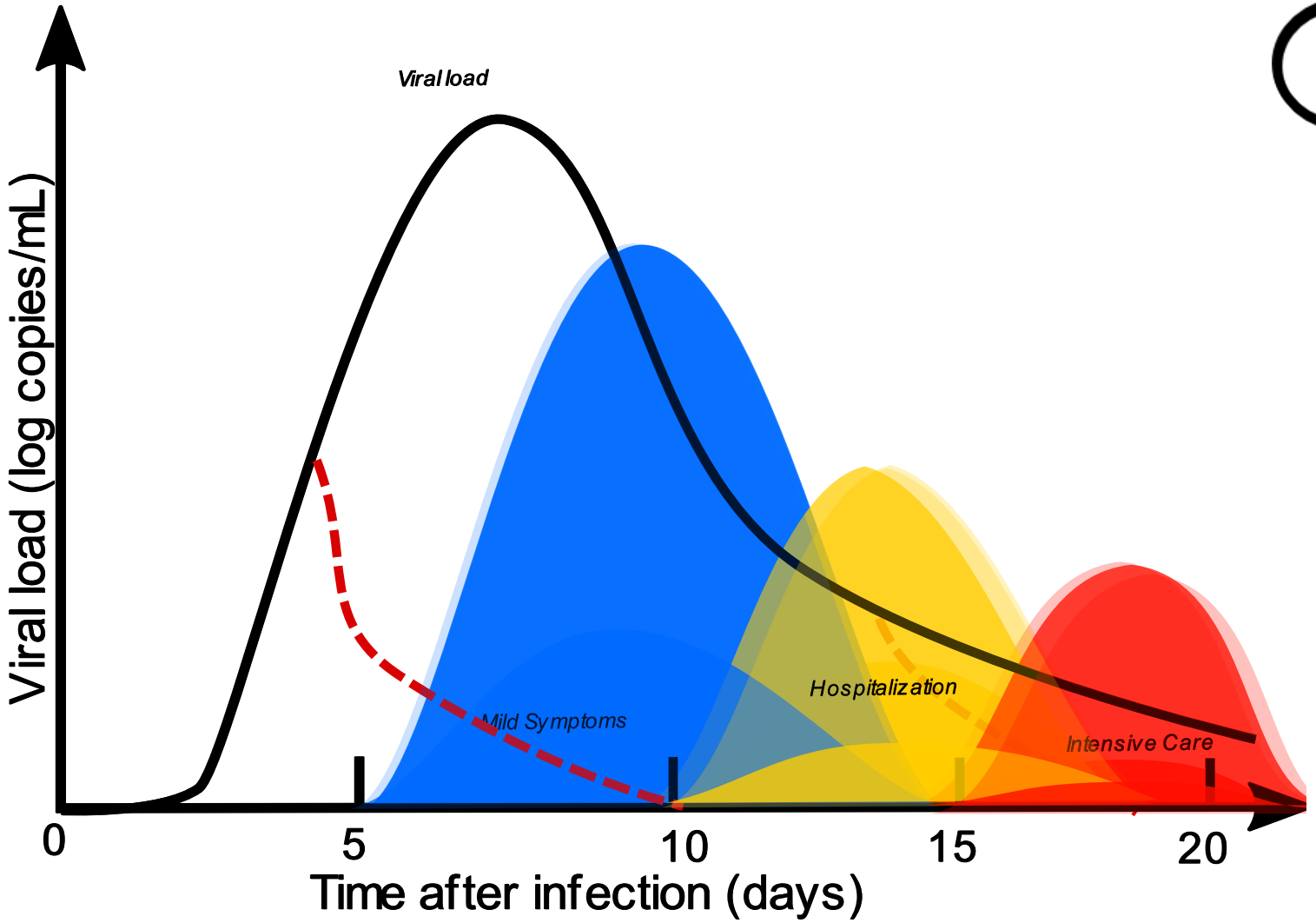


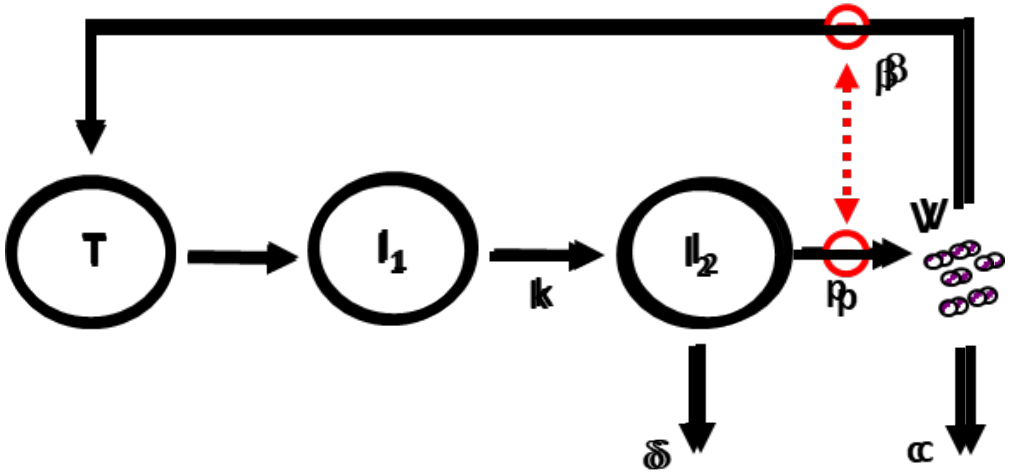




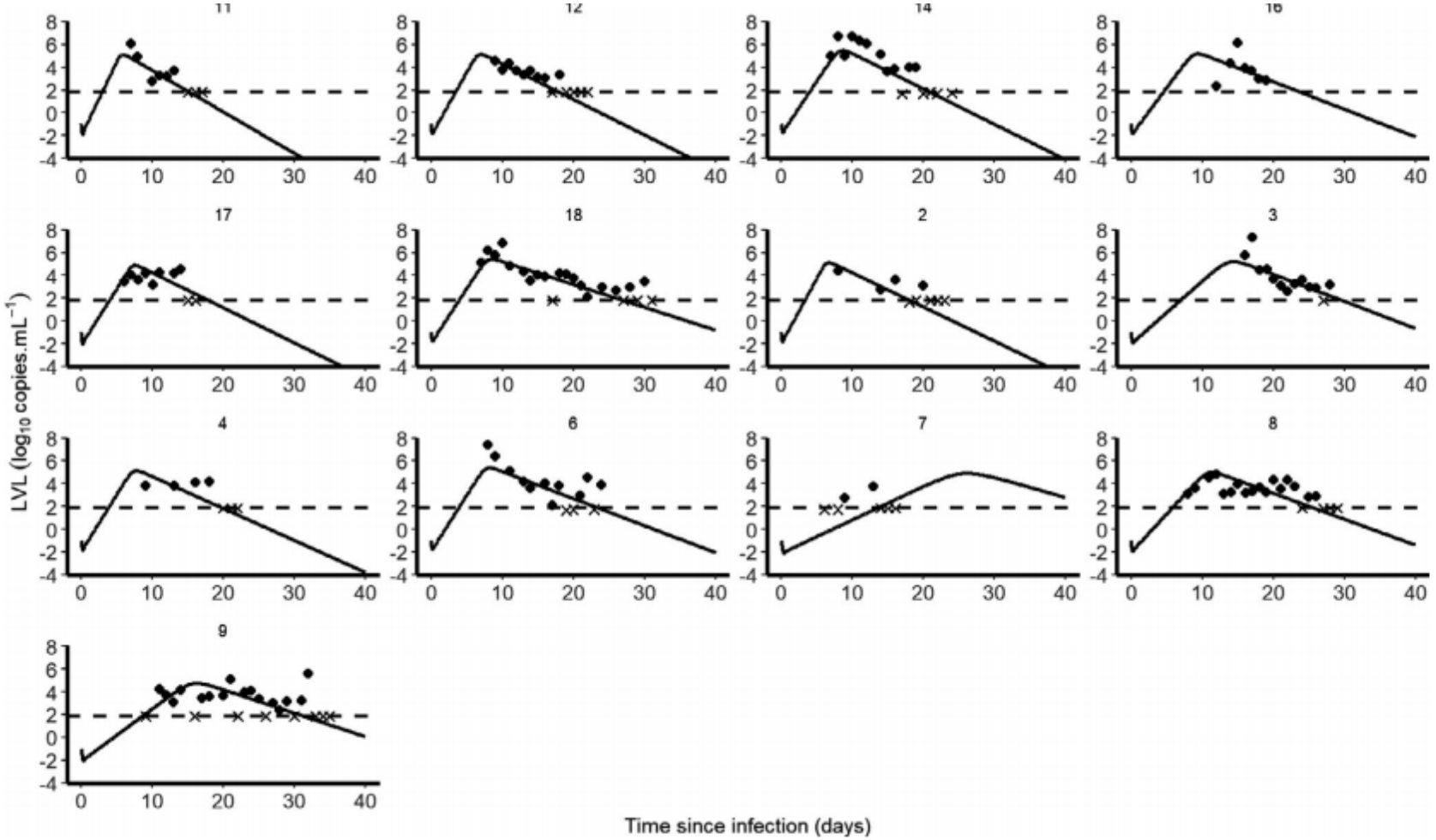
Credit: NIAID **Bonhoeffer et al, PNAS (1996)**

Timing of antiviral treatment is key to avoid disease progression





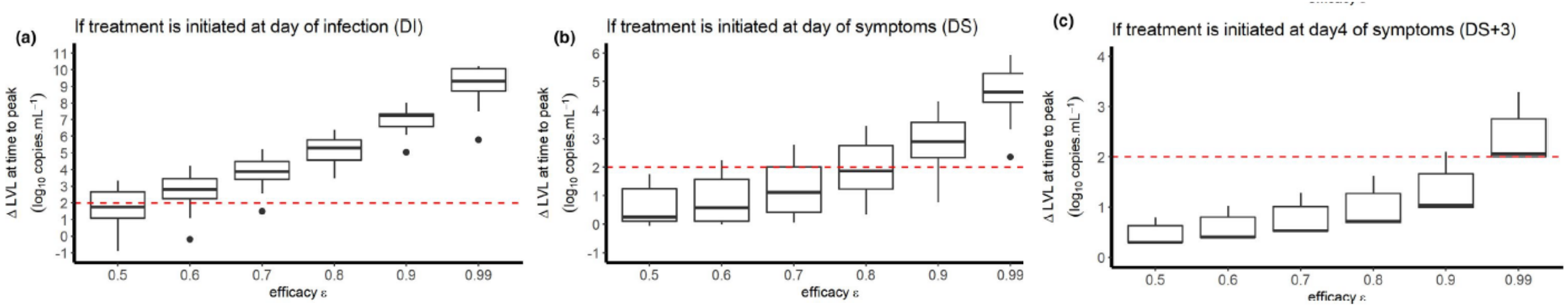
SARS-CoV-2 viral dynamics in mild patients

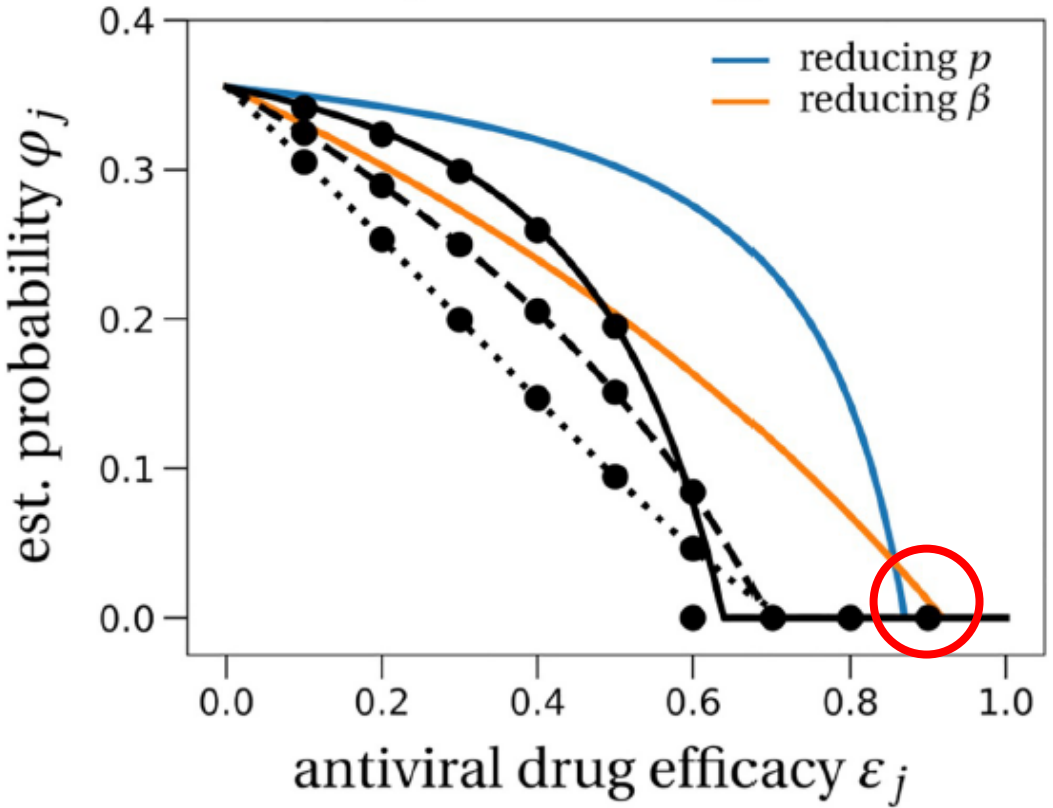


$R_0 \sim 10$ in mild infections

Young et al, JAMA 2020 ; Gonçalves et al, CPT:PSP (2020)

Timing is (almost) everything





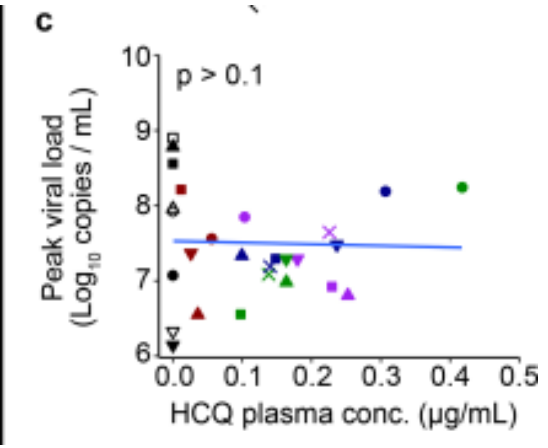
$$\varepsilon_c = 1 - \frac{1}{R_0} = 90\%$$

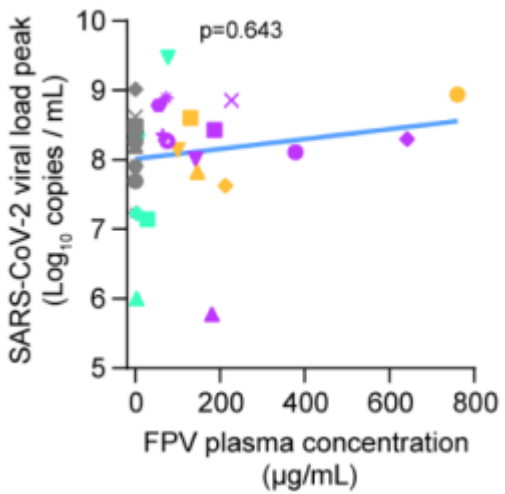
Gonçalves al, CPT:PSP (2020);
Czuppon et al., PLoS Comp Biol (2021)

Effects of repurposed drugs in experimental infection models

Drug	PK parameter	EC_{50}	Dosing regimen D0–D7	$\bar{\varepsilon} = \frac{1}{N} \times \frac{1}{7} \times \int_0^7 \frac{C(u)}{C(u)+EC_{50}} du$
Lopinavir/ritonavir	Wang *et al.*[13]	5.2 μM (unpublished)	400/100 b.i.d.	66%
Hydroxychloroquine	Morita *et al.*[14]	4.2 μM[27]	400 mg b.i.d. at D0, followed by 400 mg q.d.	6%
IFN-β-1a	Hu *et al.*[15]	175 IU/mL[29]	12 MIU at D0, D2, D5	18%
Remdesivir	EMEA guidelines[16]	1 μM[17]	200 mg q.d. at D0, followed by 100 mg q.d.	87%

- None is likely to have major effect if given after peak viral load
- Even worse in Non-Human Primate model of experimental infection !





Article

Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates

Article https://doi.org/10.1038/s41467-022-32565-w

Antiviral efficacy of favipiravir against Zika and SARS-CoV-2 viruses in non-human primates

More details on preclinical models : Maisonnasse et al, Nature (2020) ; Eloy et al, CPT (2020) ; Driouich et al, Nature Comm (2021); Marlin et al, Nature Communications (2022)

Can we use viral dynamics to optimize the use of antiviral drugs ?

- Viral kinetics in hospitalized non-treated patients
- Antiviral efficacy of remdesivir in hospitalized patients
- What can we expect from monoclonal antibodies ?

Data used in this presentation (<2021)

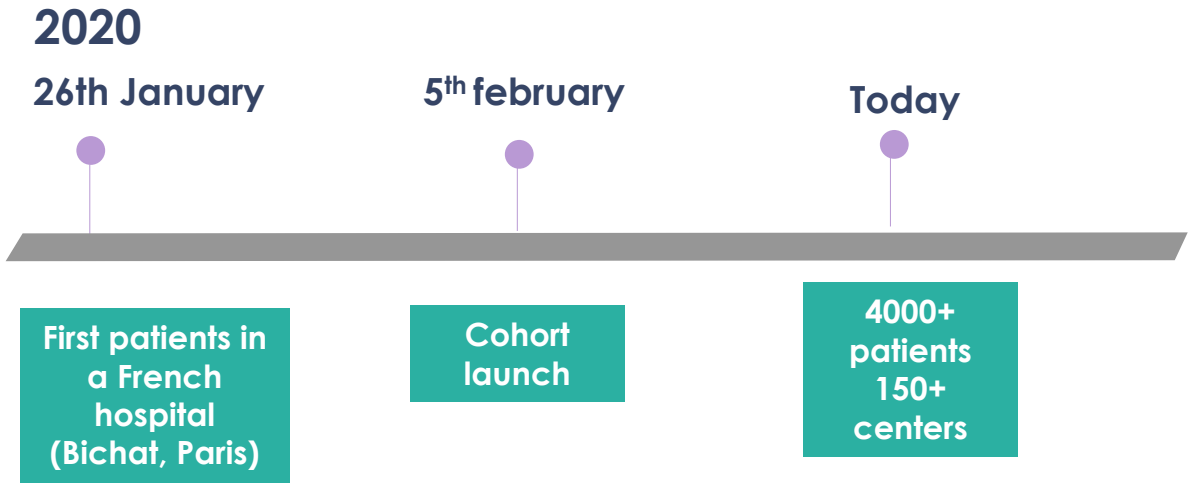
Study	Patients	Intervention & Design	Objectives
French Covid cohort	665 untreated patients hospitalized between February and April 2020	No antiviral	Build a model of viral dynamics in hospitalized patients and explore the the link with mortality
Discovery clinical trial	655 hospitalized patients between February 2020 and January 2021	Randomized to remdesivir or placebo	Estimate remdesivir antiviral efficacy
Regeneron phase 2/3 clinical trials	4,500 outpatients between September 2020 and January 2021	Randomized to REGN-CoV-2 or placebo	Estimate REGN-CoV-2 antiviral efficacy and association with risk of hospitalization

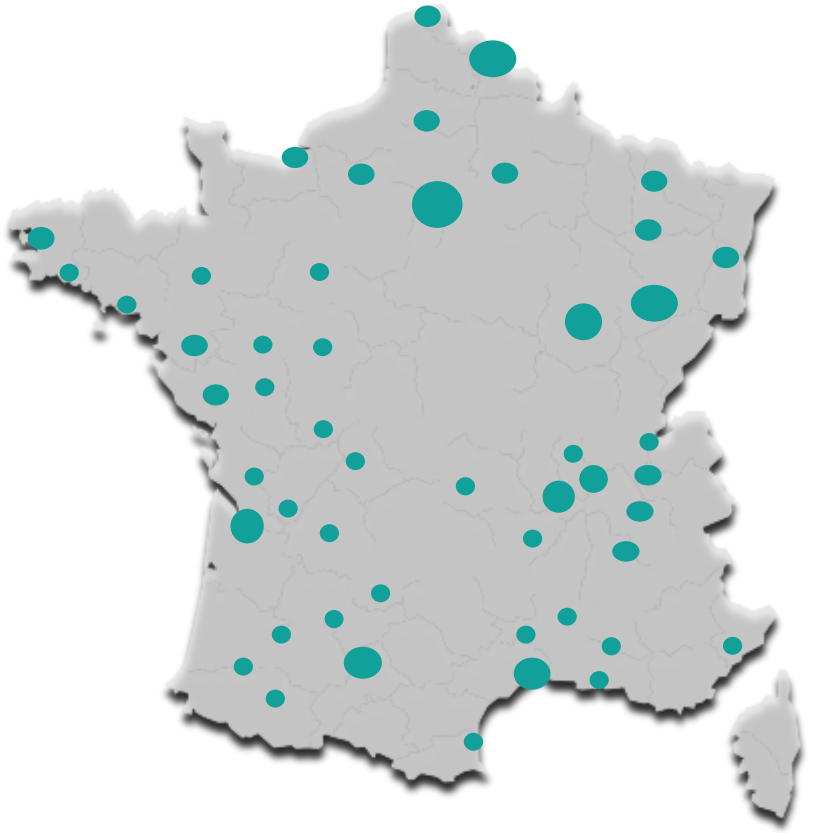
Can we use viral dynamics to better understand the role of treatment

- **Viral kinetics in hospitalized non-treated patients**
- **Antiviral efficacy of remdesivir in hospitalized patients**
- **Antiviral efficacy of monoclonal antibodies in outpatients**

French Covid Cohort

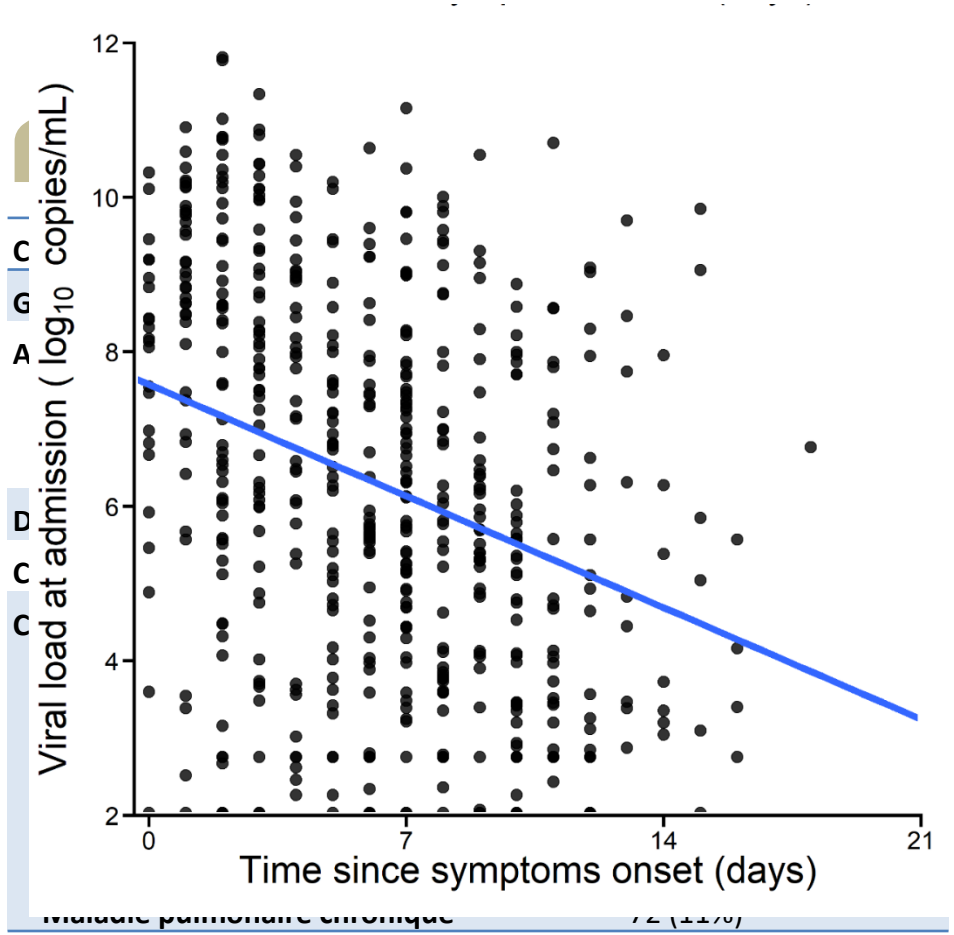
National prospective cohort (NCT04262921, PI: Jade Ghosn)

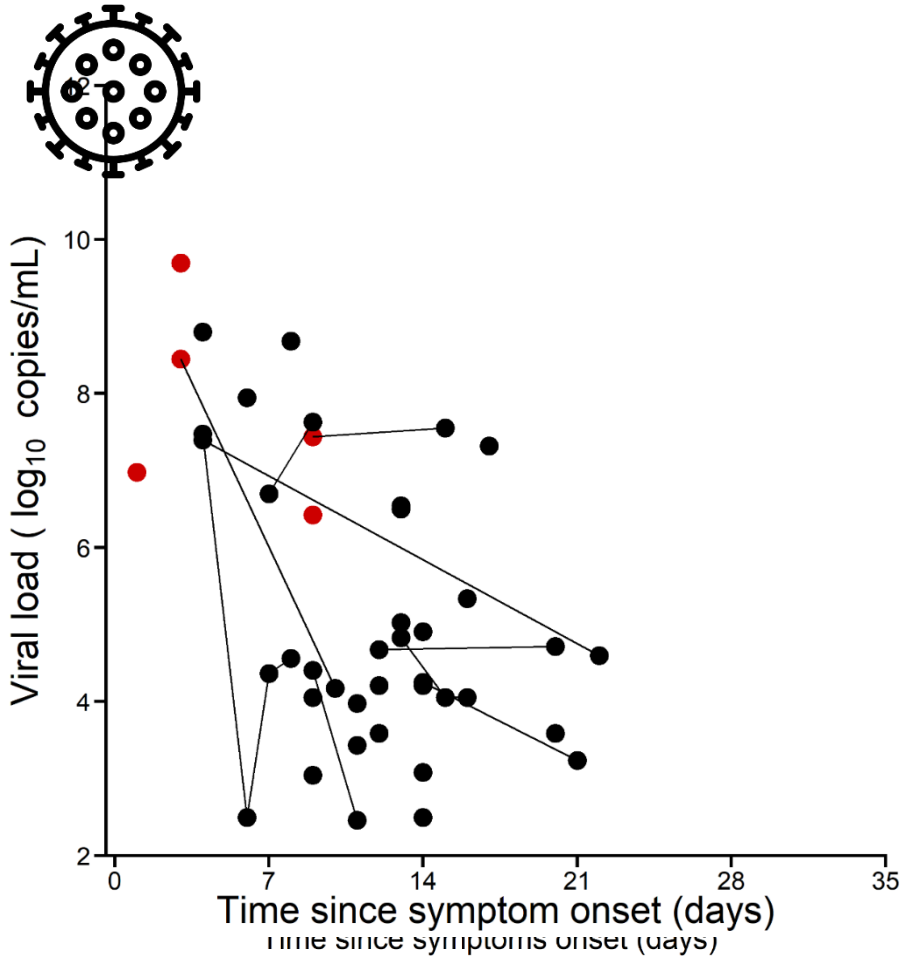




Data collected during hospitalization, up until 18 months after hospital discharge

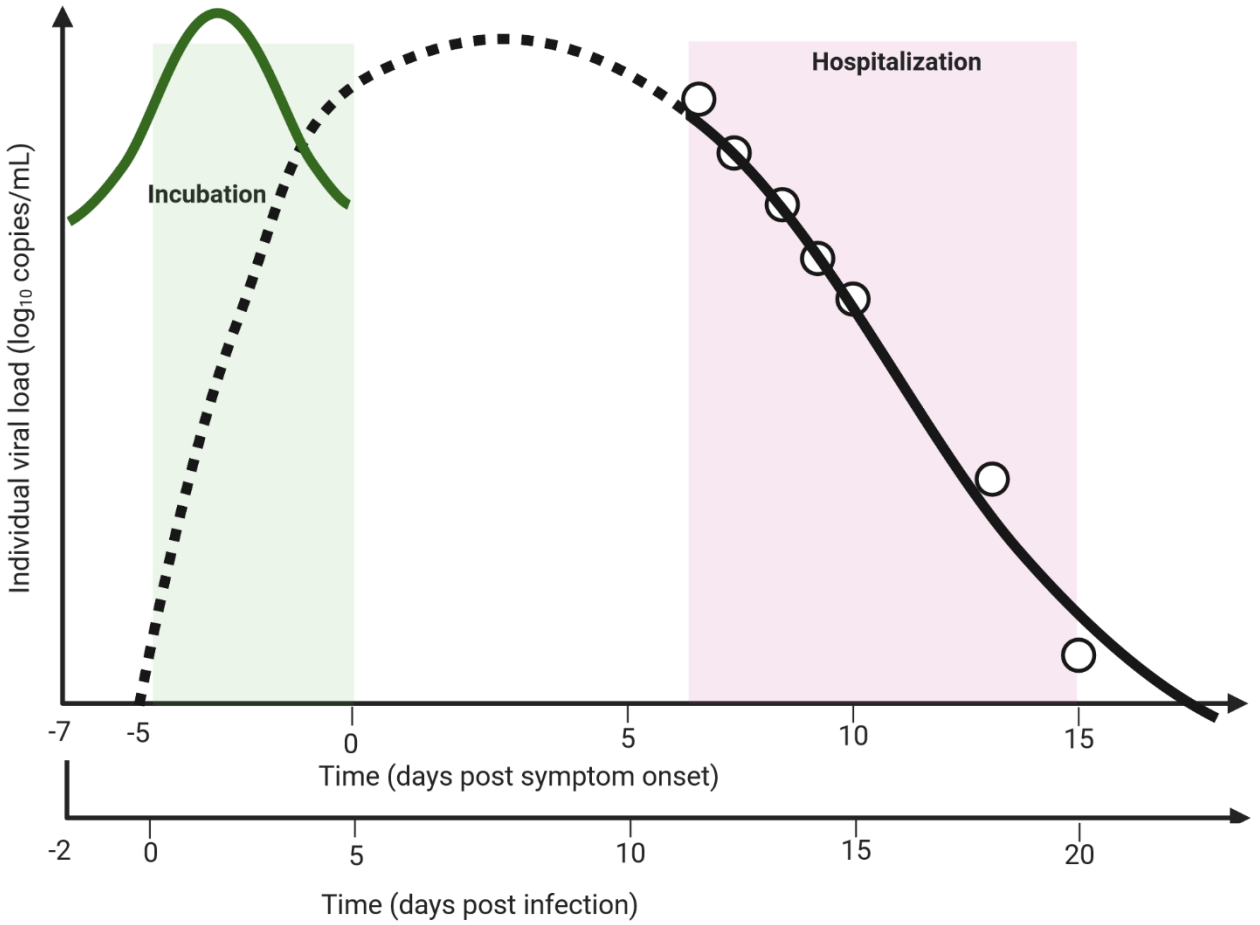
Data


Viral load at admission (log10 copies/mL)
12
10
8
6
4
2
0
7
14
21
Time since symptoms onset (days)


Viral load (log10 copies/mL)
10
8
6
4
2
0
7
14
21
28
35
Time since symptom onset (days)

VIRAL DYNAMIC MODEL

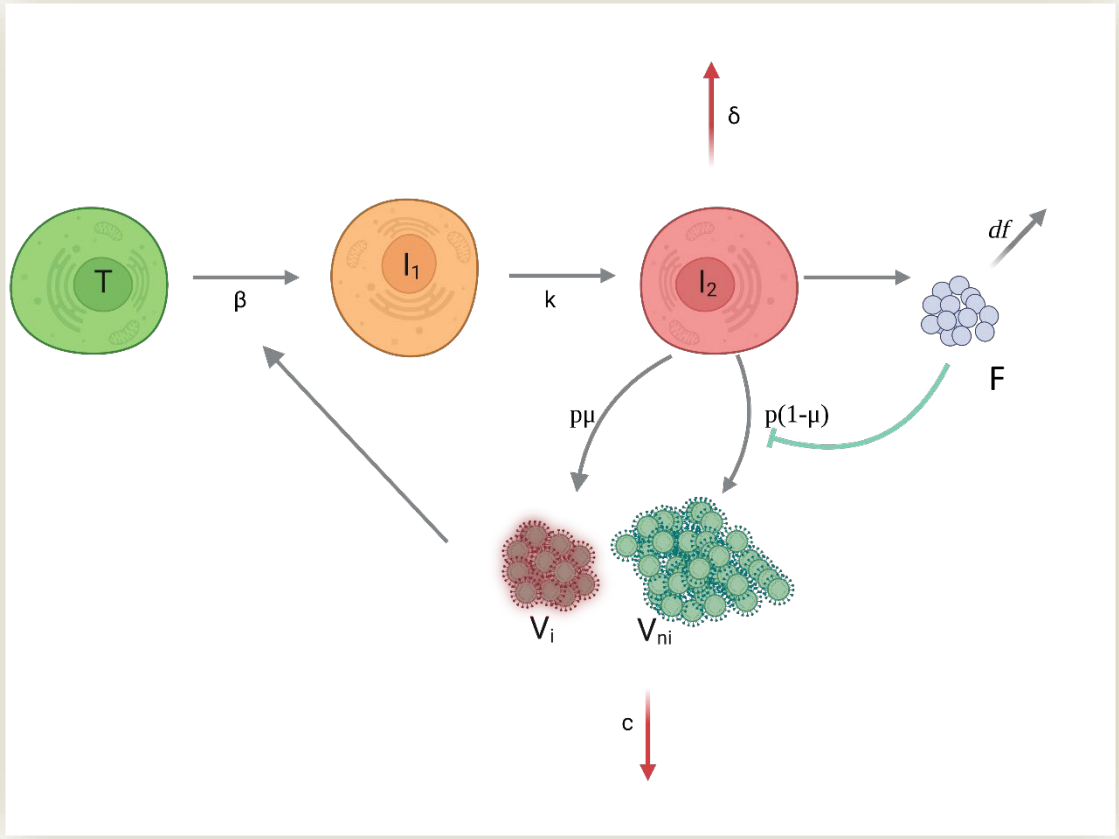
Reconstituting the time of infection based on the viral load data and the time of symptom onset



Modeling the immune response

$$\frac{V_i}{dt} = p\mu\left(1 - \frac{\phi F}{F + \theta}\right) I_2 - cV_i$$

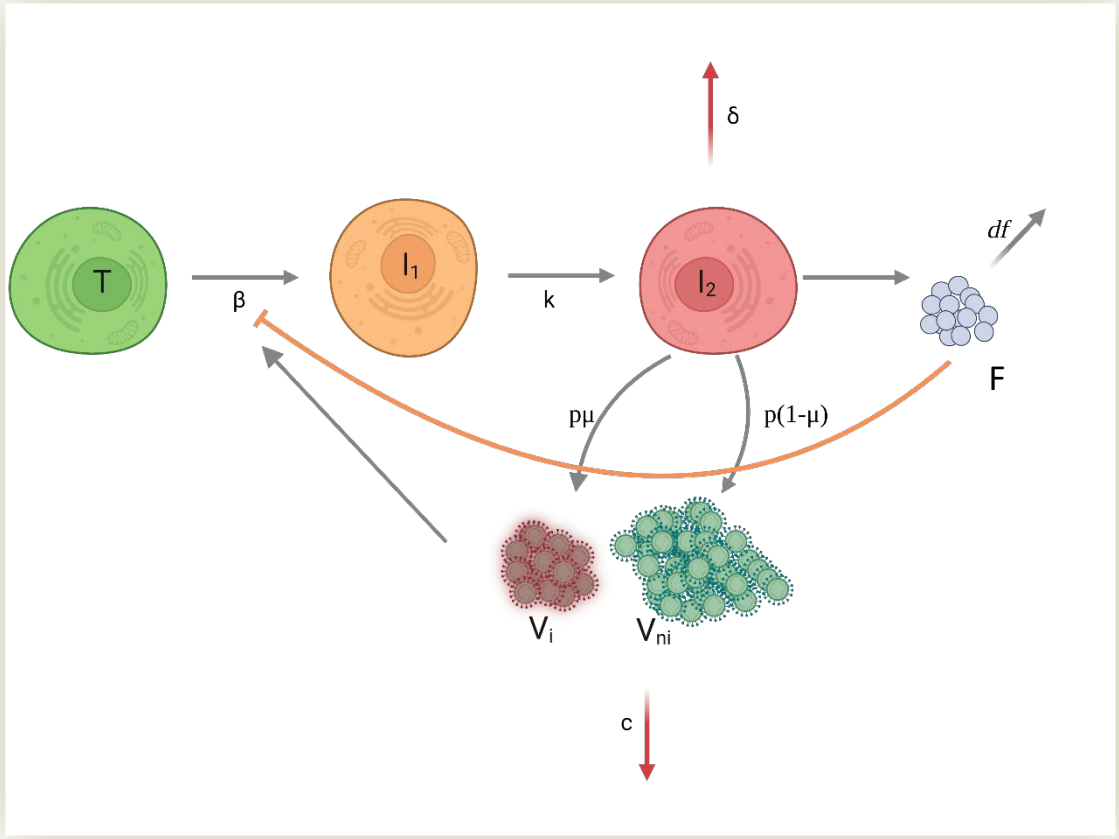
$$\frac{dV_{ni}}{dt} = p(1-\mu)\left(1 - \frac{\phi F}{F + \theta}\right) I_2 - cV_{ni}$$



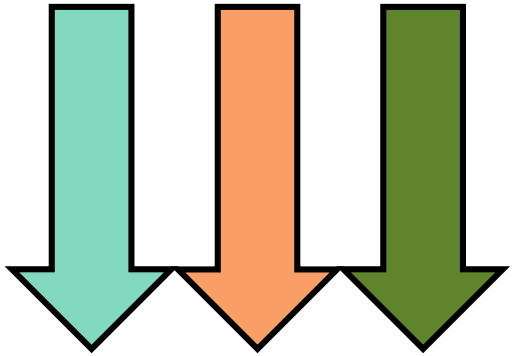
Modeling the immune response

$$\frac{dT}{dt} = -\beta\left(1 - \frac{\phi F}{F+\theta}\right)V_I T$$

$$\frac{dI_1}{dt} = \beta\left(1 - \frac{\phi F}{F+\theta}\right)V_I T - kI_1$$

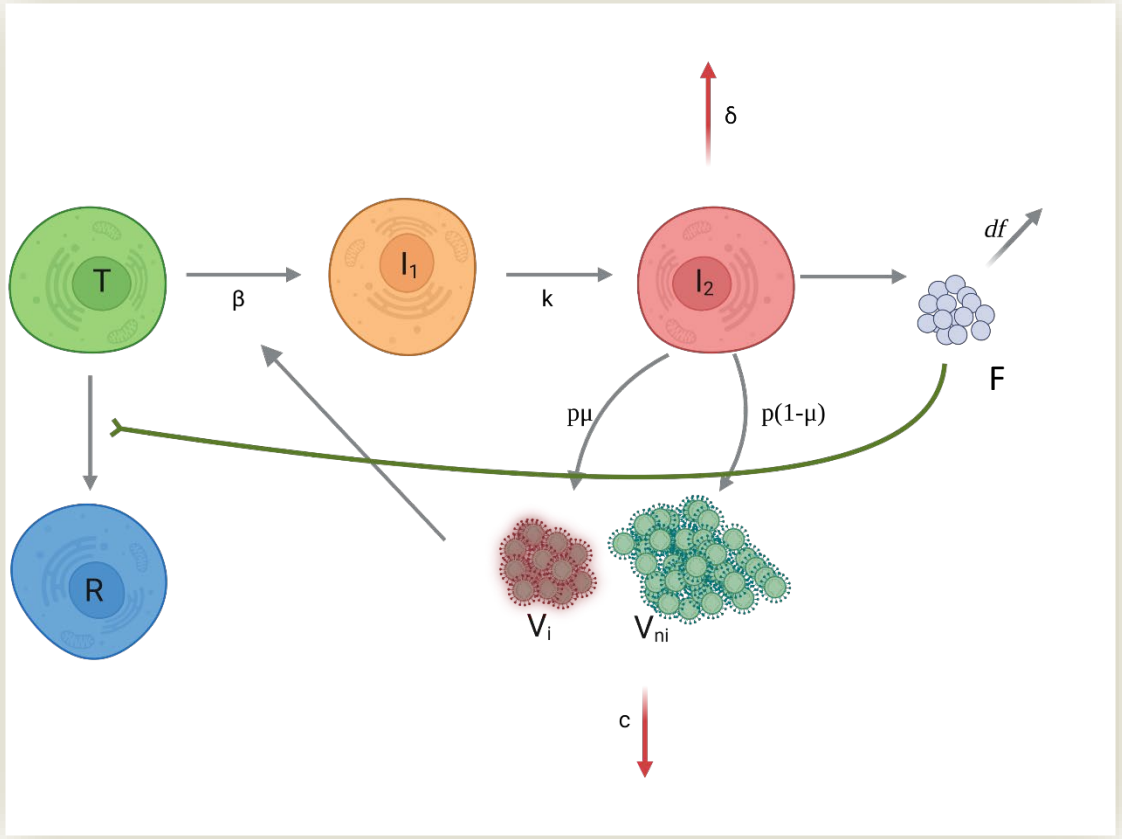


Modeling the immune response

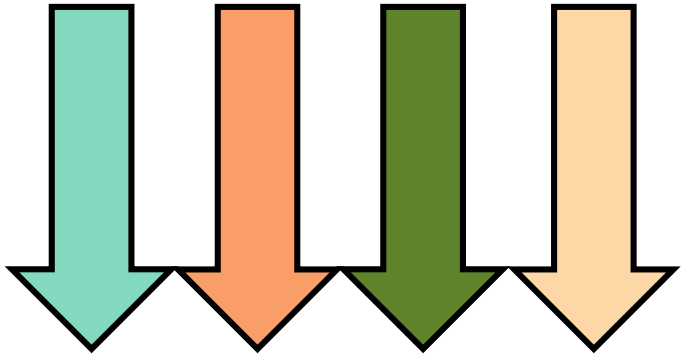


$$\frac{dT}{dt} = -\beta V_I T - \frac{\phi F}{F+\theta} T$$

$$\frac{dR}{dt} = \frac{\phi F}{F+\theta} T$$

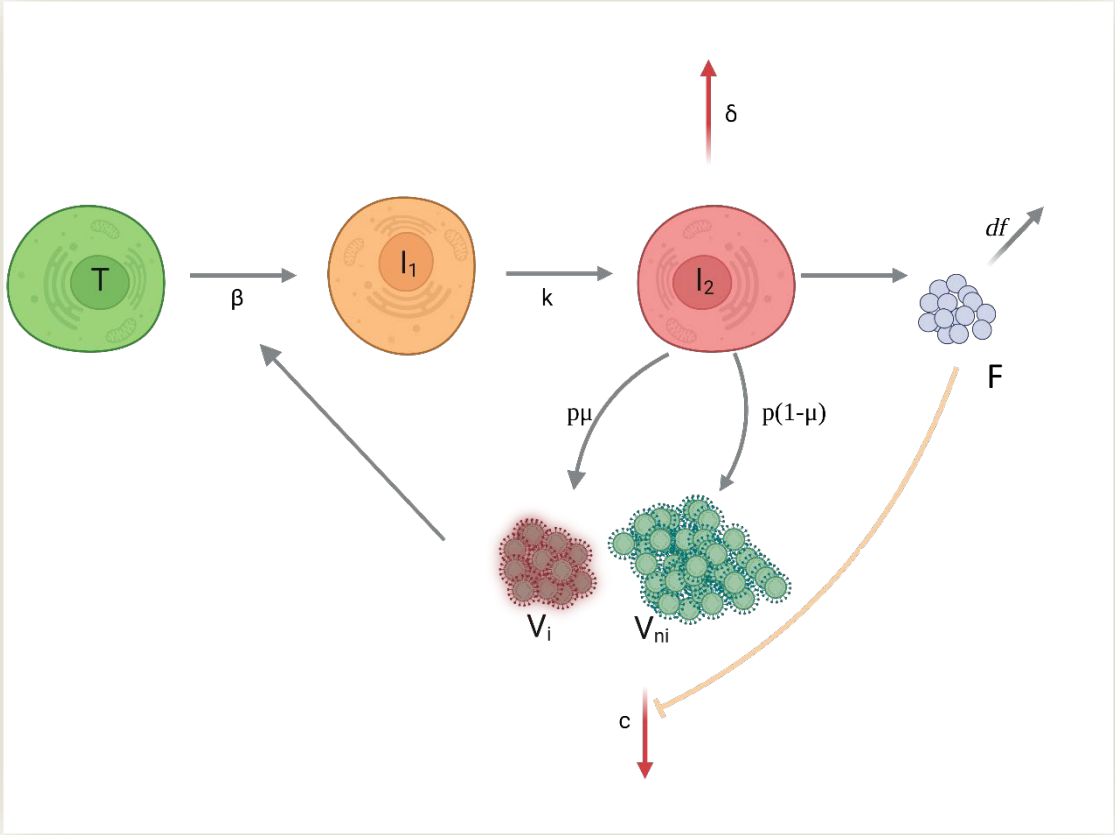


Modeling the immune response

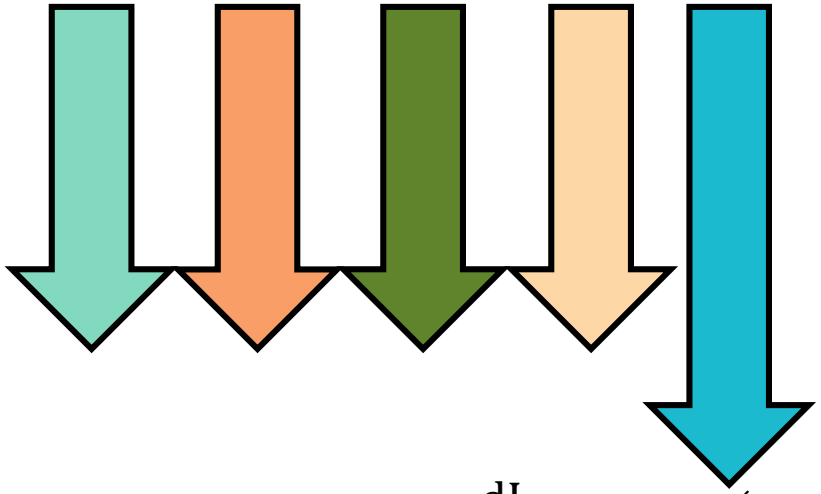


$$\frac{V_i}{dt} = p\mu I_2 - \left(c + \phi\frac{F}{F+\theta}\right)V_i$$

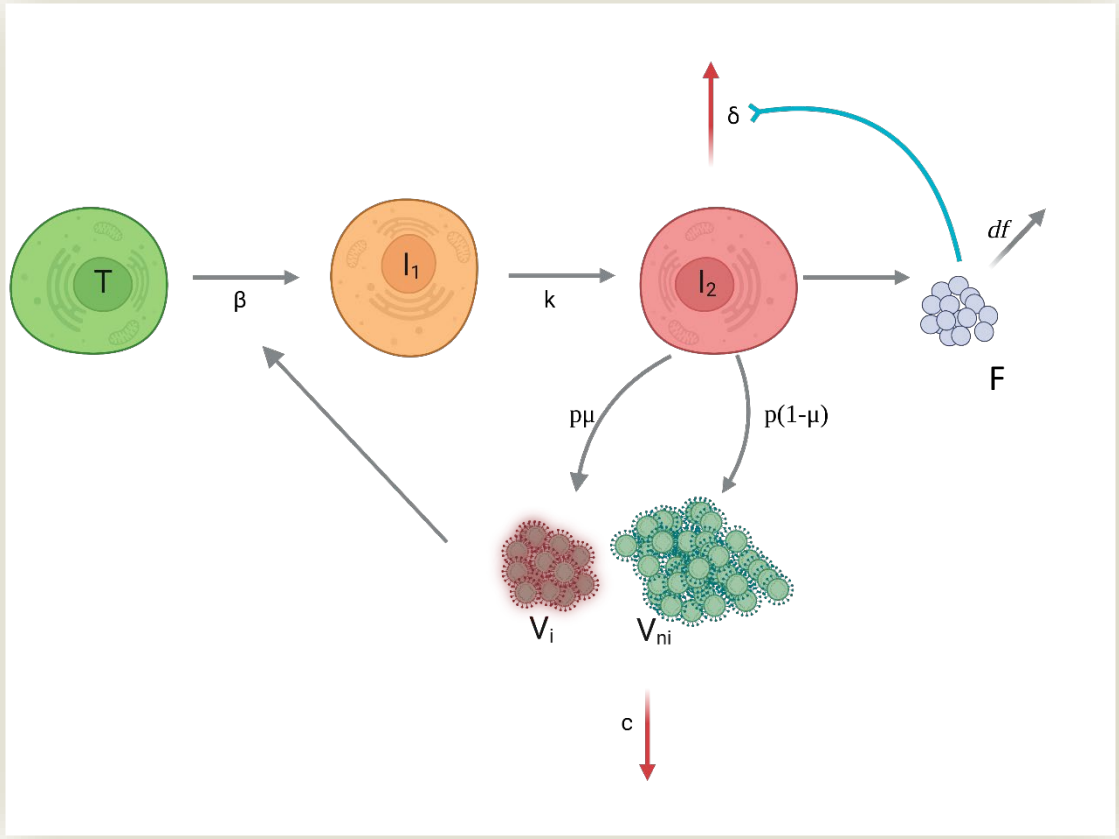
$$\frac{dV_{ni}}{dt} = p(1-\mu)I_2 - \left(c + \phi\frac{F}{F+\theta}\right)V_{ni}$$



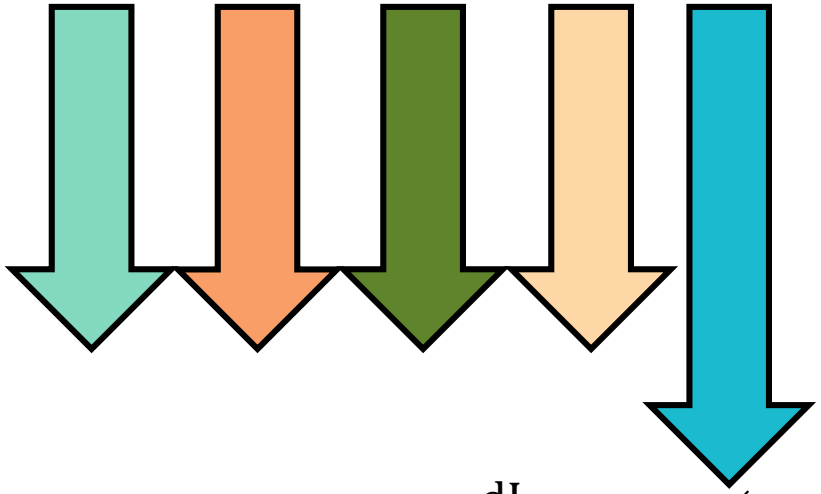
Modeling the immune response



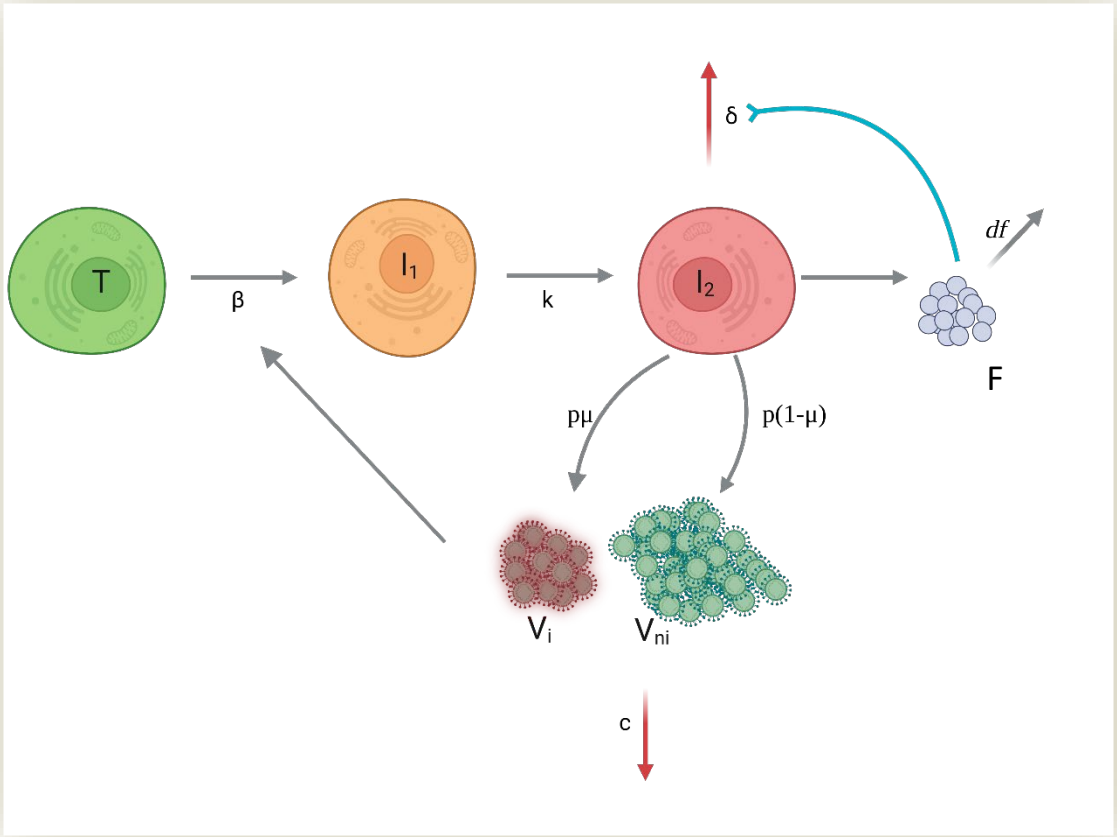
$$\frac{dI_2}{dt} = kI_1 - \left(\delta + \phi\frac{F}{F+\theta}\right)I_2$$



Modeling the immune response



$$\frac{dI_2}{dt} = kI_1 - \left(\delta + \phi\frac{F}{F+\theta}\right)I_2$$



Covariate screening

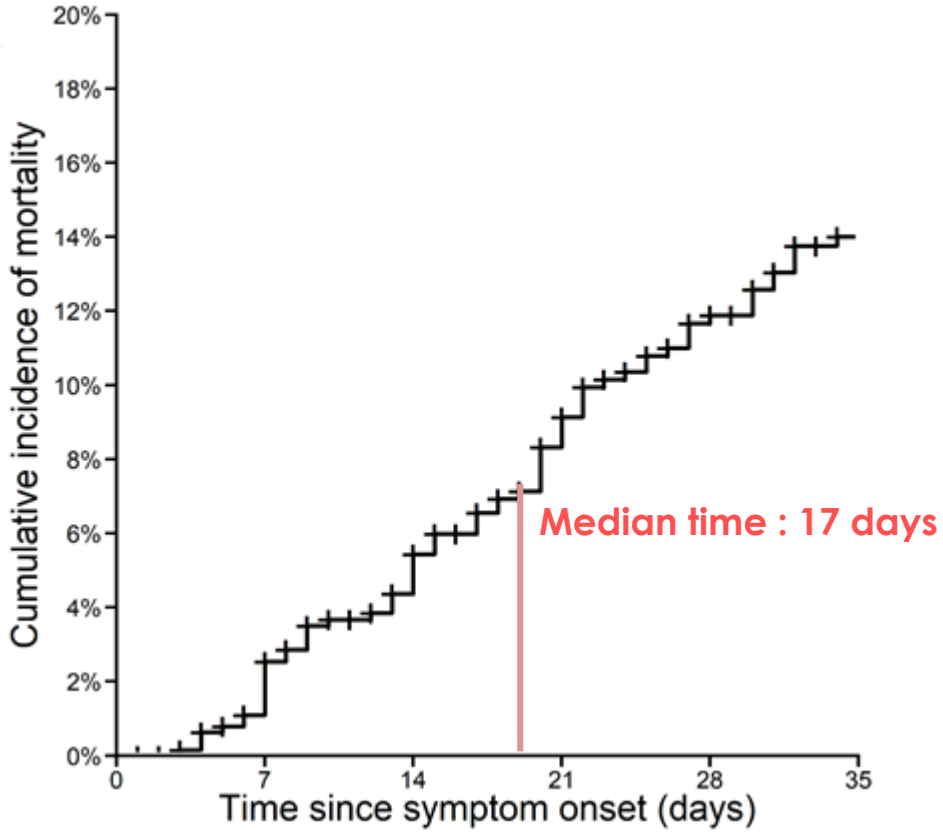
	β	p	ϕ	δ
Age				
Sexe				
MCC				
MPC				
HTA				
Obésité				
Diabète				

MORTALITY AND RISK FACTORS

12 % patients died, 231 lost to follow up at D35

MULTIVARIATE SURVIVAL ANALYSIS

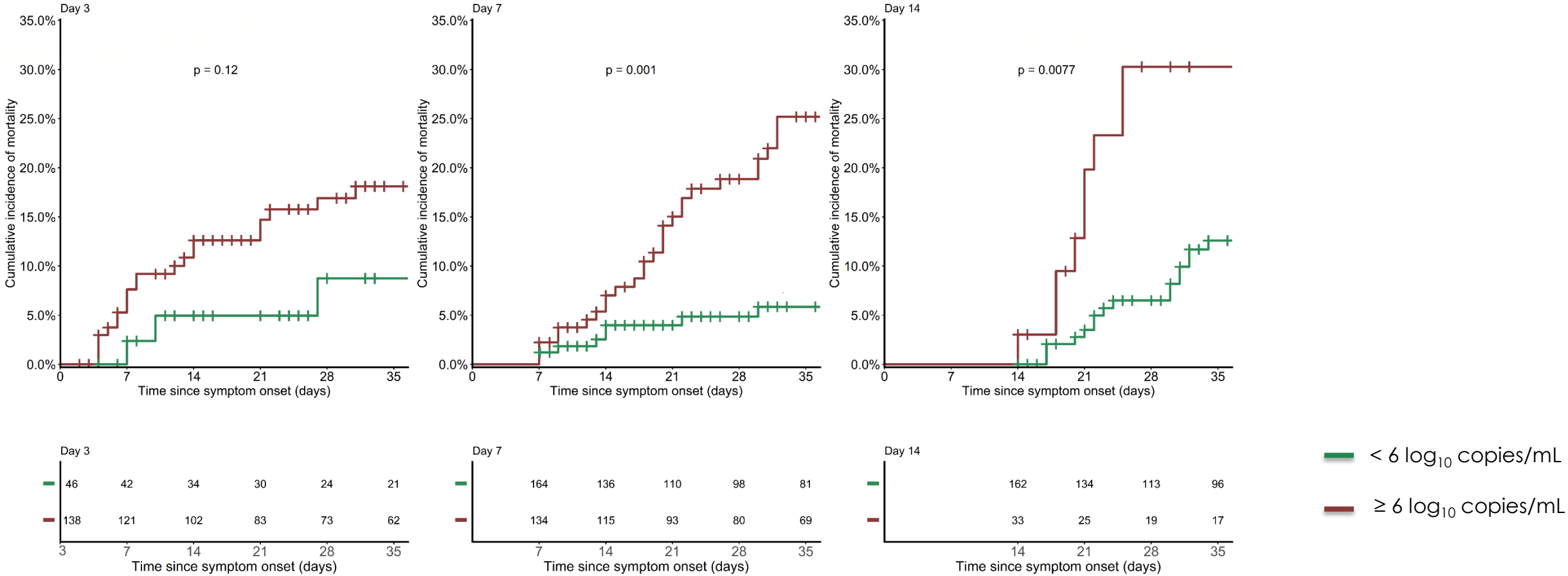
Male gender : HR = 2.63 *p-value* < 10^{-4}
≥ 65 years old : HR = 3.02 *p-value* < 10^{-4}
Chronic pulmonary disease : HR = 2.47 *p-value* < 10^{-4}



Néant et al. PNAS (2021)

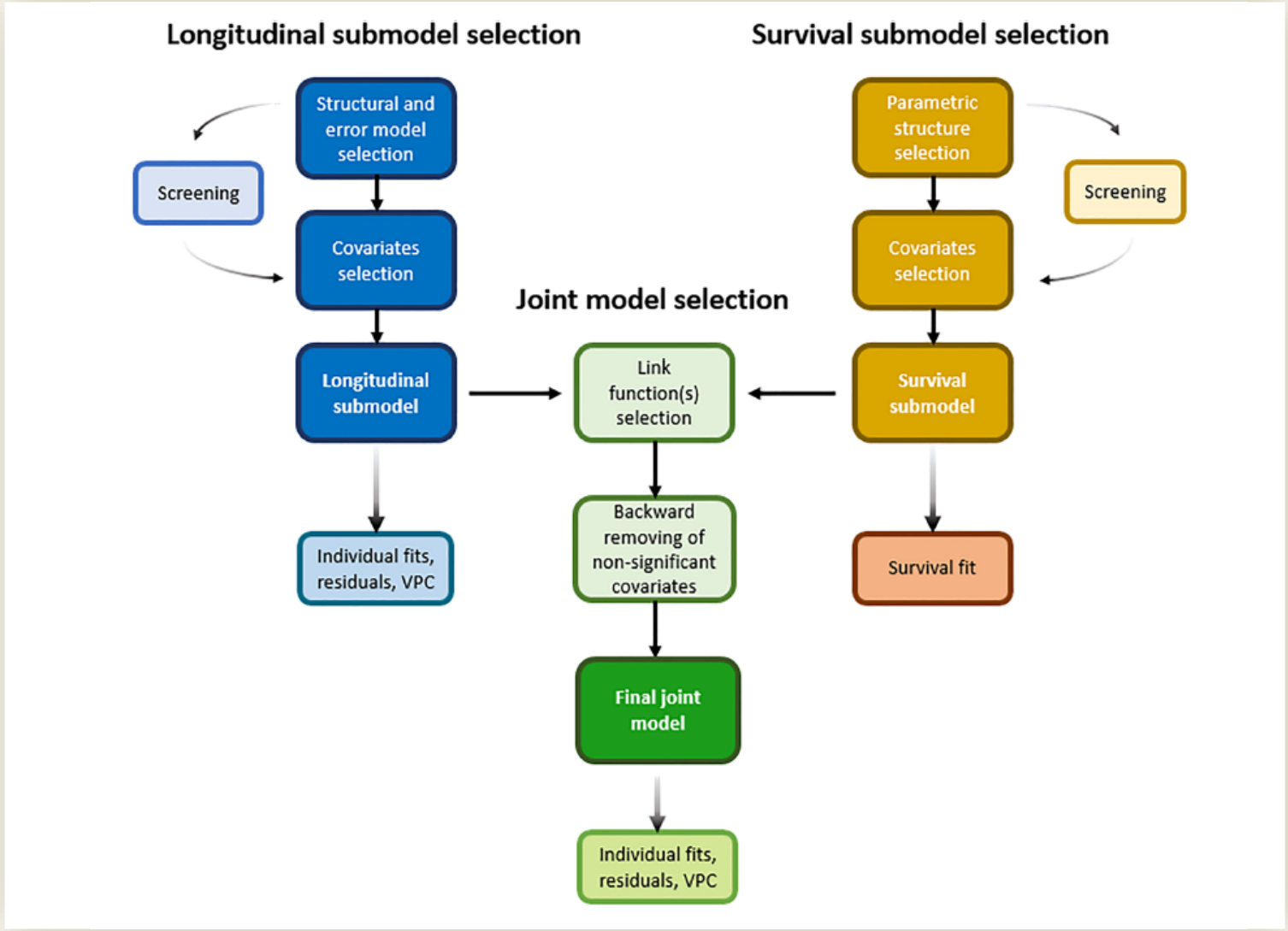
MORTALITY AND VIRAL LOAD

Mortality according to viral load at different landmark times since symptom onset



Néant et al. PNAS (2021)

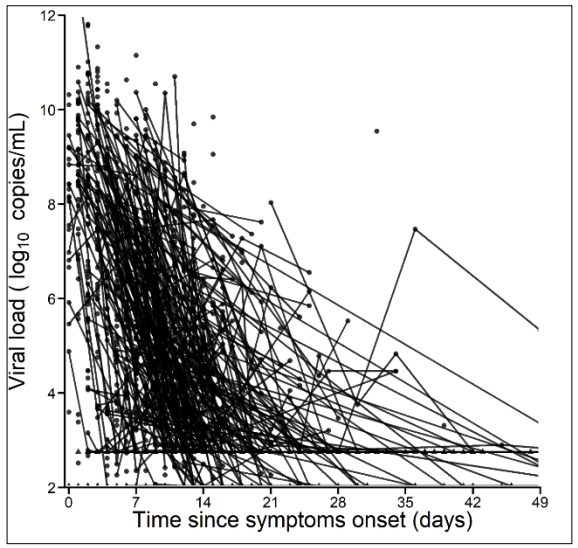
Joint modeling



Kerioui et al . *Br J Clin Pharmacol.* 2022

JOINT MODELLING

Virological data



$$\frac{dT}{dt} = -\beta V_I T$$

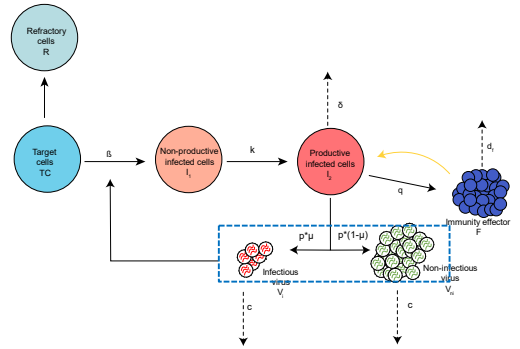
$$\frac{dI_1}{dt} = \beta V_I T - kI_1$$

$$\frac{dI_2}{dt} = kI1 - \delta I_2 - \phi \frac{I_2 F}{F+\theta}$$

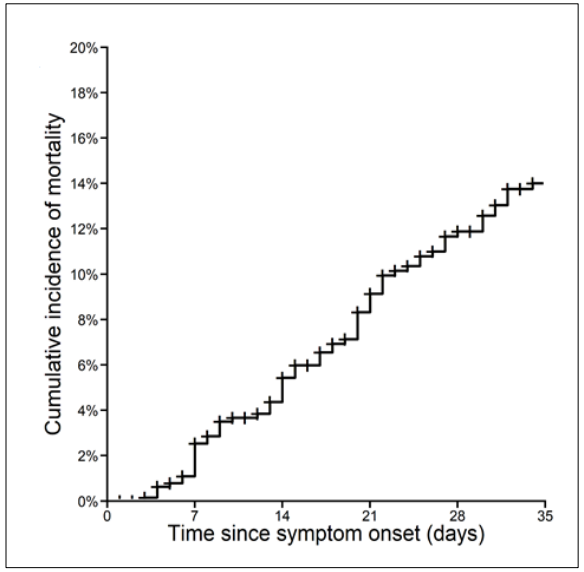
$$\frac{dV_I}{dt} = p\mu I_2 - cV_I$$

$$\frac{dV_{NI}}{dt} = p(1-\mu) I_2 - cV_{NI}$$

$$\frac{dF}{dt} = qI_2 - d_f F$$



Survival data



The survival function of patient *i*

$$S_i(t) = P(T_i \geq t) = \exp\left[-\int_0^t h_i(u)du\right]$$

depends on its instantaneous hazard function

$$h_i(t) = 0 \; if \; t \leq 0 \; ie \; until \; admission$$

$$h_i(t) = h_0 \times exp(\gamma_{RF} \times z_{RF} + \nu \times log_{10}(V_I + V_{NI})(t)) \; if \; t > 0$$

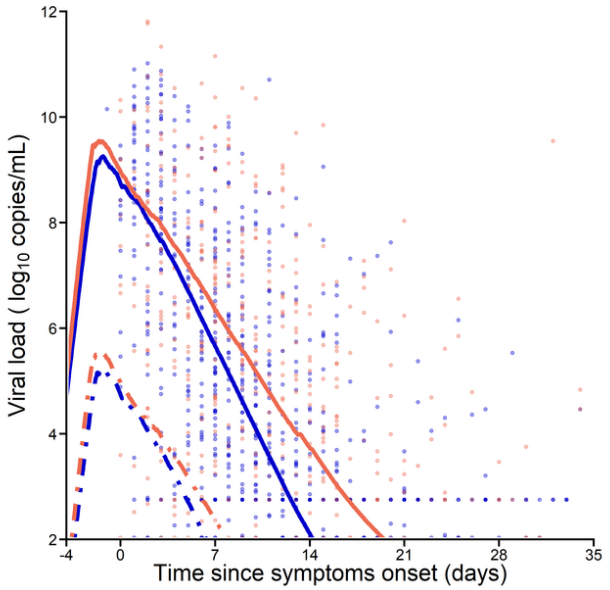
With
T_i : Last time of observation
h_0 : Baseline hazard function
z_{RF} : Presence of risk factors
γ_{RF} : log(HR) associated with the risk factors
ν : log(HR) associated with log_{10} viral load

Guedj et al, Biometrics(2010); Desmée et al, Biometrics(2016)

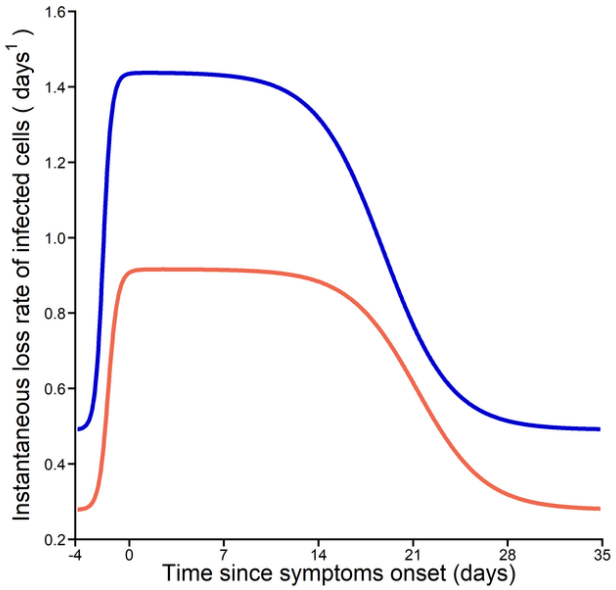
Viral dynamic submodel

Parameter	Estimation (RSE. %)
Incubation period (d)	4.8 (3.24)
β (mL.j^{-1})	1.46×10^{-5} (23.4)
pT_0 (virus.mL^{-1}.j^{-1})	1.48×10^{11} (26.8)
$\delta + \phi_{age}(< 65)$ (j^{-1})	1.25 (8.66)
$\delta + \phi_{age}(\geq 65)$ (j^{-1})	0.98 (23.3)
θ (F.mL^{-1})	70 (80.8)

a



b

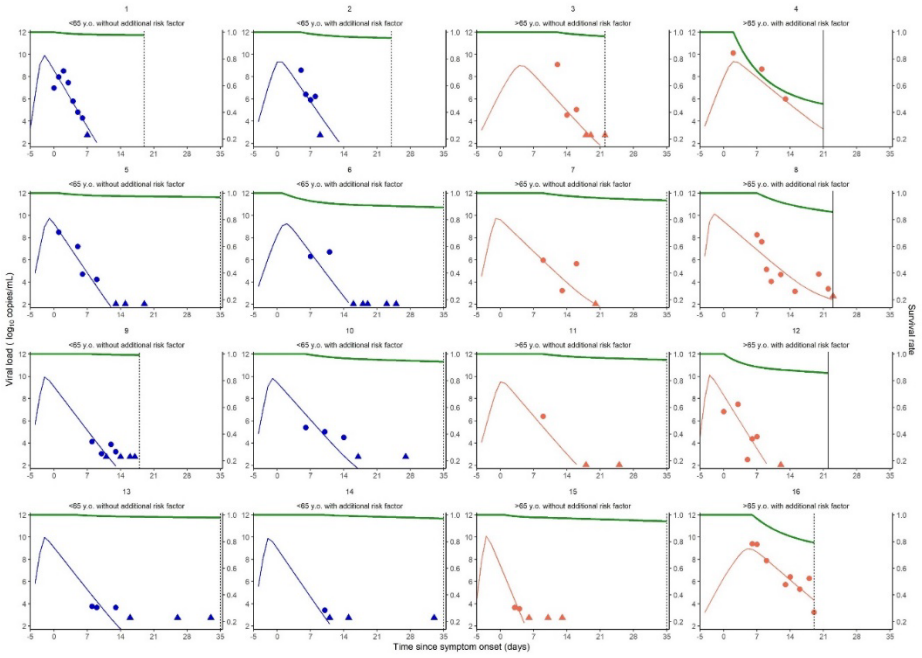


Age < 65 y

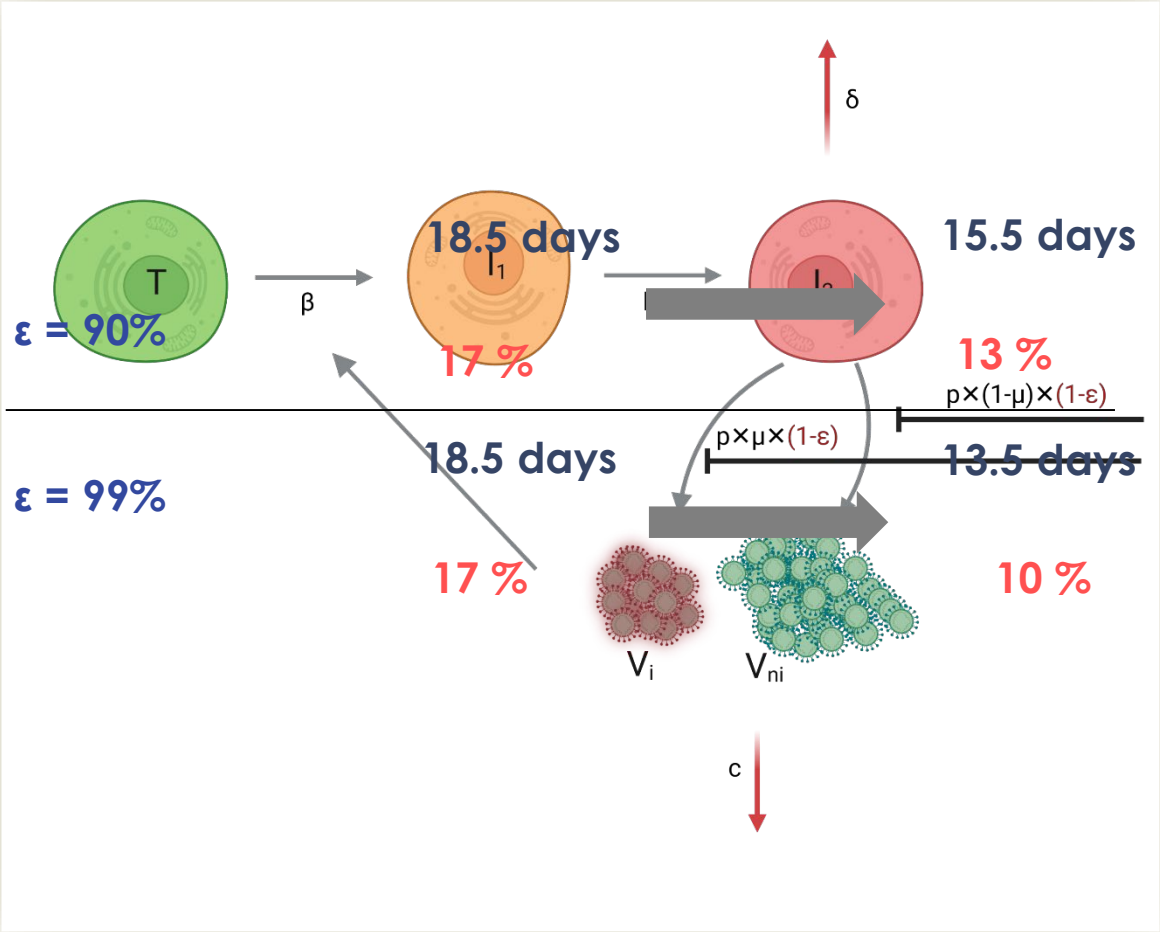
Age ≥ 65 y

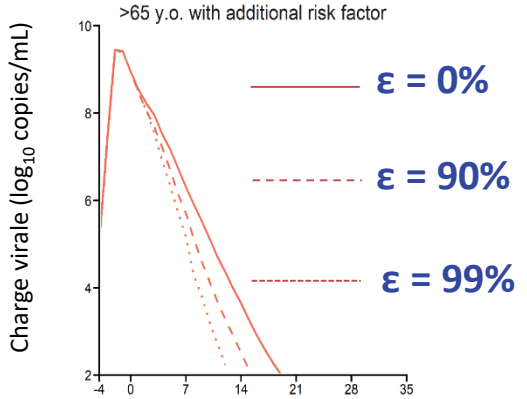
Survival submodel

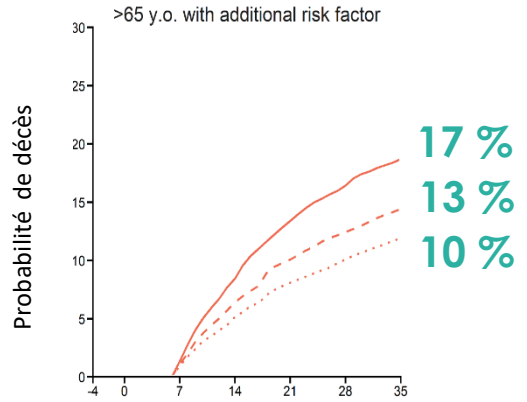
Parameter	Hazard Ratio (RSE%)
Male gender	2.55 (25.2)
Age ≥ 65	2.58 (37.9)
Chronic pulmonary disease	2.31 (36.8)
Current viral load (log_{10} copies/mL)	1.31 (17)



Prédictions





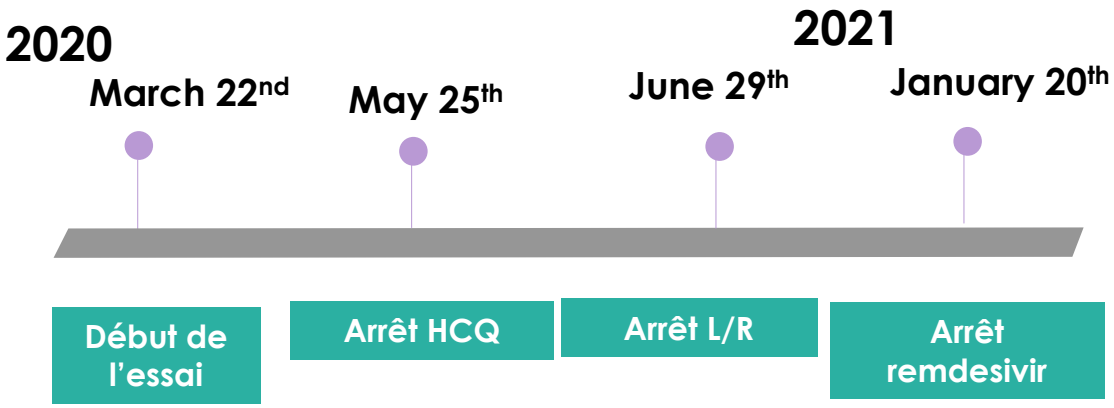


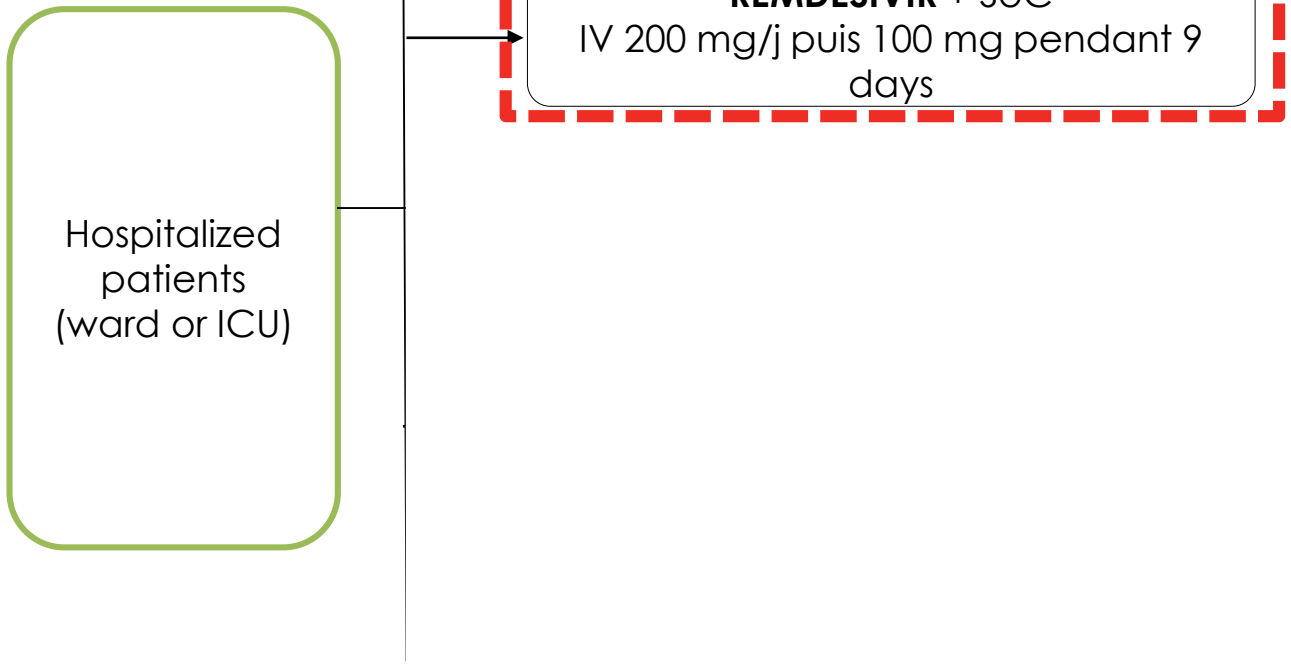
Can we use viral dynamics to better understand the role of treatment

- Viral kinetics in hospitalized non-treated patients
- **Antiviral efficacy of remdesivir in hospitalized patients**
- Antiviral efficacy of monoclonal antibodies in outpatients

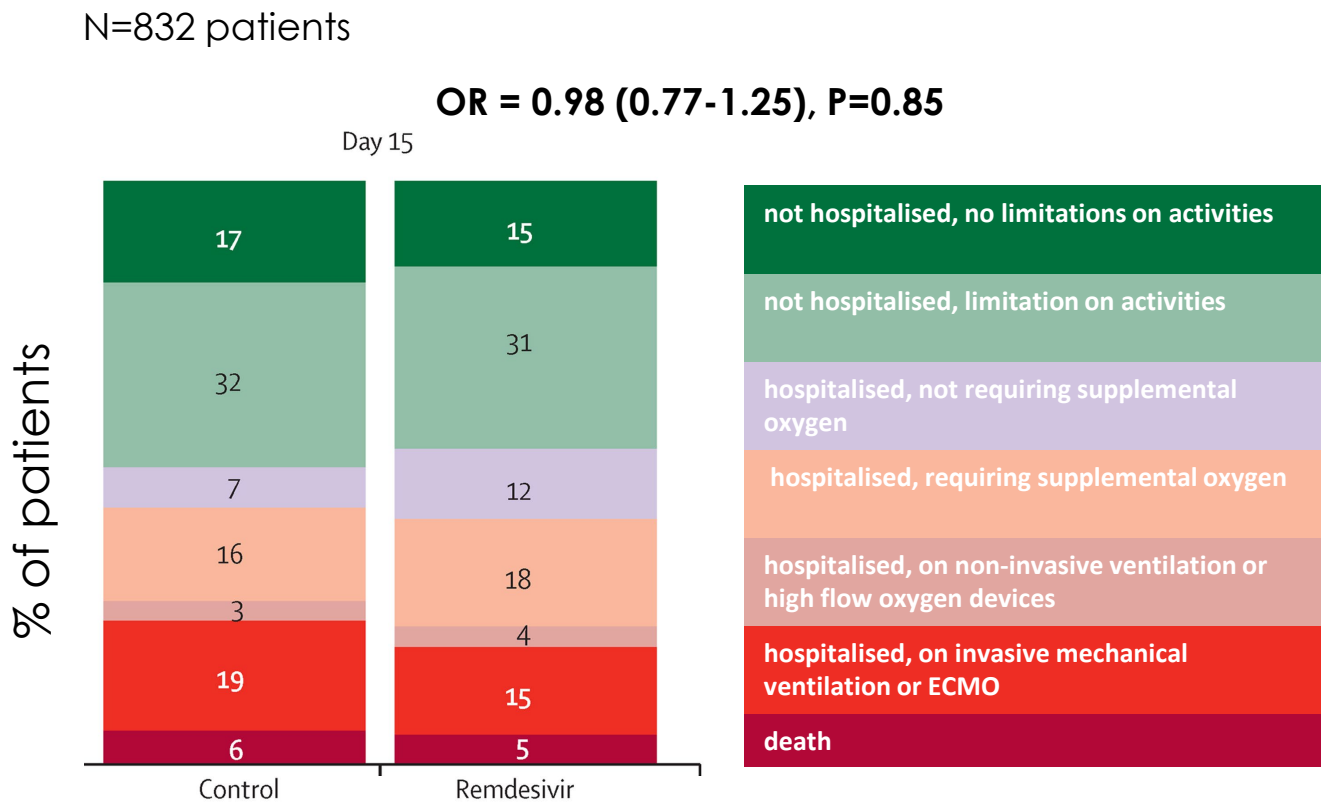
DisCoVeRy trial

European randomized clinical trial (NCT04315948, PI: Florence Ader, Méthodology: France Mentré)





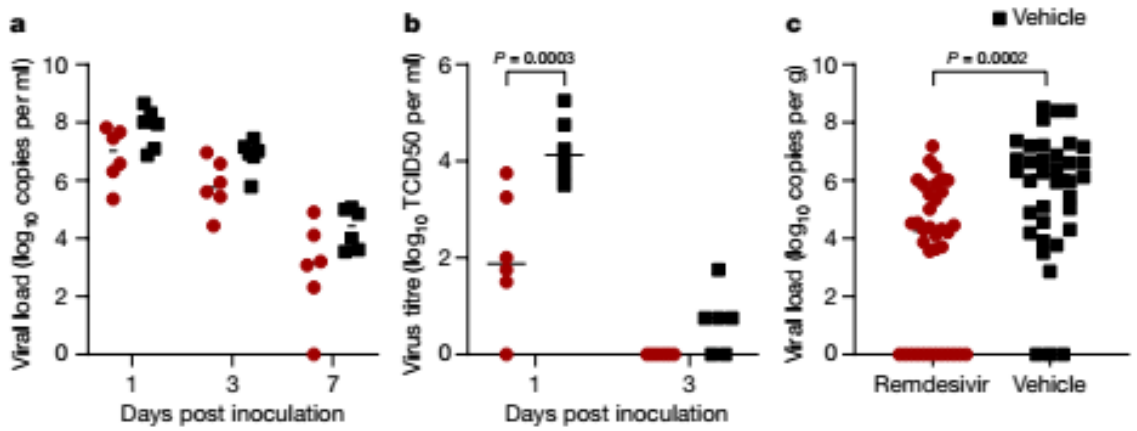
Primary outcome measure: clinical status at day 15

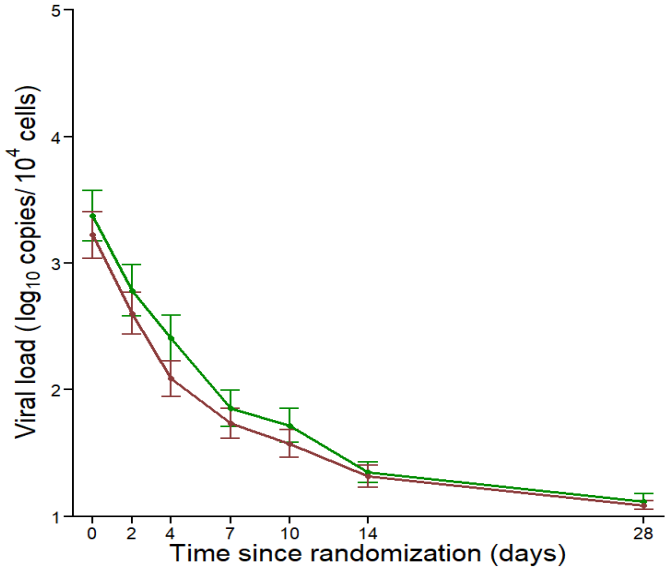


Ader et al. *Lancet Infectious Diseases* (2021)

No clinical efficacy in hospitalized patients, but is there any virological signal ?

- The preclinical efficacy of remdesivir is well documented
- But contradictory findings on clinical and antiviral efficacy but large between and within-study heterogeneity
- Discovery trial had frequent and normalized viral load data in a large cohort of patients





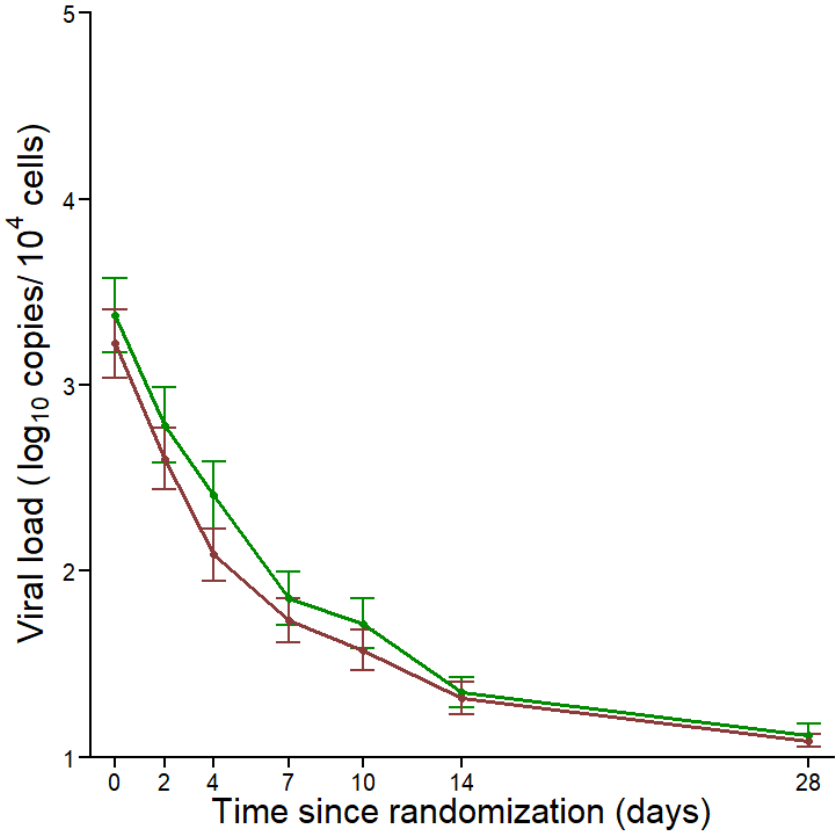
Williamson et al., Nature (2020)

Ader et al., Lancet Infectious Diseases (2021)

Patients and data

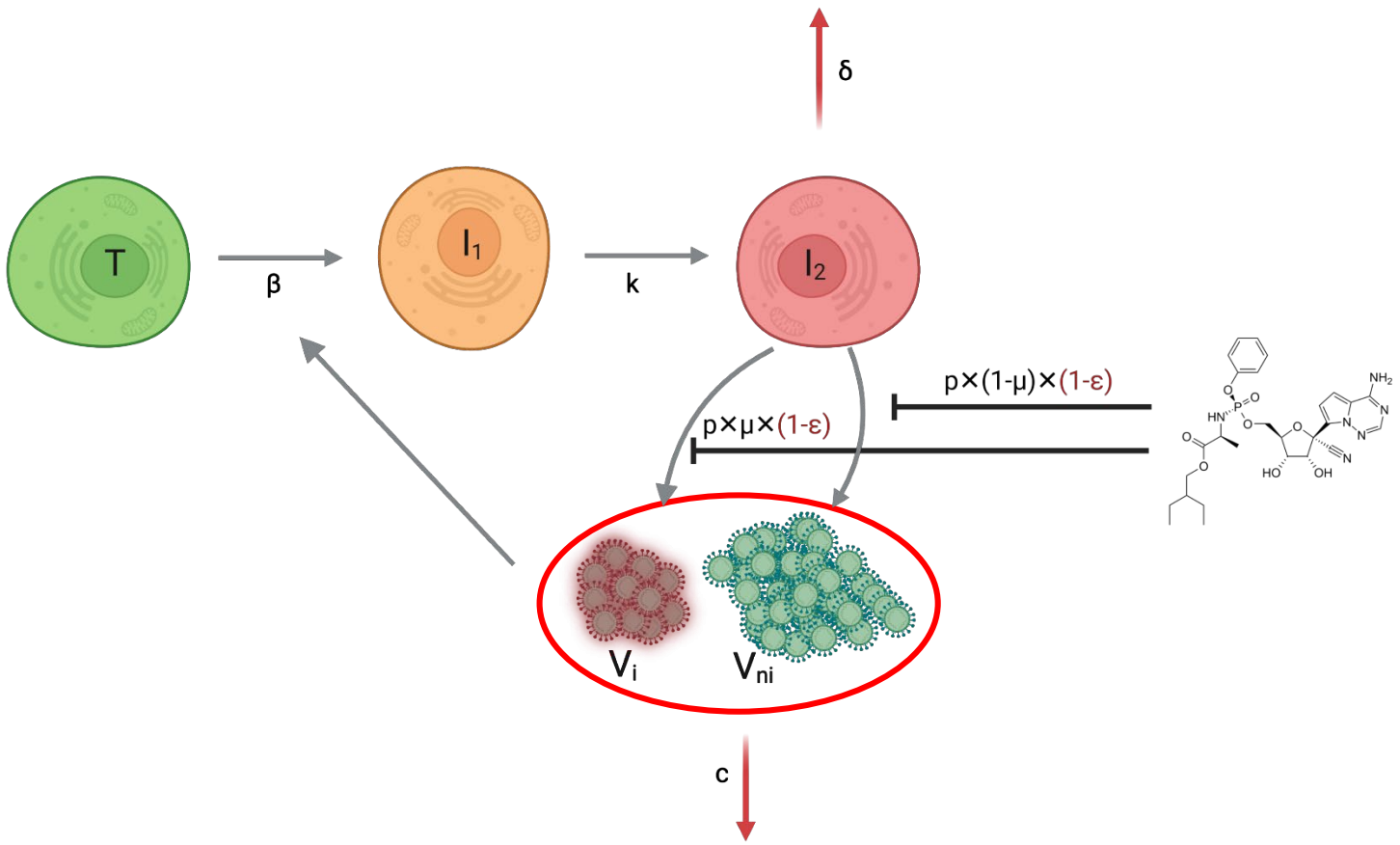
DISCOVERY

Characteristics	Standard of care (N=329)	Standard of care + Remdesivir (N=336)
	Médiane (IQR) or n (%)	Médiane (IQR) or n (%)
Male gender	222 (67.5%)	235 (69.9%)
Age	64 (53-72)	63 (55-73)
<65	169 (51.4%)	180 (53.6%)
≥65	160 (48.6%)	156 (46.4%)
Delay between symptom onset and randomization (d)	9 (7-11)	9 (7-11)
Viral load at randomization (log_{10} copies/10^4 cells)	3.2 (1.9-4.5)	3.2 (1.8-4.5)



Viral dynamic model

Target cell limited model with eclipse phase



$$\frac{dT}{dt} = -\beta \times V_I T$$

$$\frac{dI_1}{dt} = \beta \times V_I T - kI_1$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2$$

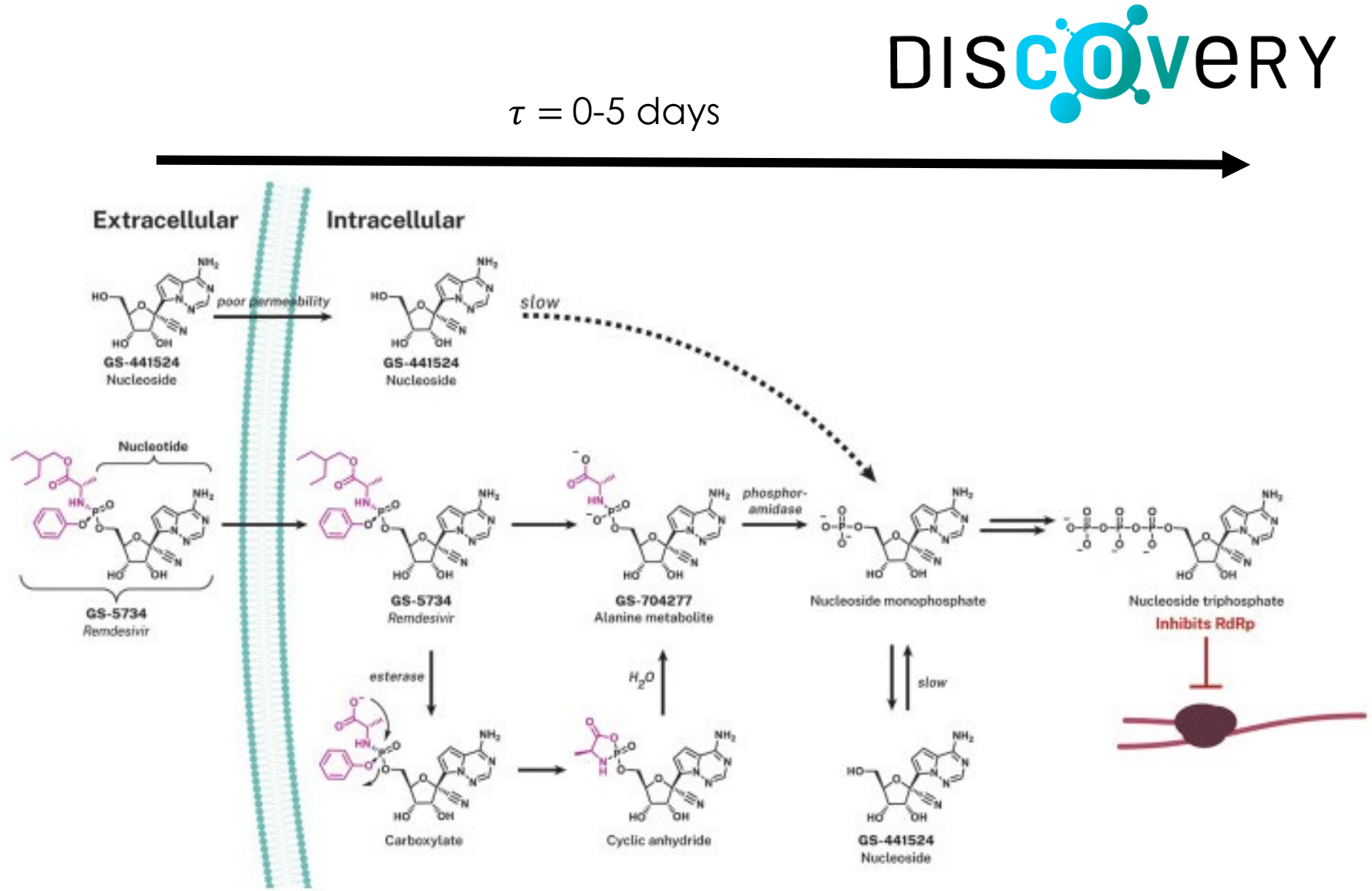
$$\frac{dV_I}{dt} = p(1-\mu)(1-\varepsilon)I_2 - cV_I$$

$$\frac{dV_{NI}}{dt} = p\mu(1-\varepsilon)I_2 - cV_{NI}$$

Lingas et al, Journal of Antimicrobial Chemotherapy (2022)

Pharmacological delay of treatment

- Model averaging [1] to take into account the uncertainty on delay τ

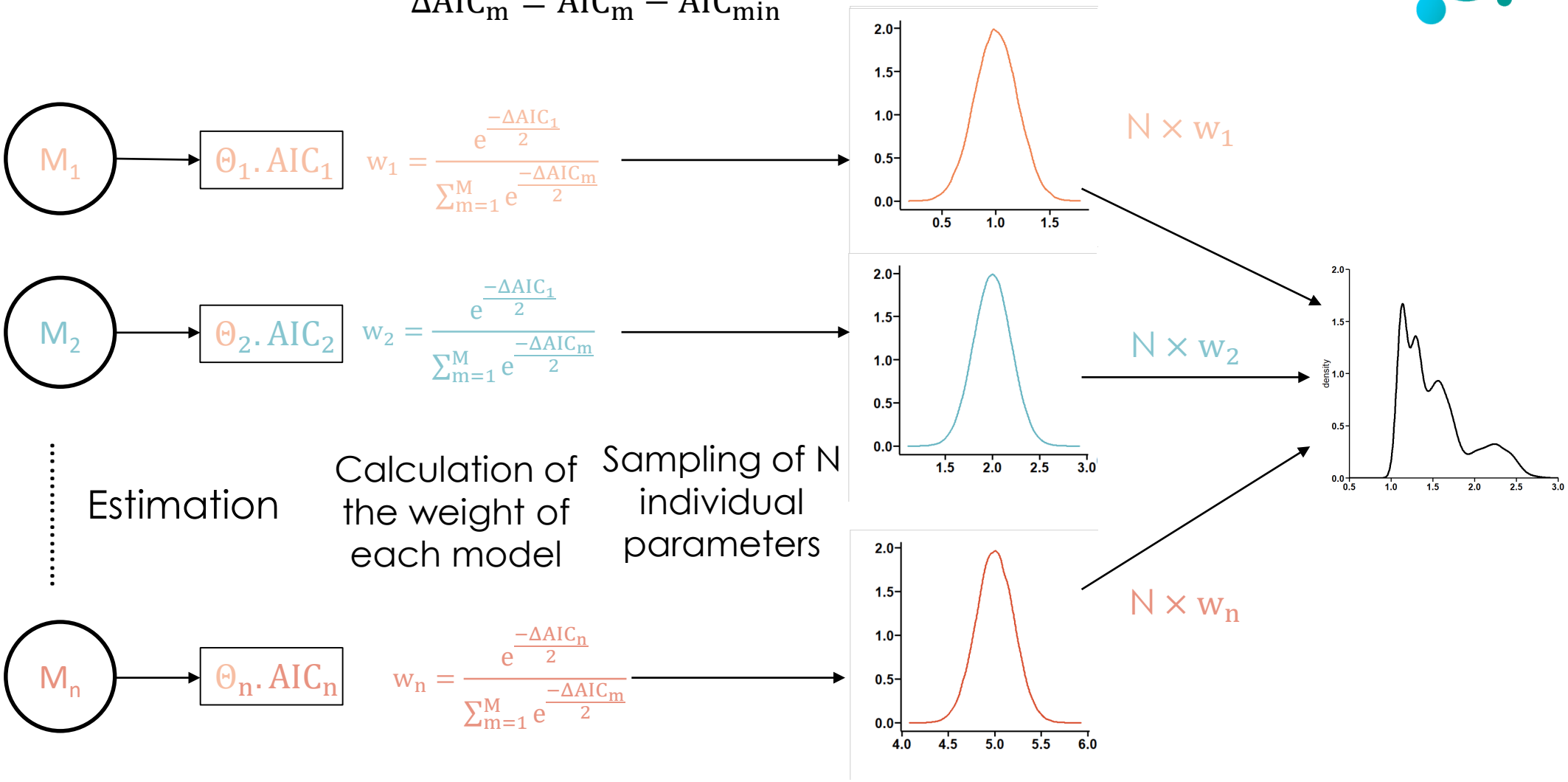


[1] Gonçalves et al. *AAPS* (2020)

Eastman et al. *ACS Cent. Sci.* (2020)

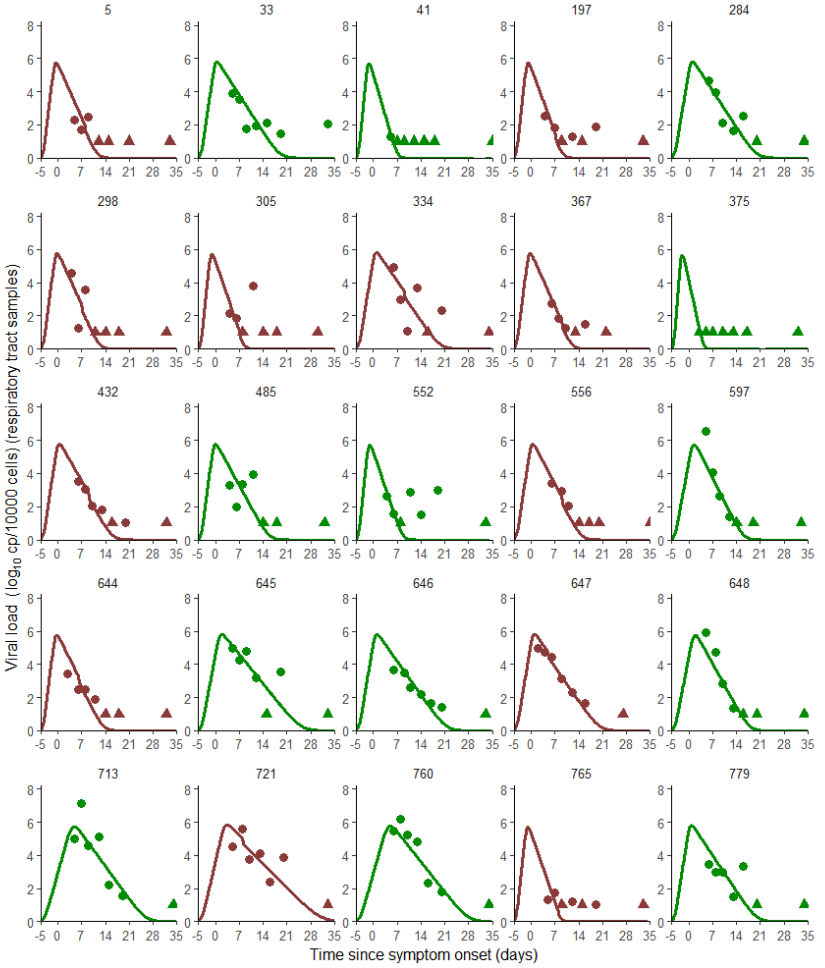
Model averaging

$$\Delta AIC_m = AIC_m - AIC_{min}$$



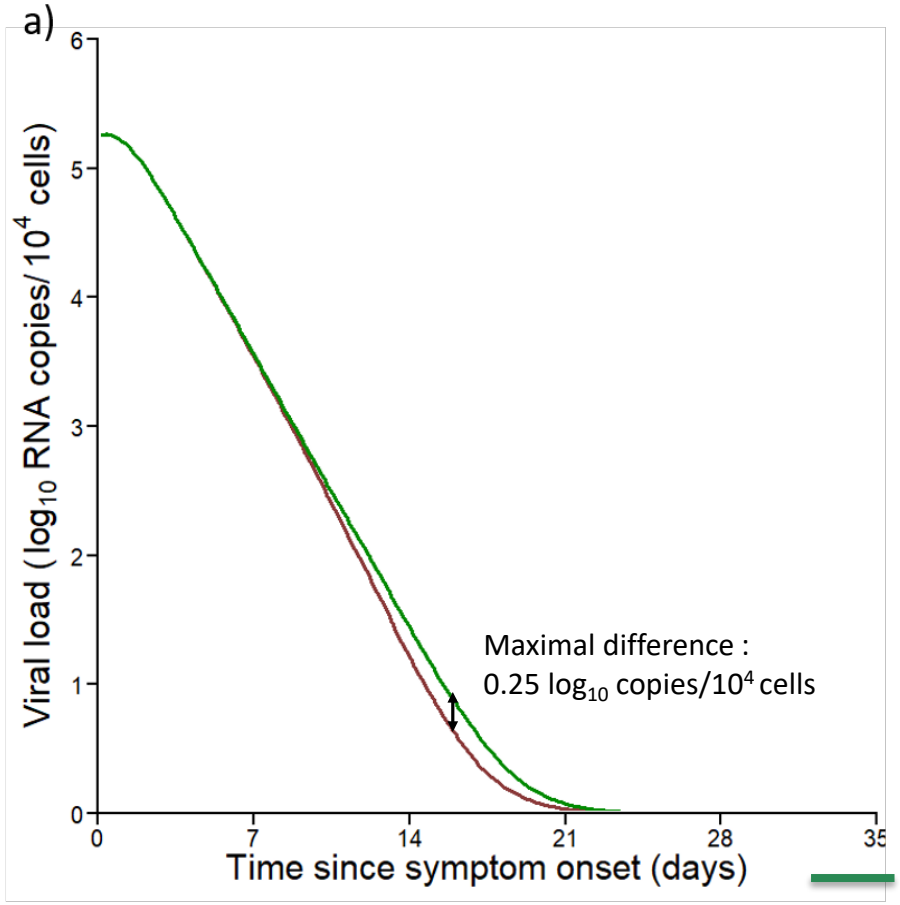
Treatment efficacy

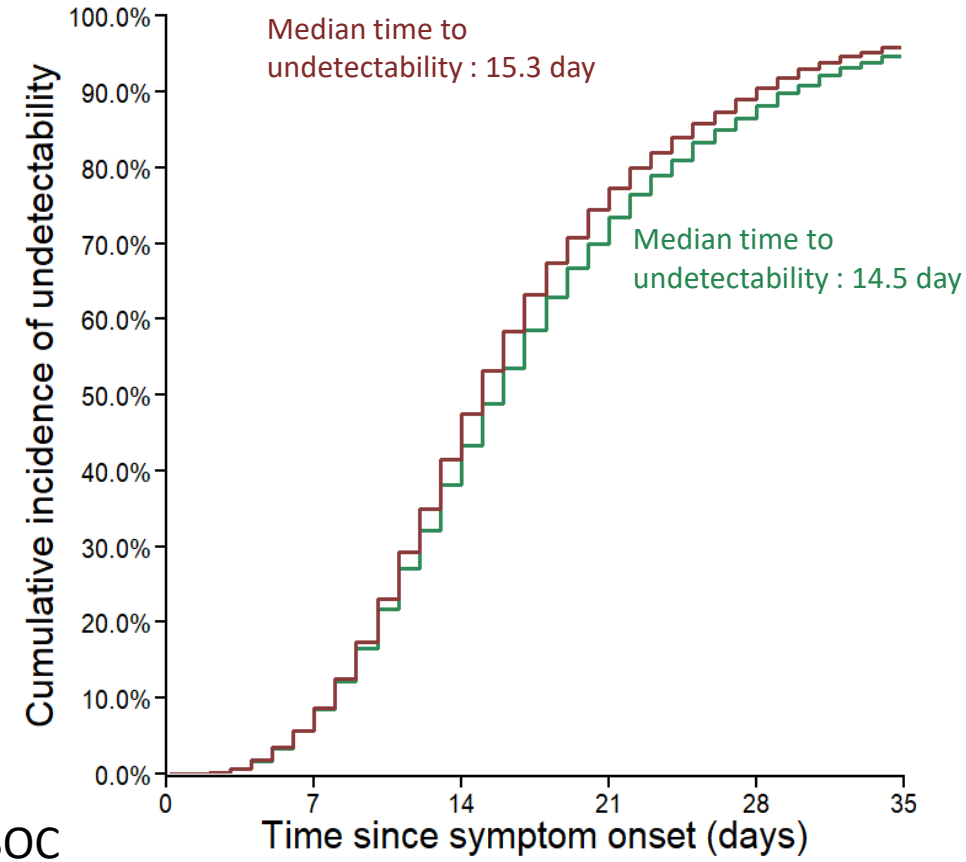
Parameter estimates		
Parameter	**Fixed effects (Median, 95% CI)**	**SD of the random effect (Median, 95% CI)**
R_0	10.60 (8.53-12.68)	0.50
$\delta_{<65}$ (d^{-1})	0.88 (0.80-0.96)	0.46 (0.41-0.51)
$\delta_{\geq 65}$ (d^{-1})	0.76 (0.67-0.84)	
p (10^6 virus.cell^{-1}.d^{-1})*	1.20 (0.66-1.72)	0.38 (0.14-0.63)
ε (%)	52 (35-69)	0.77 (0.18-1.37)
σ ($\log_{10}$ RNA copies/10^4 cells)	1.14 (1.09-1.19)	-



Analysis in all patients

Remdesivir reduces viral production by 52% (95%CI: 35-69%, p=0.0031)



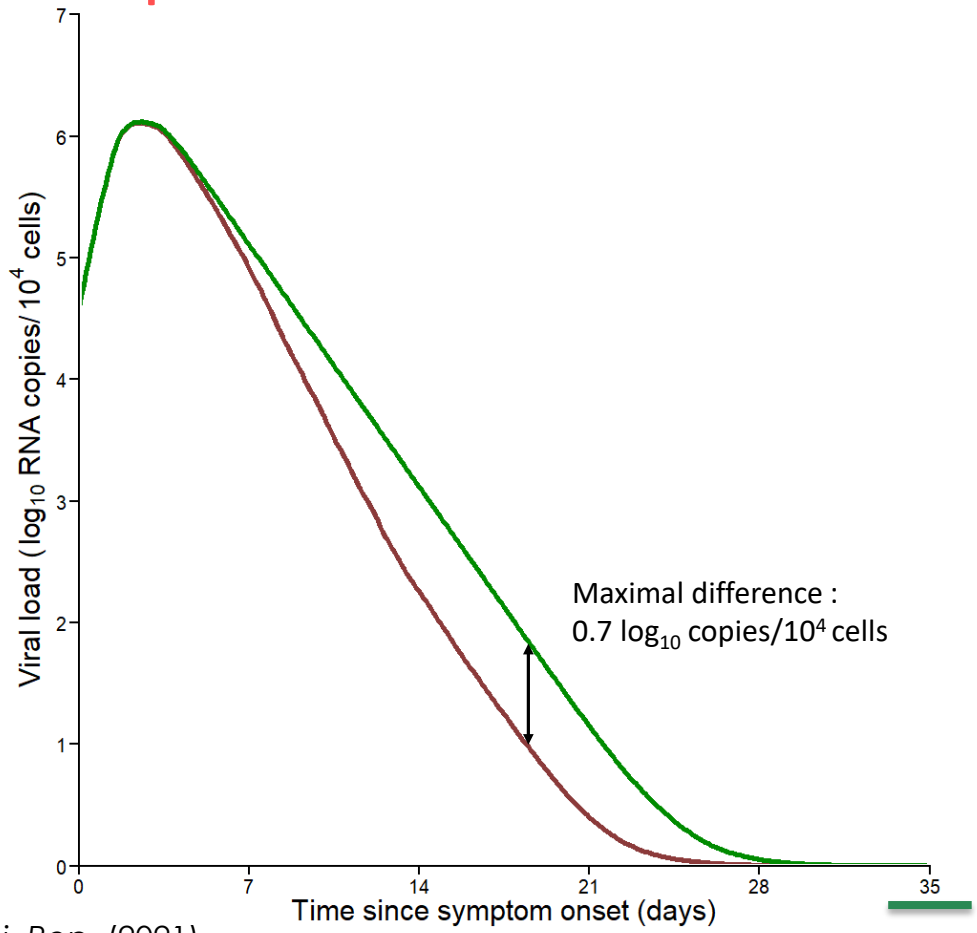


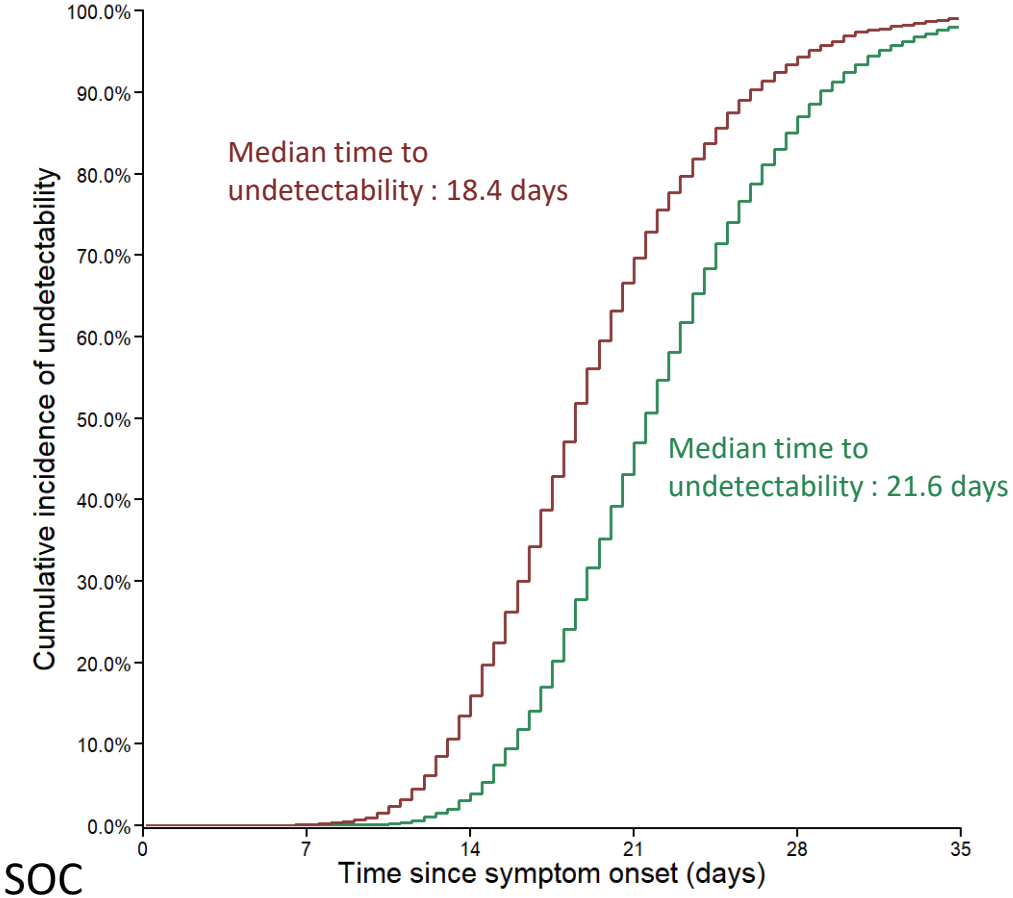
SOC

SOC+ remdesivir

Exploratory results in patients with high viral load at admission

Remdesivir reduces viral production by 80% (95%CI: 64-96%, $p<10^{-5}$)
in patients with viral load at admission $\geq$ 3.5 log_{10} copies/10^4 cells (Infectiosity threshold [1])





SOC
SOC+ remdesivir

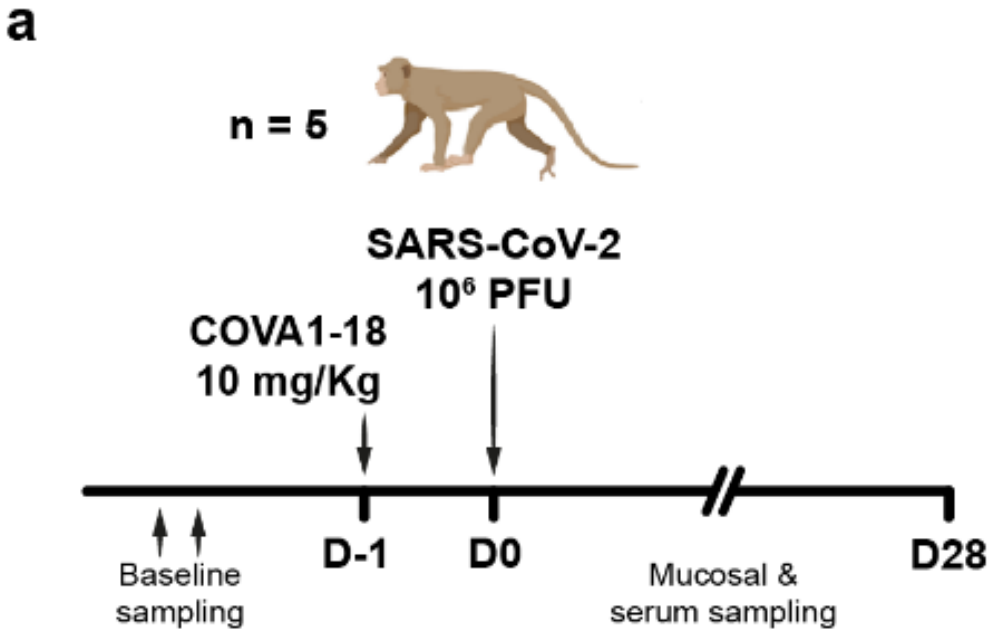
[1] Bal et al. *Sci. Rep.* (2021)

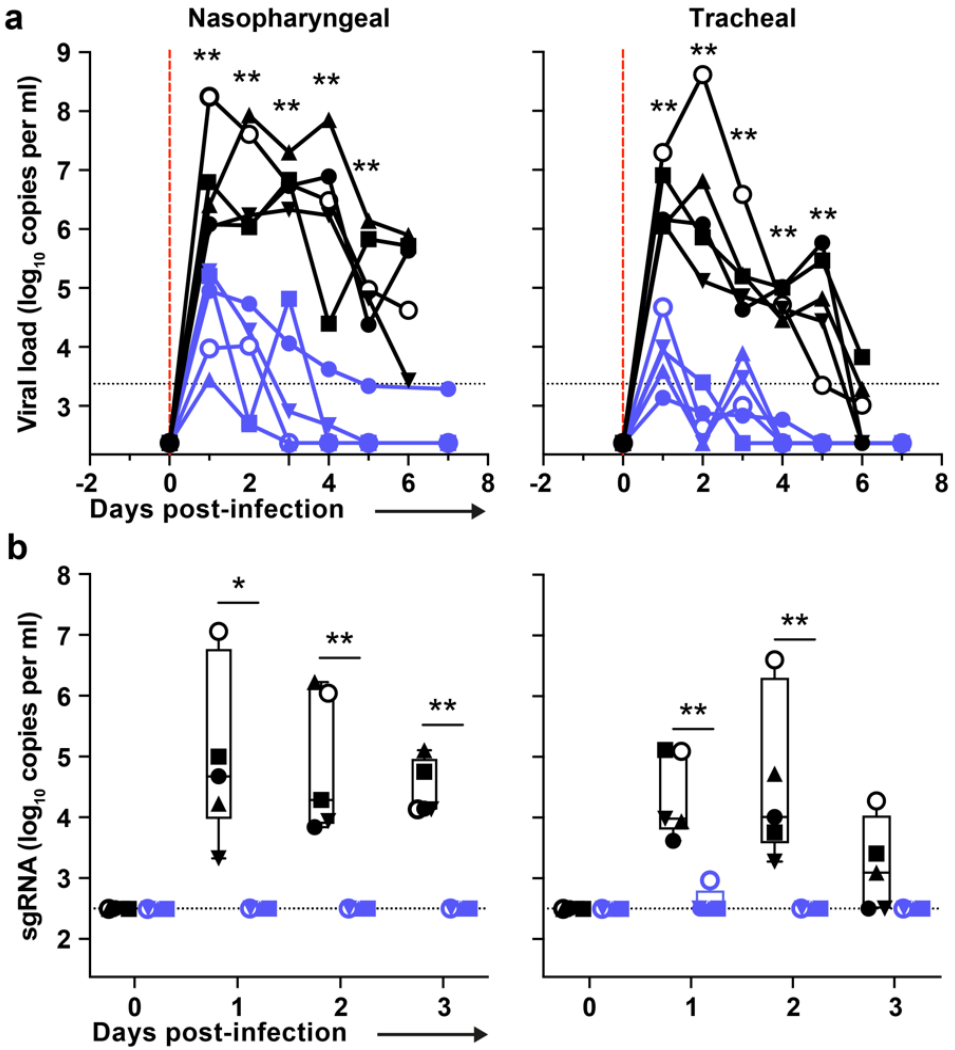
Can we use viral dynamics to better understand the role of treatment

- Viral kinetics in hospitalized non-treated patients
- Antiviral efficacy of remdesivir in hospitalized patients
- **Antiviral efficacy of monoclonal antibodies in outpatients**

Using modeling and animal data to quantify the effect of mAbs

- Most mAbs target the RBD domain of SARS-CoV-2 to prevent virus-cell interaction
- Cova1-18 is a highly efficacious mAb with efficacy in the picomolar range
- Treatment initiated prophylactically





Maisonnasse et al, Nature Communications (2021)

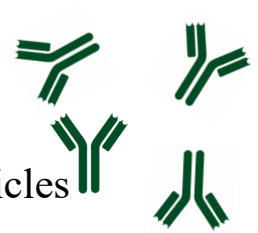
Viral dynamics during treatment with monoclonal antibodies

- Genomic RNA is a reflect of Infectious viral particles (V_I) and Non-infectious viral particles (V_{NI}).

$$V_g = V_I + V_{NI}$$

- Subgenomic RNA (V_{sg}) as a reflect of transcriptional activity:

$$V_{sg} \propto (I1 + I2)$$



COVA1-18

ODE system :

$$\frac{dT}{dt} = -\beta VT$$

$$\frac{dI_1}{dt} = \beta VT - kI_1$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2$$

$$\frac{dV_I}{dt} = p\mu I_2 - cV_I$$

$$\frac{dV_{NI}}{dt} = p(1-\mu)I_2 - cV_{NI}$$

Gonçalves et al, PLoS CB (2021) ; Maisonnasse et al, Nature Comm (2021)

Viral dynamics during treatment with monoclonal antibodies

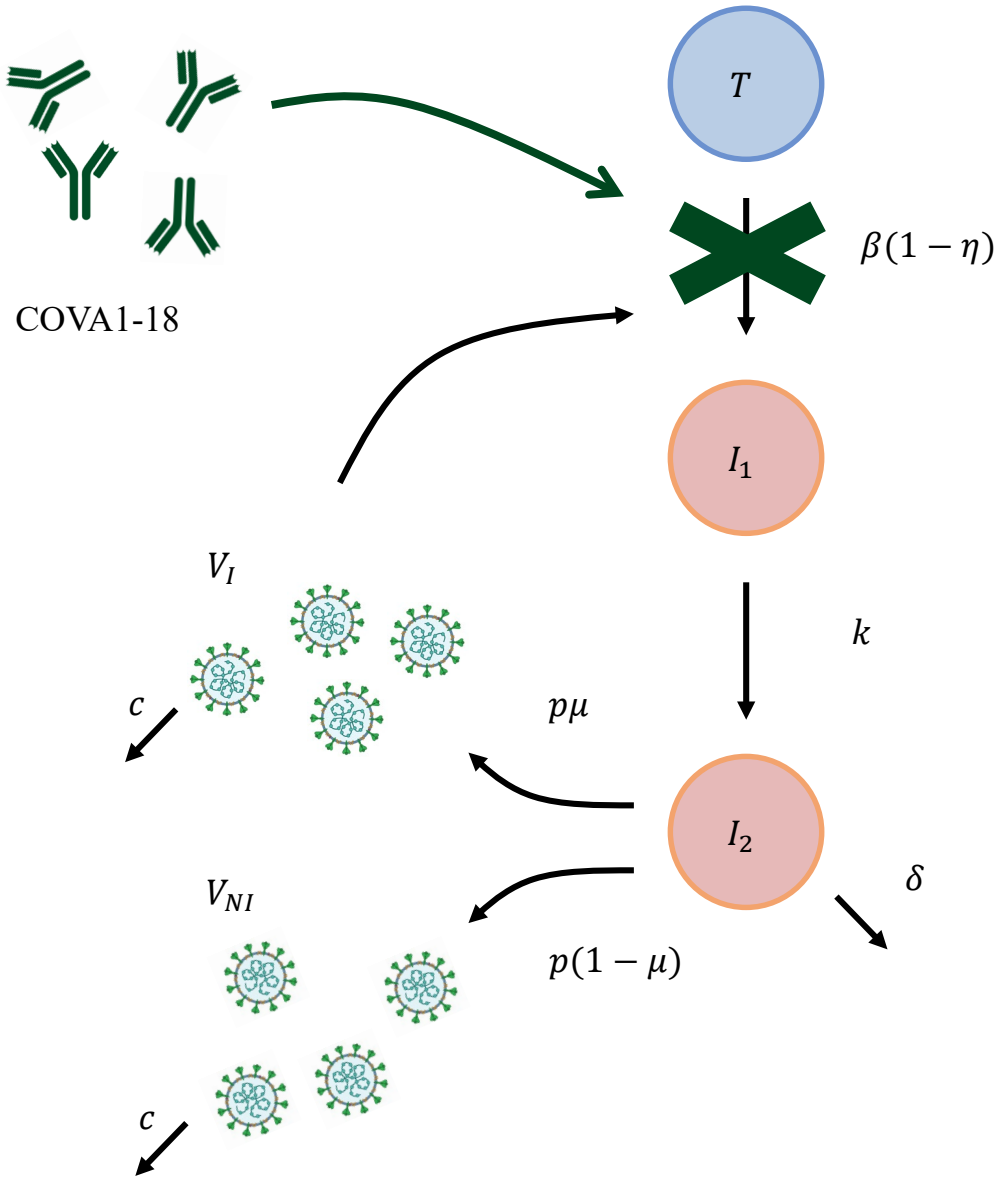
COVA1-18 blocks the virus/cell attachment

$$\eta(t) = \frac{C(t)}{C(t) + EC_{50}}$$

With :

- $C(t)$: COVA1-18 **plasma** concentration used as a driver of the efficacy

- EC_{50} : Concentration required to obtain 50% efficacy.



ODE system :

$$\frac{dT}{dt} = -\beta(\mathbf{1}-\boldsymbol{\eta})VT$$

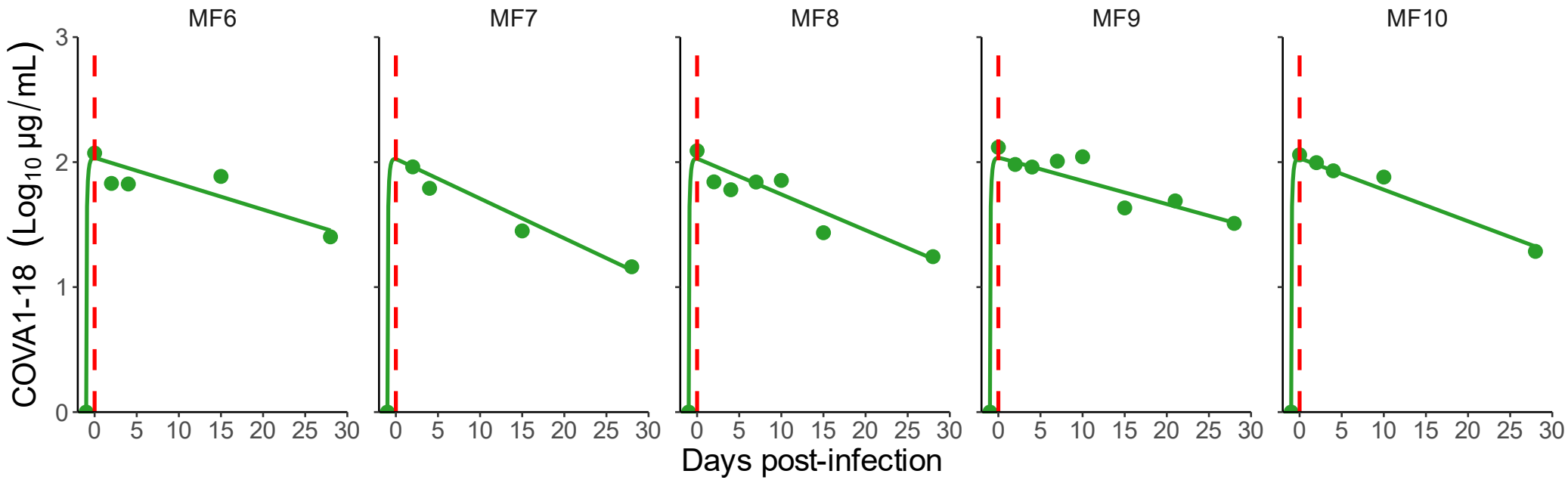
$$\frac{dI_1}{dt} = \beta(\mathbf{1}-\boldsymbol{\eta})VT - kI_1$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2$$

$$\frac{dV_I}{dt} = p\mu I_2 - cV_I$$

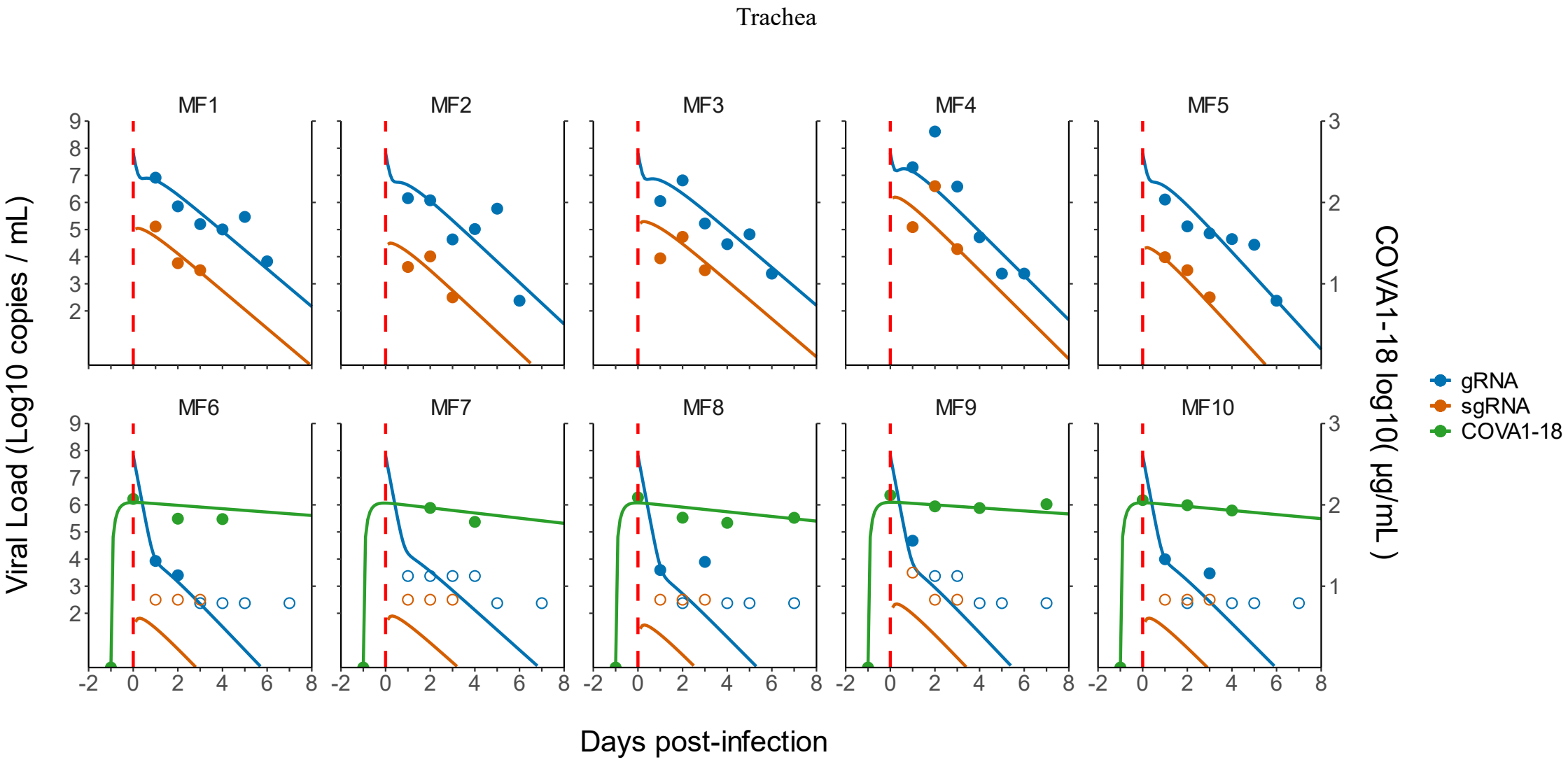
$$\frac{dV_{NI}}{dt} = p(1-\mu)I_2 - cV_{NI}$$

Plasma PK of COVA1-18

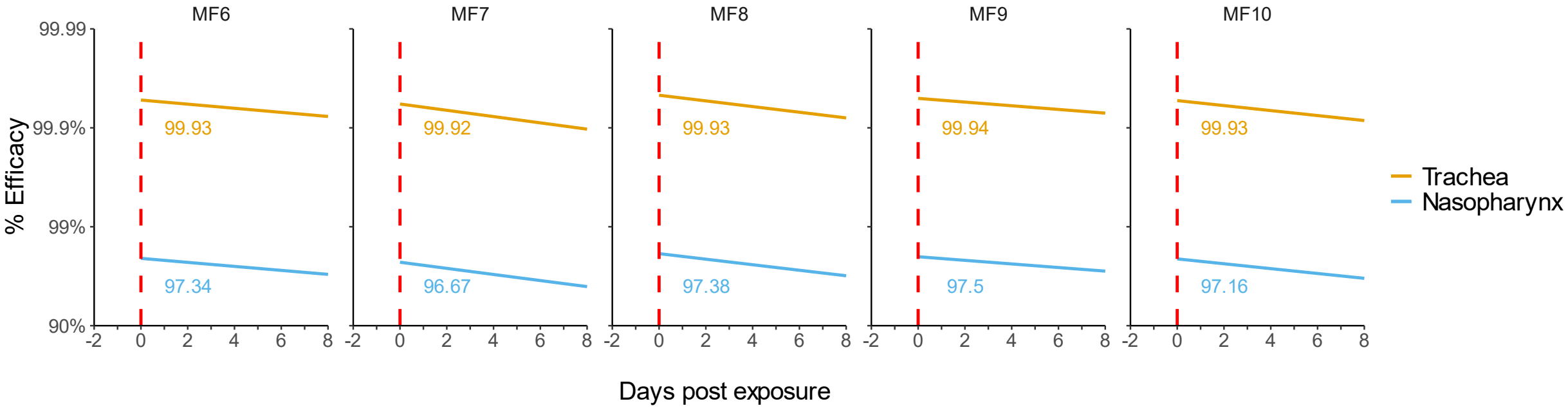


Antibody Half-life of 12.7 days

Individual fits



Drug efficacy in blocking viral infection is >95%

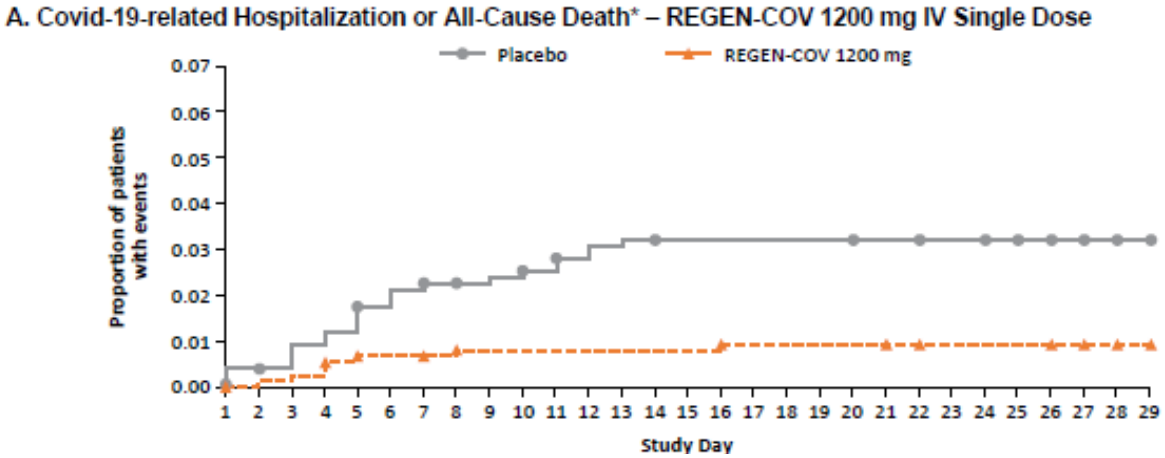


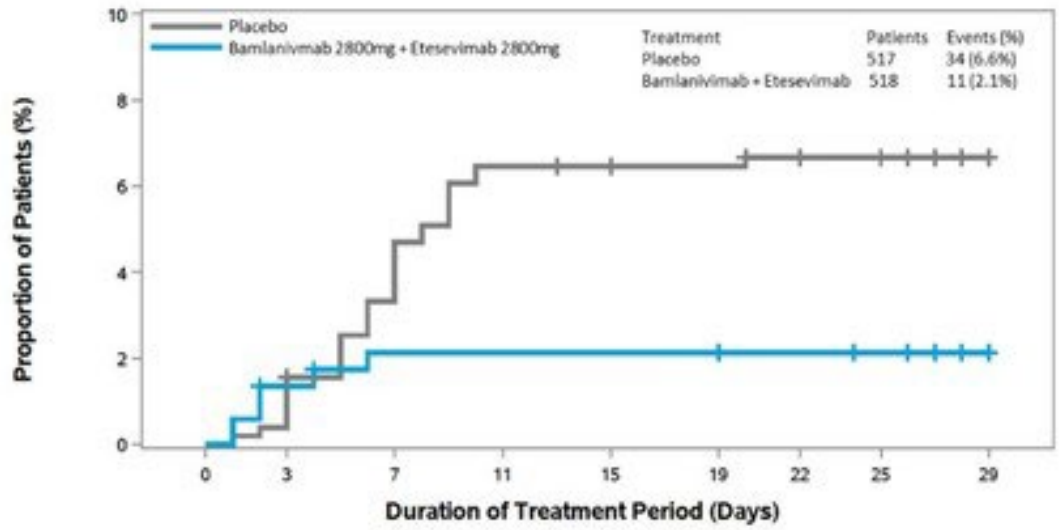
Efficacy is consistent over all animals :

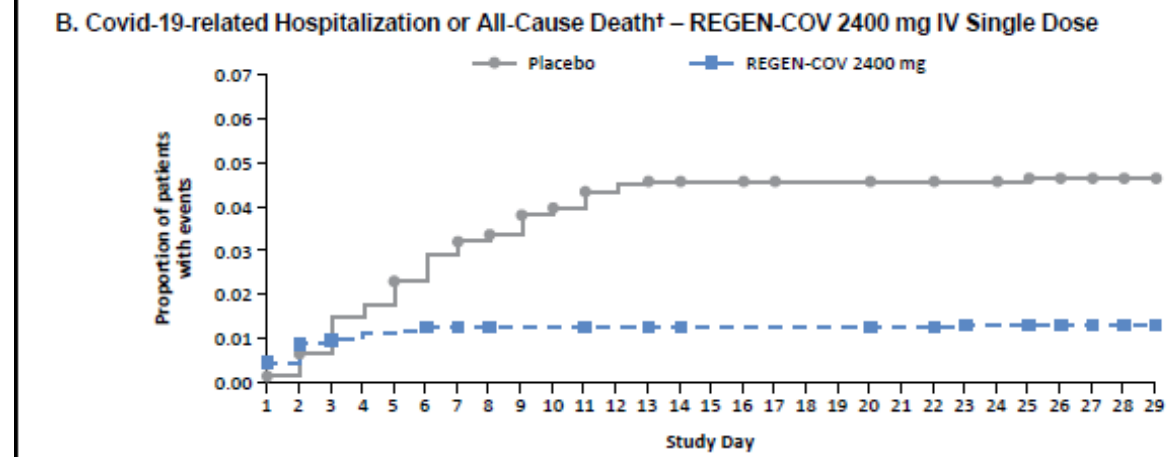
- $\overline{\eta}_{trachea} > 99.9\ \%$
- $\overline{\eta}_{nose} > 96\ \%$

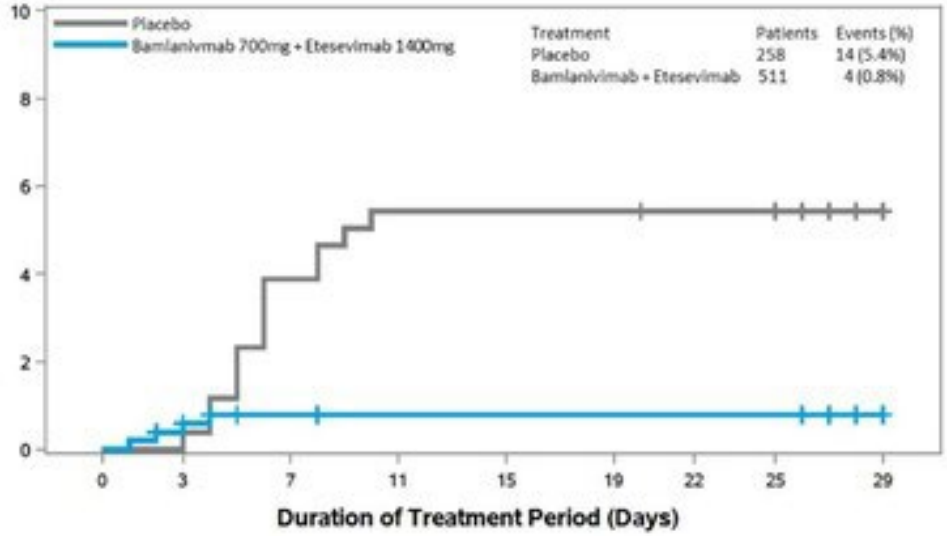
Could be relevant as a PreP in human infections with a lower viral inoculum

Monoclonal antibodies reduce the risk of disease progression by ~70% if given <7 days from symptom onset









Dougan, NEJM 2021; Weinreich et al, NEJM 2021

Modeling and the role of antiviral treatment

- Modeling identifies some important features of viral dynamics
  - Incubation period is ~5 days (prior to Omicron) and the peak of viral load is close to symptom onset
  - Age is associated with prolonged viral shedding
  - Viral dynamics is an independent predictor of disease progression in both outpatients and hospitalized patients

- Timing of antiviral treatment is key to reduce the risk of disease progression
  - Blocking viral production or infection >90% is needed to prevent progression
  - Even if administered late, antiviral treatment can reduce the mortality in patients that have high viral load (eg, positive antigen test)
  - Monoclonal antibodies have a high efficacy and reduce the number of at risk patients with extended shedding
  - Efficacy jeopardized by Voc and need now to account for resistance and relapse
  - Small molecules can be alternatives to monoclonal antibodies if they pass the pharmacological threshold

Implications

2021

April 12th

First inclusion in France

Patients hospitalisés avec le COVID-19 sous assistance respiratoire (service de salle)

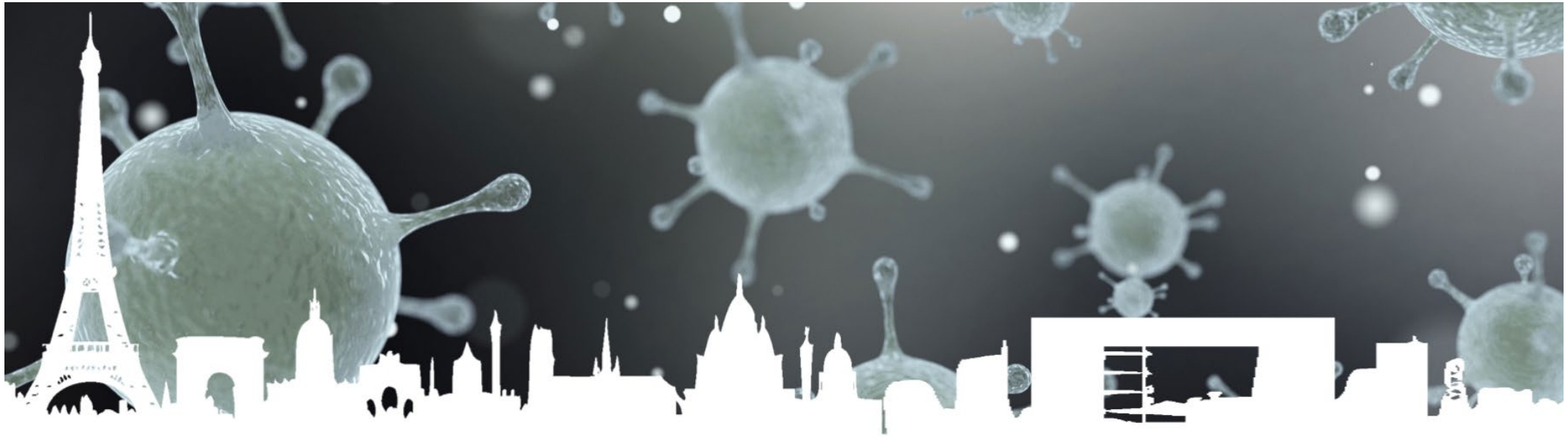
- Placebo + standard of Care (SoC)
- AZD7442 + SoC
  IV 600 mg day 1

Primary end-point : WHO 7-point ordinal scale at day 15 (antigene positive patients)
Key secondary end point: Time from randomization to sustained recovery
(being alive and at home for 14 consecutive days prior to Day 90)

AZD7442 [1] : cocktail de deux mAb synthétisés avec une technologie d'extension de la demi vie

[1] Dong et al. *Nat Microbiol.* (2021)

Join our group for a Postdoc in Paris !



Post doctoral position in mathematical modelling (COVID19) in Paris

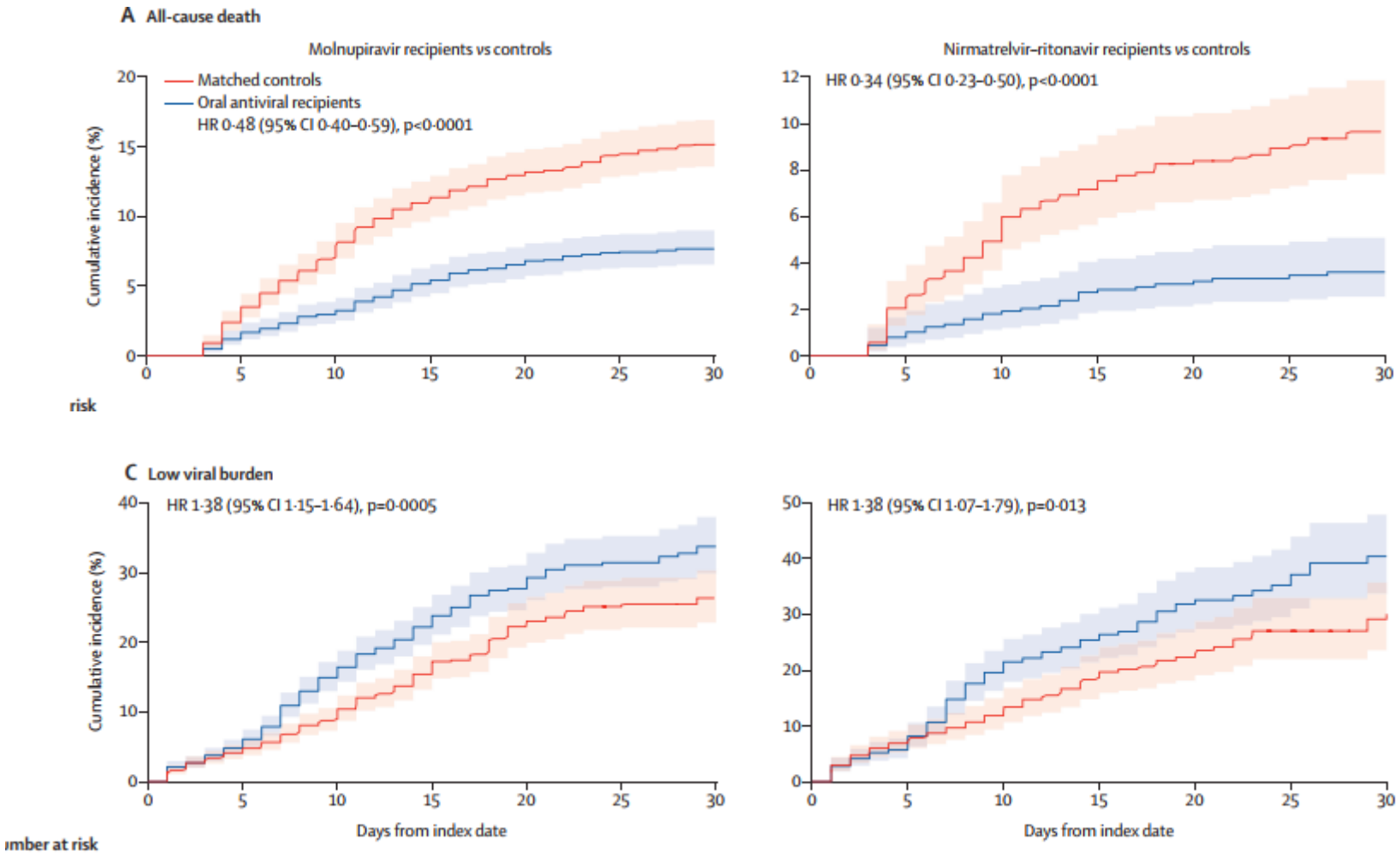
Two post-doctoral positions in mathematical modelling of infectious diseases of 24 months each are available to work in Paris between Institut Pasteur and Inserm (UMR 1137) within the European project ORCHESTRA.

PostDoc position (2y) in Paris for studying viral and immune dynamics of SARS-CoV-2 infection

ORCHESTRA

For more information: **jeremie.guedj@inserm.fr**

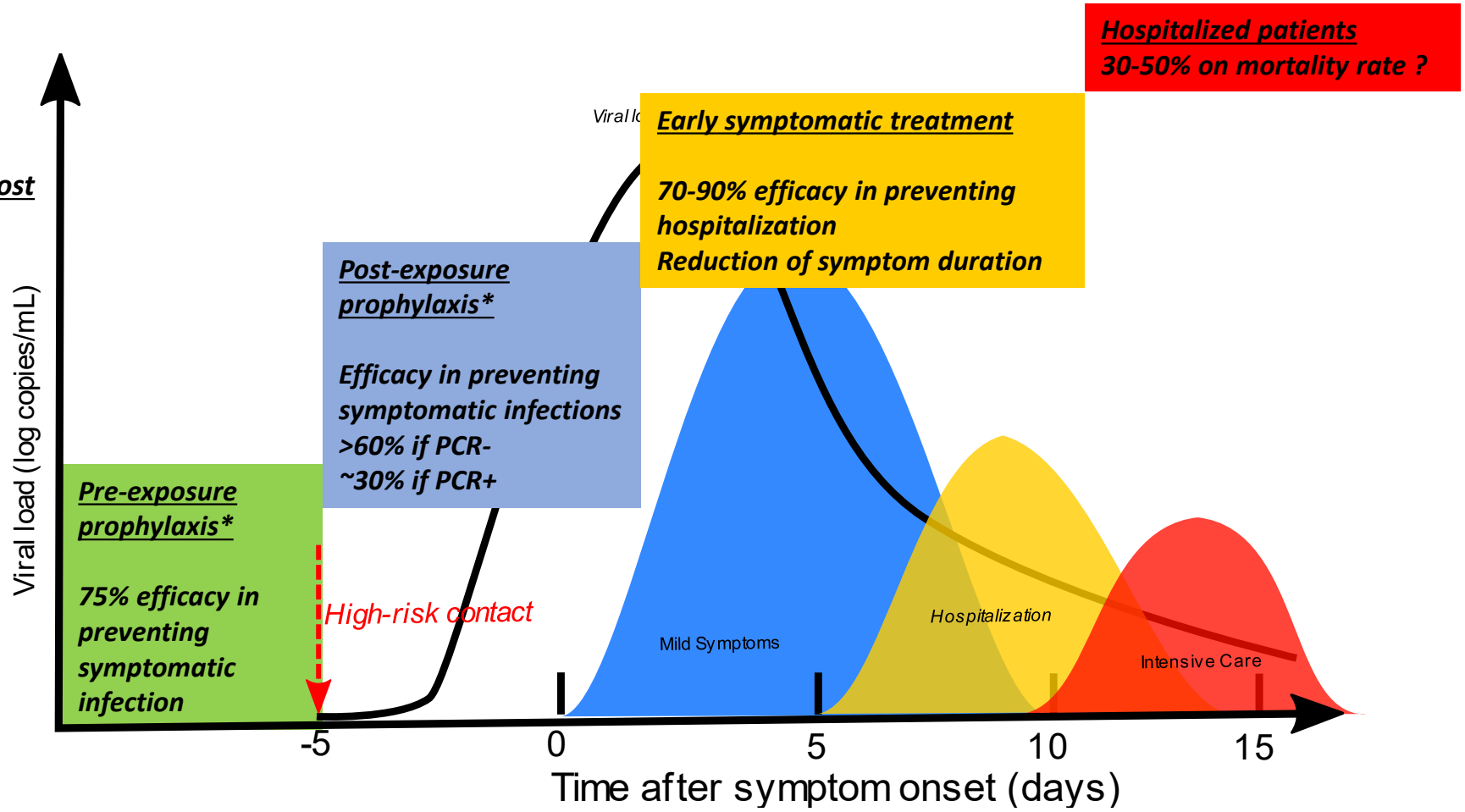
Effectiveness of early oral antivirals in hospitalized patients



Wong et al, *Lancet Infectious Diseases,* 2022

Antiviral treatments and treatment efficacy : where are we ?

**** Results obtained in 2020-2021 with mAbs <u>that have lost most or all activity against omicron variants</u>***



Dougan, NEJM 2021; Hammond, NEJM 2022 ; Levin, NEJM 2022 ; O'Brien, NEJM 2021 ; Recovery Collaborative Group, The Lancet 2022 ; Weinreich et al, NEJM 2021; Wong et al., 2022

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French Covid & Discovery study groups

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Ping Zhao, BMGF
Lulla Opatowski, Pasteur Institute
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Colin Pillai, CP+
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Nadège Néant, INSERM
Hind Zaaraoui, INSERM

DISCOVERY

FRENCHCOVID

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